ORIGINAL ARTICLE

The Prevalence of Smoking and its Impact on Disability in Multiple Sclerosis

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ABSTRACT

Introduction: Etiology of multiple sclerosis (MS) involves multi-factorial inter-actions among genetic and environmental factors. Cigarette smoking is one of the most important environmental factors that increase the disease risk by about 50%. The aim of this research was to assess the prevalence of smoking in MS patients compared to the general population, and to assess the association between smoking and physical disability in MS patients.

Materials and Methods: A cross-sectional study included 100 MS patients and 50 healthy people. For estimation of the degree of physical disability, the Expanded Disability Status Scale (EDSS) was used, and for clinical and demographic data a general questionnaire was used. In order to collect data on the smoking, the questionnaire for examining risk factors for vascular disease among patients with MS was used.

Results: Analysis of smoking incidence showed that, between MS and control group, smoking was a dependent variable ($\chi 2$ = 6.258, p = 0.04). There was no statistically significant difference in the number of cigarettes, nor in the duration of smoking. There was no significant correlation between smoking in MS group and the index of disease progression (r=0.216, p=0.133). Also, the relationship between EDSS and smoking had no statistical significance, as well as between the disease course and smoking ($\chi 2$ = 1.531, p = 0.216).

Conclusion: Although it seems reasonable to restrict or refrain from smoking in patients with MS there was no significant evidence of smoking and disease progression correlation.

Keywords: multiple sclerosis, smoking

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INTRODUCTION

Multiple sclerosis (MS) is a chronic, autoimmune, inflammatory, demyelinating disease of the central nervous system and one of the most common causes of disability in the category of younger adults.[1] The disease has a very heterogeneous clinical course and symptoms. Since the average duration of the disease is longer than twenty years, the accumulation of clinical manifestations may significantly affect the daily living of patients.[2] The etiology of MS involves multifactorial interactions among genetic and environmental factors. Genetic predisposition is only a part of the risk for developing MS, while lifestyle and environmental factors are key participants in the development of the disease. The influence of these factors on the pathogenetic mechanisms is very important and some of them can be modified. Proven risk factors for developing the disease are female gender, smoking, low levels of vitamin D, dietary habits, Epstein Barr virus infections and obesity in childhood and adolescence.[3]

Cigarette smoking is, however, one of the most important environmental factors that increase the risk of disease by about 50%. These are data from previously performed studies that indicate

that the precise effects of smoking on the onset and development of MS vary in different contexts and different populations.[4] Since the '60s of the last century, smoking has been identified as a significant risk factor for the occurrence and progression of MS. Israeli researchers found a greater percentage of smokers among MS patients than in the general population (44: 36%).[5] Several other studies based on same questionnaire also confiremd the above findings.[6,7]

Recently, considerable research was focused the nicotine metabolite (cotinine) in the blood, and it was shown that nicotine alone was less important for the onset and progression of the disease than the non-nicotine substances produced by the combustion of tobacco. Most of these studies were related to patients tested after the diagnosis of MS.[8-10] A prospective study by Salzer et al. confirmed that smoking was as a risk factor for MS; the risk for MS was increased by 50% in patients with elevated levels of cotinine in the blood.[11]

According to the study of Hedstrom et al, patients who were smokers and treated with interferon beta 1b therapy had an increased risk of the development of neutralizing antibodies to the drug in comparison to the non-smokers. Such a correlation was not observed in former smokers.[12] Olsson and co-workers showed that smoking had a significant impact on the occurrence of neutralizing antibodies to natalizumab, which reduces or disables the therapeutic effect of this drug. It was also shown that smoking is associated with a greater number of relapses in natalizumab-treated MS who were smokers compared to those who did not smoke.[13] The effect of smoking on the presence of antibodies against John Chunningam (JC) virus in the population of MS patients was also studied, and it was established that smoking is not associated with an increased prevalence of the presence of this virus.[14]

AIM OF THE STUDY

The aim of this study was to assess the frequency of cigarette smoking in a population of MS patients, compared to the general population matched by gender and age, as well as to estimate the potential connection of smoking and physical disability measured by The Expanded Disability Status Scale (EDSS) in patients suffering from MS.[15]

METHODS

This cross-sectional study was conducted as part of the examination of patients affected by MS in ambulances or during hospitalization at the Department of Neurology, University Clinical Center of the Republic of Srpska, Banja Luka. The sample consisted of 100 MS patients (MS group) and 50 healthy people (control group). The inclusion criteria were: MS disgnosed according to the McDonald criteria, patients age 18-69 years, and consent to participate.[3] The exclusion criteria were: An exacerbation of the last month, and the use of corticosteroids of the last month.

The study was conducted for twelve months. Participants, both MS patients and healthy people, were introduced with the basic elements of research and voluntarily signed the consent for participation in the study. The study was approved by the Ethics Committee of University Clinical Center of the Republic of Srpska, Banja Luka, Republic of Srpska, Bosnia and Herzegovina. A general questionnaire, consisted of questions related to the clinical characteristics of patients: age at onset of MS, duration of illness, the course of MS and value of EDSS score at the time of testing was used. In order to determine the degree of physical disability, the Expanded Disability status scale (EDSS) was used.[15] In order to collect data on risk factors, it the questionnaire for risk factors for vascular diseases in patients with MS was used. The questionnaire was based on the literature data for the purpose of scientific research at the Institute of Epidemiology, School of Medicine, University of Belgrade. Data were related to the smoking status of participants (yes/no, ex-smoker), the number of cigarettes smoked per day and the duration of smoking habit (from- to).

Statistical analyses included methods of descriptive statistics (mean, standard deviation, mode, median, skewness/kurtosis), $\chi 2$ test, Student t-test, variance analysis (ANOVA), correlations (Pearson's and Spearman's tests) and regression analysis.

RESULTS

Regarding clinical data relevant to this study, it is important that when it comes to the course of MS, the majority of our patients (72%) had a relapsing-remitting form of MS, 27% had a secondary progressive MS, and 1% had primary progressive MS. The average value of EDSS score in MS group was 3.7 ± 2.1. The mean age of study subjects at enrolment was 41.9±10.1 (range 20-64) in MS group, and 42.1±12.3 (range 18-63) in control group. Out of the 100 subjects in MS group, 25 were male and 75 female, and out of 50 subjects in control group 14 (28%) were male and 36 (72%) were female.

A detailed analysis of the frequency of smoking in studied groups showed that smoking was a dependent variable ($\chi2$ = 6.258, p = 0.04). Figure 1 shows that the structure of the response varied between the MS and control group.
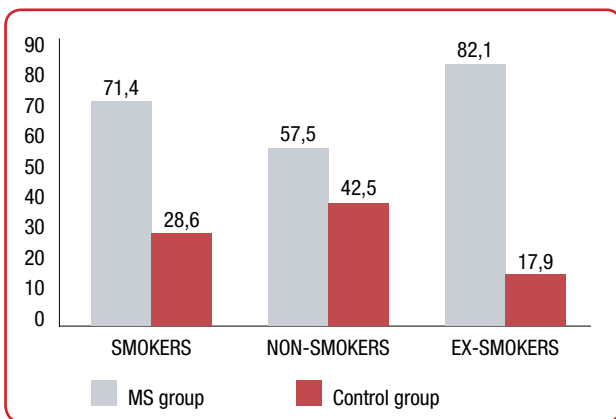

Figure 1: Representation of smoking in the control and MS group (%)

Among smokers, analyzed in both groups, there was no statistically significant difference in the number of smoked cigarettes nor the duration of smoking (table 1).

Table 1: Representation of smoking in the control and experimental group (%)

Group	Number	Number of cigarettes		Duration of smoking (years)	
		Average value	Standard deviation	Average value	Standard deviation
MS	58	15.17	8.10	18.47	10.54
Control	19	16.12	6.77	23.16	10.18

In terms of connection between smoking in the MS group and index of disease progression, the Pearson correlation coefficient was used. However, in relation to the analyzed variable, the correlation coefficient had a low absolute value, which means that there was no statistically significant correlation with an index of disease progression (r=0.167, p=0.251). The Spearman correlation coefficient showed that the relationship between EDSS and smoking had no statistical significance.

In order to establish a possible relationship between the disease and smoking the chi-square test was used, but no significance was found ($\chi2$ = 1.531, p = 0.216).

DISCUSION

A significant number of studies showed that smoking significantly increased, by 50%, the risk for developing of MS.[5, 6, 8, 16-19]

Results of this study showed that smoking, was a dependent variable (p = 0.04). Data from this survey also showed that the proportion of smokers in MS groups was statistically significantly different, as confirmed by the chi-square test. There were 71.4% of smokers in the MS group and 28.6% in the control group. Specifically, while in the experimental group share of smokers and ex-smokers dominates, the same share does not apply to the control group. Pekmezović and co-workers conducted a survey in the Belgrade area and showed that smoking is significantly more frequent in the group of patients with MS than in the control group. They also found that smoking was a significant and independent risk factor for MS.[20] This was also shown in two studies by Hedstrom et al, where smoking was identified as a risk factor for the development of MS.[21,22]

Salzer et al. found that patients with higher risk were young adults up to 26.4 years of age.[11] The same researchers evaluated the risk of passive smoking exposure on the occurence of MS and concluded that the risk was significantly higher in patients who were exposed to inhalation of tobacco smoke than those who were not. This risk increased with longer exposure to the

smoke.[23] They also analyzed blood samples in women who smoked during the gestation period and did not observe a higher risk of MS after childbirth, nor after 26.4 years of age of children whose mothers smoked during pregnancy. A weak link between smoking during pregnancy and the postpartal onset of MS was also shown by Montgomery and al.[24] In a study published in 2007 it was shown that children whose parents smoke have a greater risk of developing MS, and this risk increased with higher exposure to passive smoking.[25] Another research showed that there was a significantly higher risk for the development of MS in children who had a clinically isolated syndrome, and who were exposed to passive smoking compared to those who were not.[26] Similar results related to young adulthood and exposure to risk factors (elevated BMI, cytomegalovirus infection, the level of vitamin D), and smoking as the most important risk factor for the appearance of the MS in that age were provided by other researchers.[27, 28, 29]

The results of our study showed that there was no statistically significant difference in the number of cigarettes smoked, nor in the duration of smoking. However, Iranian researchers in a study published in 2013 in a population of patients with MS established that the risk of MS was significantly higher in male smokers and in those who were taking of large amounts of cigarettes.[30] The same year, the results of another study showed the similar results as the above-mentioned one, with addition that this group of researchers found a statistically significant positive correlation between the number of cigarettes (more than ten) during the day, and the development of secondary progressive MS.[31]

In our study, we did not find correlation between the disease and smoking, nor the impact of smoking on the index of the disease progression. This can be explained by a certain specificity of our participants who were under regular medical control and without any significant influence of other comorbidity conditions. The high percentage of participants of the MS group (82.10%) were former smokers, in contrast to the control group where the percentage was 17.90%. The study of Hernan et al. showed that smokers with the relapsing-remitting (RR) form of MS are three times more likely to move to secondary progression than non-smokers, as only 20 of the 179 patients who had never smoked or were former smokers had a progressive course of the disease.[7] In the study of Sundstrom et al, out of 122 patients with newly diagnosed MS, 72% of

them were ex-smokers, and those who started smoking before the age of 15 developed the secondary form of the disease after an average of six years of follow up. Forty percent of ex-smokers who started smoking after the age of 15 years developed a secondary progression, and it happened with only 26% of non-smokers.[8]

Di Pauli and associates observed 129 patients with the clinically isolated syndrome (CIS) who were at high risk for the MS according to the MRI and cerebrospinal fluid analyses. After the period of three years, 75% of smokers developed MS, compared to 51% of non-smokers.[32]

In contrast to these results, Seine et al. examined 205 women with clinically definite MS from Portugal and noted that smoking had a protective effect on women with ApoE4 allele. Smokers had lower scores on the EDSS and MSSS scale.[33] Only one study, by Pittas et al, took into account the potential confounding effect of other habits of people with disease.[34]

In several studies, cigarette smoking is shown to be a factor associated with an increased level of gadolinium discolored lesions, and the volume of T2 hyperintense lesions on MRI, and brain atrophy. However, none of these studies had a control group of people without MS, which would give more informative results.[35, 36] Several other studies have shown a positive correlation between cigarette smoking and disease progression.[37] Manouchehrinia et al. analyzed data from 895 patients, where 49% were smokers at the time of onset of the disease and achieving the diagnosis. Their results showed that smoking was associated with increased severity of the disease and more rapid progression. In fact, the cessation of smoking before or after the diagnosis of the disease was associated with a slower progression.[38] Results from a study done in 2012 showed that cigarette smoking increased the risk of reaching the value of six on the EDSS, in relation to other factors that have been analyzed (coffee and alcohol drinking, consumption of fish).[39]

Despite the above data that unambiguously showed the impact of smoking on the onset and progression of MS, it has not yet been determined exactly what would be the mechanism responsible for these results. This refers to the biochemical processes related to smoking, genetic mechanisms and influence on the development of comorbidities, which could have an impact on MS.[10,38,40] Probably, there are more associated

CONCLUSION

Although it seems reasonable to restrict or refrain from smoking in patients with MS there was no significant evidence of smoking and disease progression correlation. The individuals with a history of MS in the family, should be advised about the impact of smoking in MS, and the importance of preventing their children's exposure to passive smoking.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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