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Stress as Provoking Factor for the First and Repeated Multiple Sclerosis Seizures

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ORIGINAL PAPER

ABSTRACT

Introduction: Multiple sclerosis is an inflammatory, autoimmune, disease of the white mass of the brain, which sometimes may involve the gray matter (subcortical and ones in the anterior horns of the spinal cord) with the chronic nature and generally with progressive course. As a possible cause of this disease state are listed genetic predisposition, early viral infections and environmental factors, with special effects of stress as a provoking factor in first episode of the disease and relapses because stress leads to modulation of the immune system and immune response to various causes. **Goal:** To determine the existence of intense stressful events as a factor in the development of the first episode of illness and worsening of the seizures. **Material and methods:** We analyzed all newly discovered cases of multiple sclerosis over a two year period (January 2010 – December 2011) during the first or second hospitalization, and worsening of seizures for previously diagnosed patients in this period. In order to confirm the MS diagnosis are taken history, neurological examination, MRI of the brain, VEP, CSF examination and for those with repeated hospitalization only follow-up of EDSS scores trough neurological examination. **Results:** During the two year period there were 109 newly diagnosed cases of MS from which 80 F and 29 M (ratio 2.7:1), aged 17-59 years, mean age 32.93±9.69 years and 41 patients (29 F and 12M with seizures worsening in previously diagnosed disease. Disease duration was from 6 months to 17 years. 72.94% had relapsing-remitting course of the disease (RRMS) and 27.1% had secondary progressive type (SPMS). Stress as a provoking factor preceded in 47.44% the first episode of the disease, infections (respiratory) in 18.3%, and the pregnancy with postpartum period in 8.77% women, whereas in the group of patients with previously diagnosed illness relapse (n=41) showed that the infection is most common precipitating factor which preceded relapse in 58.54% of patients, stress in 29.02%) and the pregnancy with postpartum period in 12.5% of patients. **Conclusion:** An intensive stressor is certainly one of the triggers for the development of Multiple Sclerosis, as the first episode and worsening of previously established disease.

Key words: multiple sclerosis, stress, precipitating factor.

1. INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) characterized by the deterioration of myelin and axons in various parts of the brain and spinal cord (1, 2). It more often affects women than men (ratio from 3:1 to 1.8:1). MS is a disease with 1000 faces, depending on the process localization. The disease is characterized by dissemination in time and space and the clinical course with remissions and exacerbations. Exacerbations are a reflection of increased inflammatory activity in the CNS, which is immune mediated (2, 3).

Occurrence or relapse of the disease is associated with many factors including: age, gender, latitude, migration,

race, family history and exposure to viruses. Among the factors that may trigger the first episode of MS and exacerbations are: stressful events, viral infections, vaccinations, physical trauma, anesthesia, excessive physical activity and puerperium (4).

The term „stress“ (first described by Selye in 1946) is defined as a situation in which, homeostasis – the natural balance is endangered and the same is reestablished by complex physiological and behavioral responses of the organism. Stressors can be physical and emotional/psychological whereby is not only important their intensity but also duration (5).

The idea that mental stress could lead to disease onset

dates back to the first MS description from the mid-19th century. Charcot believed that „grief, agitation or adverse changes in the social environment may be associated with the development and exacerbation of the disease“. Since then many studies has been published and shown that healthy people who were exposed to a strong stressor, in this case the death of a child, were at increased risk of later developing MS. On the other hand, large cohort study by Riise and colleagues, published in 2011, shows that stress does not have great role in the disease development, but that further studies are needed in order to rule out stress as a potential risk factor for the disease occurrence (6).

Possible mechanism by which stress can influence the onset and exacerbation of disease symptoms is modulating the immune response via the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic. Clinical and molecular studies of MS and its experimental animal models, autoimmune encephalitis (EAE), showed interference in communication between the immune system and the two main systems in response to stress, HPA axis and autonomic nervous system (ANS). Insensitivity immune answers to the glucocorticoid and β -adrenergic modulation can lead to excessive immune responses (7). Exposure to chronic stress reduces the number and/or function of glucocorticoid receptors in immune cells so that they become less sensitive to the regulatory control of cortisol. This glucocorticoid resistance was observed among patients with relapsing-remitting MS during the initial, inflammatory phase of disease. On the other hand, acute stress, as shown in the studies, increases the permeability of the blood-brain barrier (BBB) and disease activity, mobilization of mast cells, and cytokine production by Th1 and Th2 lymphocytes (8). Conducted is a study on 14 healthy medical students in order to assess the association between psychological stress event (final exam) and serum levels of TNF- α , which is an important proinflammatory cytokine, involved in the pathogenesis of MS. The results showed that there are continuous reduced levels of TNF- α in the serum until the day of the exam, accompanied with a significant increase in the level the day after. This fluctuation of TNF- α during acute stress may trigger clinical exacerbations in patients with MS (9).

Clinically the disease may manifest itself in many forms.

Relapsing-remitting multiple sclerosis (RRMS). This is the most common type of MS, approximately 60-65%. Characterized by the initial seizures of worsening followed by complete recovery in the beginning but later usually incomplete, so that the neurological damage is summarized after few seizures.

Secondary progressive multiple sclerosis (SPMS) occurs in approximately 30-35% of MS cases. Over time, accumulating irreversible neurological deficit. Almost 90% of those with the RR form for a period of 25 years progress to the SP form of MS.

Primary progressive multiple sclerosis (PPMS) occurs in approximately 10% of patients, where from the very beginning of the disease there is progressive accumulation of neurological deficits without periods of remission.

Progressive relapsing multiple sclerosis (PRMS) is progressive from the start with superimposed relapses. Progression of the disease is dominant, so it is considered that

the PRMS and PPMS are very similar and occurs in about 5% of patients.

Approximately 3-5% of patients have benign disease with mild clinical course with no relapses or with slightly prominent neurological symptoms, where in a 10 years period or more EDSS have minimal changes (10).

2. GOAL

To establish the existence of intense stressful events as triggers in the onset of the first seizure of the disease, but also deterioration of seizures in the later course.

3. MATERIAL AND METHODS

We analyzed all newly discovered cases of multiple sclerosis over a two year period (January 2010 – December 2011) during the first or second hospitalization, and worsening of seizures for previously diagnosed patients in this period. In order to confirm the MS diagnosis are taken history, neurological examination, MRI of the brain, VEP, CSF examination and for those with repeated hospitalization only follow-up of EDSS scores trough neurological examination.

Special attention was paid to possible intense stressful event, which preceded the condition (in the preceding 6 months) as follows:

- Death of close family member (spouse, child, father, mother, brother or sister);
- The death of other family member or close friend;
- Problems in a relationship or marriage: conflicts, separation, divorce;
- Loss of job or severe stress at work, school;
- Own illness (except MS), trauma, surgery;
- Serious illness of close relatives;
- Interpersonal conflict: family and others, including family financial problems;
- Other: death of relatives, pet death, lawsuits.
- Pregnancy and the postpartum period: if it is recorded within one year before the first symptoms of the disease or its worsening.
- Infection (respiratory or urinary) which preceded the seizure of the disease.

4. RESULTS

In this two-year period (January 2010–December 2011) there were 109 newly diagnosed MS cases from which 29 M (26.6%) and 90 F (82.56%). The man to women ratio was 1:2.71 aged 17-57 years. There was a statistically significant difference in the number of men and women ($p < 0.0001$).

Analyzing the age of illness onset, at age 10-19 years there were 4 patients (3.66%) (3F and 1M), at age 20-29 years 29 patients (26.60%) from which 7M and 22 F, aged 30-39 were 36 patients (33.02%) of which 8 M and 28 F, aged 40-49 years were 37 patients (33.94%) from which 9M and 28F and aged over 50 years 13 patients (11.92%) from which 9F and 4M.

Most patients belonged to age group of 30-39 years with a total of 36 patients (33.02%) and the 40-49 age group or 37 patients (33.94%).

The average age when developing multiple sclerosis was 32.93 ± 9.69 years. For men illness started at average age of 33.07 years, while for women at age of 32.89 years. There was no statistically significant difference in age at the occurrence

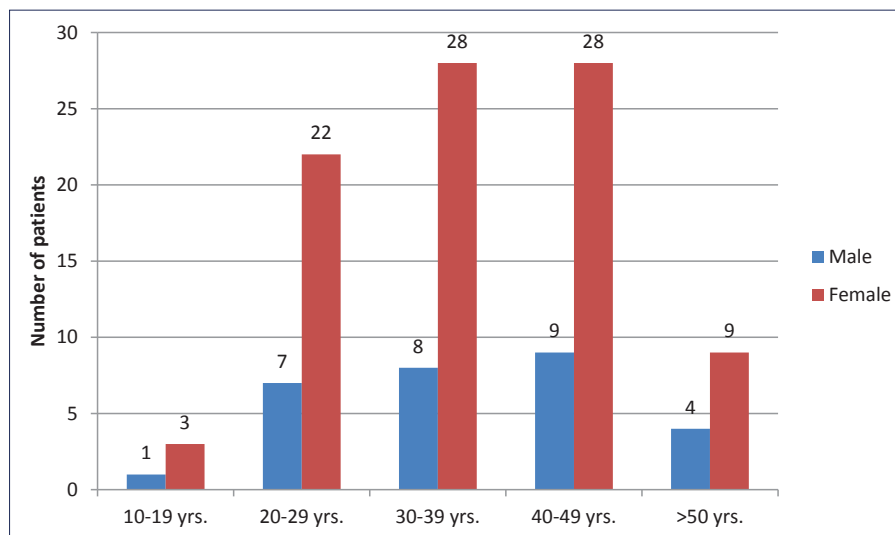


Figure 1. Distribution of patients by gender and age groups

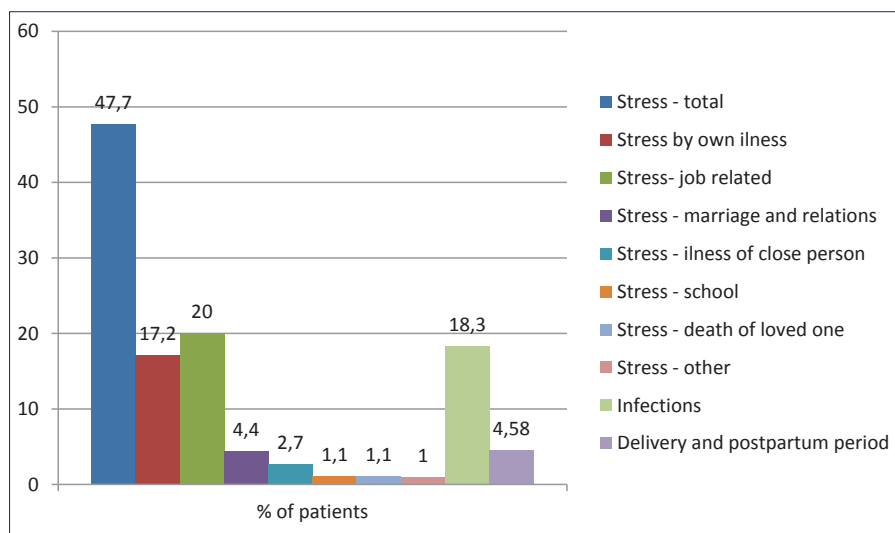


Figure 2. Percent of patients with stress, infection and delivery with postpartum period that preceded the illness onset

of MS between men and women ($p=0.9311$).

The most common type of MS is RRMS (relapsing-remitting multiple sclerosis), which was recorded in 79 (72.5%) patients from which 53 (48.62%) female and 26 (23.85%) male. SPMS (secondary progressive multiple sclerosis) was recorded in 30 patients (27.5%) or 24 female (22%) and 6 males (5.5%).

4.1. Analysis of the role of stress as a provocative factor in multiple sclerosis onsets

In patients with newly diagnosed disease, stress was recorded in 47.70% respondents (33F and 19M) and in 17.2% the stress caused by their own illness (excluding multiple sclerosis), due to surgery or trauma, in 20.0% the stress factors were the problems related to job, job loss or severe stress at work, problems in marriage and interpersonal relationships in 4.4%, the disease of close person 2.7%, examination periods in school for 1.1%, in 1.1% cases the stress related to the death of a loved one and other stressors in 1% of cases.

Besides the stress, among newly discovered cases are infections (mainly respiratory) in 18.3% (20 respondents or 15F and 5M) and delivery with postpartum period as

a possible trigger of the disease in 4.58% of cases (5 patients).

It was noted that there was a statistically significant difference between female patients in whom the infection preceded the disease and those who did not ($p<0.0001$), or statistically for significantly greater number of patients did not preceded the disease. It has been observed also for pregnancy and the postpartum period that there where a significant number of patients ($p<0.0001$) in which pregnancy and childbirth did not preceded the disease. On the other hand there was no statistically significant difference in the number of patients in whom stress did not preceded the disease ($p=0.8949$).

With repeated exacerbations ($n=41$) stress preceded in 39.0% cases (12F and 4M), mostly related to problems in marriage and family at 18.0%, own illness (other than multiple sclerosis) in 11.0%, stress due to illness of a family member in 5.5% and in 3.3% of cases due to problems at work and job loss, while the loss of a loved one was present in 1.1% of cases.

Infections (mainly urinary tract infections), preceded at 46.3% (19 respondents, 18F and 1M), and delivery and postpartum period in 5.50% (6 patients).

In the majority of patients the infection was preceded clinical exacerbation of disease. There was

no statistically significant difference in the number of patients in whom infection was not preceded by exacerbation ($p=0.8642$), as well as the number of patients in whom stress did not preceded the exacerbations ($p=0.4032$). On the other hand, for significantly larger number of patients ($p=0.0096$), pregnancy and postpartum period did not preceded the exacerbation of the disease.

The results show a statistically significant difference ($p<0.0001$), between the number of newly diagnosed patients, in which the diagnosis is preceded by stress as compared to patients in whom the infection is preceded the first episode of illness. In patients with relapses no statistically significant difference was found between those in which the stress preceded the deterioration of illness in comparison with those which deterioration is preceded by the infection ($p=0.3239$).

Comparing the effects of provocative factors (infection, stress, pregnancy and the postpartum period) on the occurrence of the disease and its course, or exacerbation, it is seen that there is a statistically significant difference between the effects of infection on the occurrence of the disease and its

exacerbations in females, or significantly greater impact of infections on relapse than on the occurrence of the disease ($p < 0.0001$). (Figure 1 and 2).

In male subjects, it was observed that there was a statistically significant difference between the person in whom the infection existed before the first episode of the disease and those who did not ($p = 0.0020$), or there was statistically significantly greater number of patients in which the infection did not precede the disease. On the other hand, there is no statistically significant difference in the number of male patients in whom stress did not precede the disease compared to those who had previous stress ($p = 0.5373$).

5. DISCUSSION

From the total number of newly diagnosed MS patients, 80 patients were female (73.30%) and 29 (26.60%) male, with a ratio of 2.7:1. These data correspond to previous epidemiological researches which detected significantly higher occurrence of disease in women. In most studies the ratio of female: male is 2:1, however, more recent studies point to the growing incidence of multiple sclerosis among women. In a longitudinal study conducted in Canada has been concluded that in the last 50 years there has been a significant increase in ratio between women and men which now exceeds 3.2:1 for specific populations. Similar results were obtained in a study on the U.S. population by W. Noonan et al., where the ratio of women: men ranged from 1.9:1 to 3.6:1 for individual age groups (4,11).

The average age of respondents was 32.93 ± 9.69 years with a range from 17-57 years and there is no statistically significant difference in age between the genders. These results are consistent with the studies by B. Yamout et al. where average age was 39.6 ± 10.9 years and X.J. Liu et al. with an average age of 37.44 ± 12.24 years. Study by Alajbegović A. et al. on the epidemiological characteristics of multiple sclerosis in Bosnia and Herzegovina has reached results that the average age is 41.22 ± 9.39 years, in age groups 30-39, 40-49 and 50 and over, there were 22 (30.99%), 31 (43, 66%) and 11 (15.49%) patients. Data from these studies correspond to the results of this study in which patients are most commonly in the age group of 40-49 years, where we have recorded 37 patients (34%) and age group of 30-39 years with 36 patients (33%) (2, 12, 13).

The average duration of illness was 3.93 ± 4.85 years with a range from 6 months to 17 years, which is consistent with studies by Potagos C. and al. where the average duration of disease was 3.6 years and X.J. Liu et al. where the disease lasted for an average of $2:53 \pm 1:35$ years (7, 13).

The disease occurred at an average age of 32.93 ± 9.69 years in a range from 17-57 years. According to literature data, the mean age for occurrence is approximately 30 years, where about 70% of patients are aged 20-40 years. The disease rarely occurs before the age of 10 and after 60 years of age, although there are case reports of occurrence and the age of 3 and 67 years. In a study by Confavreux C. and al. which included 1844 patients who were treated at the Clinique de Neurologia in Lyons, France, the average age of first occurrence of symptoms was 31 ± 10 years with a range of 5-67 years. This research is consistent with these data and highest number of patients was in the age group

of 20-29 and 30-39, or a total of 77 patients (70.6%) (14).

The most common type of multiple sclerosis in this study was RRMS (relapsing-remitting) with a total of 79 patients (72.94%), while the SPMS (secondary progressive multiple sclerosis) was observed in 30 patients (27.1%). There was no cases of PPMS (primary progressive multiple sclerosis) or PRMS (progressive remitting multiple sclerosis). In a study by Alajbegović A. et al. RRMS was present in 60.56% and SPMS in 19.72%, while for 11.25% of patients was not known the type of multiple sclerosis. In a study on the French population in 58% of the patients was diagnosed RRMS, SPMS in 27% and in 15% PPMS (14,15).

The study evaluated the incidence of stress as a provocative factor for the occurrence of the first seizure of the disease and its exacerbations. To determine the importance of stress as a provocative factor we made the comparison of the influence of stress with two provocative factors which in previous studies been shown to play an important role in disease onset and its deterioration, such as infections and pregnancy or postpartum period. For newly discovered cases stress was previously present in 47.70% cases and in 17.02% the stress was caused by their own illness (excluding multiple sclerosis), surgery or trauma in 20% of cases, the stress related to problems with work or education, job loss, severe stress at work, problems in marriage and interpersonal relationships in 4.4%, the illness of close person in 2.7%, the examination periods in school in 1.1%, in 1.1% cases of death of a loved person and in the 1.1% other stressors. In the seizure worsening, stress preceded in 39% of cases: problems with marriage and in family in 18%, own illness (except MS) in 11%, the stress due to illness of a family member in 5.5%, stress due to problem at work in 3.3% and the loss of a loved one in 1.1% of cases. For women it was found that stress preceded disease in a significant number of cases, 49.12% in relation to infection (12.28%), and pregnancy including postpartum period was recorded at 4.58% of patients. On the other hand, for the exacerbation was not statistically significant difference in the frequency of these three factors: stress is preceded in 39.0% cases, infections 46.3%, and pregnancy/postpartum period at 5.50% of patients. The infection was found to be more common as a precipitating factor in recurrent exacerbations than the first episode of the disease.

Pregnancy represents a state of relative immunosuppression, because the fetus carries antigens originating from the father and probably high levels of estrogen associated with pregnancy contribute to this condition. Estrogen is associated with a Th-2 type immune response and suppression of microglia activity and is proven to suppress experimental allergic encephalomyelitis (EAE) in animal model of MS. This was confirmed by clinical studies. The Pregnancy in MS (PRIMS) study, the first large prospective study that followed a total of 269 pregnancies in 254 women up to 24 months after the birth. The annual relapse rate was dramatically decreased during pregnancy. Compared with the mean relapse rate of 0.7 ± 0.9 in the year before pregnancy, it was observed reduction by two-thirds to 0.2 ± 1.0 during the third trimester ($p < 0.001$). In contrast, 3-month postpartum period is characterized with increased rates to 1.20 ± 2.0 ($p < 0.001$). Thereafter, the rate of recurrence is reduced by a

rate of reference period (16).

Findings of studies that examined the role of stress in the onset of multiple sclerosis are contradictory. Cohort study in Denmark has examined the association between risk of MS and a well-defined major stressful life event: death of a child. Followed are two large groups of parents: 21062 who had lost a child younger than 18 years between the 1980 and 1996 and 293745 in a control group of parents who were not exposed to this stressor. Parents who were exposed to the stressor were at increased risk of MS, but this risk was significant only in 8 years follow up (17).

The belief that stress provoked exacerbations is widespread among patients with MS. However, the nature of the relationship between stress and MS is a complex activity. Different stressors may have different effects and impact of stressful life events may depend on the balance between positive and negative events. While there are studies that have examined the role of stress in the development of MS vary, most studies agree that stress has an important role as a provocative factor for exacerbation of the disease. A prospective study by Buljevac D. et al. followed 73 patients with RRMS during 1.4 years. The patients reported events that they considered to be stressful. The period at risk is defined as a period of 4 weeks after stressful events is reported. The study results showed that the stressful event is associated with 2.2 times greater risk of exacerbations (18). The one-year prospective study of Greek authors monitored 37 women suffering from MS. Followed are the characteristics of stressful life events and the resultant level of anxiety in patients to determine their role in the occurrence of relapse. It was found that the number and intensity of stressful events is not associated with increased risk. Significant risk of relapse is associated only with reported 3 or more stressful events. They are associated with 6.7 times greater risk of exacerbation during the 4 weeks that follow (19). In a meta-analysis by D.C. Mohr's et al. which covered 14 studies of which seven were case-control and 7 prospective cohort. Two studies have analyzed the impact of stress on the first exacerbation that led to the diagnosis of MS, while other studies have followed exacerbations after the diagnosis. A meta-analysis found a moderate, but clinically significant relationship between stress and illness exacerbations. In a study of MS relapse during the Israeli-Lebanese war in July 2006 among Lebanese patients, the number of relapses during the war period was almost three times higher than in the similar period in the years before and after the war. These clinical findings were confirmed also by radiological findings, where more patients during the war had Gd+ lesions on MRI (33%) than in the control period (13%). Study by K.D Ackerman and al. followed 23 patients with MS during one year. The results of this study also confirmed previously observed results that stress is associated with the appearance of exacerbations. In addition, wide range of stressors (from mild to marked and from different sources) is equally associated with exacerbations (8, 20).

Depression is one of the earliest and most common psychological symptoms of MS. In a study conducted at the Neurological Clinic of Clinical Center, University of Sarajevo 56% of patients with MS had a depressive disorder. It is certain that these psychological disturbances in patients

with MS significantly affect the perception of stressful life events and their effect on the disease. Physical disability and cognitive deficits may interfere with normal life of the patients while reduced quality of life continues to promote emotional and mental problems (21). Six-year prospective study by C. Schwartz and associates (101 patients with MS and 96 healthy individuals as control) given the results that the increased rate of reported stressful life events increased the risk for disease progression (OR=1.13, $p<0.0003$) and on the other hand, when a higher rate of disease progression is present it also increases the rate of reported stressful life events (OR=2.13, $p<0.0001$) (22).

Study by I. Grant and associates reached results that within 6 months before the disease-MS 76.92% patients had experienced significant stressful life events (23). Another study showed that 79% of patients with MS reported stressful events during the 2 years preceding the illness (compared with 54% of controls during the same period) (24). Study by Ackerman and associates in patients with confirmed MS showed that 85% of patients with exacerbations had a stressful event in a period of 6 weeks prior to deterioration (20). Stress can suppress the immune reaction, which can lead to increased sensitivity to infection, on the other hand infection continues to deteriorate the physical condition of the patient which makes it more sensitive to the effects of stressors (25).

In our study, relapse of disease was preceded by infection in 46.3% of patients. Studies which have examined the effects of stress and infection on the course of MS have shown that infection and stress act independently of one another and patients who experienced an infection and stressful life events had an increased risk of exacerbation of the disease, which is equal to the product after the action of the independent risks of stress and infection (26, 27).

6. CONCLUSIONS

Multiple sclerosis is more common in women than men and usually occurs at age between 20-40 years.

Stress is a very important provoking factor for the occurrence of the first episode of illness and worsening of seizures later in the course.

In addition to stress, infection is often provoking and trigger factor for exacerbations.

Pregnancy has a much smaller role in the development of both new and recurrent seizures of disease, while postpartum period is a common cause of disease worsening.

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