Observational Record Study of Patients with Multiple Sclerosis Presenting to the Neurology Outpatient Clinic of Kocaeli University Faculty of Medicine Hospital

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Abstract

Objective: Multiple sclerosis (MS) is a chronic inflammatory, demyelinating, and neurodegenerative disease with complex etiological factors. Variability in the MS distribution has spurred numerous studies linking it to the environmental and genetic factors. This study aimed to evaluate the demographic, environmental, clinical, and radiological attributes of patients with MS in relation to established and emerging risk factors.

Materials and Methods: A cross-sectional assessment of 250 patients (out of 607 initially examined) was conducted from the Kocaeli University Faculty of Medicine Neurology Outpatient Clinic, noting their clinical and laboratory data. These data were subsequently acquired from hospital records. Statistical analyses included the use of the Kolmogorov-Smirnov test, Student's t-test, analysis of variance, Mann-Whitney U test, Kruskal-Wallis test, and Spearman's correlation analysis.

Results: The mean age of patients with MS was 40.31±11.6 years, with women constituting 70.7% of all patients. The main initial attack symptoms corresponded with the following lesion sites: supratentorial (38.7%), brainstem (32.4%), optic nerve (22.3%), and spinal region (6.7%). Lifestyle factors revealed that 55.6% of patients consumed salty foods and 48.4% smoked. Furthermore, a significant 68.8% of patients were found to have vitamin D (vitD) deficiency, with an average level of 16.3±8.41 ng/mL. A significant correlation was observed between vitD deficiency and increased disability (as measured by the expanded disability status scale) and lesion counts.

Conclusion: This study reinforces the association between vitD deficiency and the progression and severity of MS. The findings highlight the need for addressing modifiable risk factors such as vitD intake, smoking, and dietary habits for the management and prevention of MS.

Keywords: Multiple sclerosis, vitamin D deficiency, epidemiology, risk factors

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelination of the central nervous system and is the leading cause of morbidity in young adults. In addition to demyelination, the ensuing axonal degeneration is currently known as the primary cause of irreversible neurological disability in MS. In this regard, MS is described as an inflammatory, demyelinating, and neurodegenerative disease (1) and has a variable geographical distribution. Although MS is more common among Caucasians and those of European descent, it is less frequent among Asians and African-Americans. Its prevalence increases proportionally with distance from the equator, excluding the polar regions. This trend might be associated with vitamin D (vitD) deficiency. Some epidemiological studies have been conducted on communities migrating from countries with low MS prevalence to those with higher prevalence. If the age during migration is <15 years, the prevalence matches that of the adopted country. For those migrating after the age of 15 years, the prevalence aligns with their country of origin. This phenomenon is believed to be a result of complex interactions between environmental factors such as sunlight exposure, temperature and humidity changes, dietary habits, bacterial or viral infectious agents, and genetic factors (2). Despite that the etiology of MS remains unclear, the disease is believed to occur as a result of an autoimmune response in the central

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nervous system, triggered by environmental factors such as viral infections in genetically predisposed individuals. Besides these, studies targeting the etiology of MS have implicated factors, such as obesity, well-water consumption, keeping pets, trauma, accidents or surgeries, chemical agents, organic solvents, vaccinations, pregnancy, vitD deficiency, smoking, and climatic conditions (3). Among these, vitD deficiency, smoking, and adolescent obesity have been frequently discussed in recent years due to their preventable nature. This study aimed to record demographic, environmental, clinical, and radiological findings of patients with MS into a computerized database, facilitating comparisons with results from national and international centers. The data generated in this study are expected to provide significant contributions to both national and international epidemiological and clinical research.

By systematically examining the demographic, environmental, clinical, and radiological characteristics of patients with MS in the context of established and emerging risk factors, this study aimed to provide valuable insights that can inform preventive strategies, therapeutic interventions, and further investigations into the multifaceted nature of MS.

Materials and Methods

Study Groups

In this cross-sectional study, 250 patients aged ≥18 years, who were followed up at Kocaeli University Faculty of Medicine Neurology Outpatient Clinic for MS and within the MS spectrum, were included. This study has no exclusion criteria, and a total of 607 patients, 429 women and 178 men, were examined. Among the examined patients, 181 women and 69 men, totaling 250 patients, were included in the study. After recording the clinical and laboratory data of patients using a standard form, they were sourced from hospital records. The participants' age, gender, disease duration, expanded disability status scale (EDSS score), and radiological findings were recorded. The study was approved by the Ethics Committee of the Kocaeli University Faculty of Medicine (protocol no: 2014/264, date: 14.10.2014). The study participants were informed about the study, and an informed consent form was signed.

Statistical Analysis

Statistical evaluations were performed using the IBM SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). The data normality was assessed using the Kolmogorov-Smirnov test. Numeric variables displaying normal distribution were expressed as means ± standard deviations, non-normally distributed numeric variables were expressed as medians (25th-75th percentiles), and categorical variables were presented as frequencies (percentages). Between-group differences for numeric variables with normal distribution were determined by the Student's t-test and one-way analysis of variance, whereas numeric variables without normal distribution were evaluated using

the Mann-Whitney U test and Kruskal-Wallis test. For multiple comparisons, the Tukey and Dunn tests were employed. Relationships between numeric variables were assessed using the Spearman's correlation analysis, and relationships between categorical variables were evaluated with the chi-square test. A p-value of <0.05 was considered statistically significant.

Results

The average age of the general patient group examined was 40.31±11.6 years. The average ages of 429 female patients (70.7%) and 178 male patients (29.3%) were 40.68±11.6 and 39.40±11.6 years. Of the 250 patients studied, 181 were women (72.4%) and 69 were men (27.6%). The average ages of female and male patients were 38.20±10.74 and 37.93±10.67 years, respectively. The average age during the diagnosis for the included patients was 33±9.05 years: 33±9.77 and 32.55±10.15 years for female and male patients, respectively. No significant difference was observed between the two groups (p=0.650). The average disease duration for all patients was 6.40±5.61 years: 6.43±5.77 and 6.55±5.19 years for female and male patients, respectively. No significant difference was observed between the two groups (p=0.805).

The locations of the patients' lesions were grouped into two main categories. In 60 patients (23.7%), lesions were located at the juxtacortical and/or periventricular regions, whereas in 190 patients (76.3%), lesions were present in all of the juxtacortical, periventricular, and infratentorial regions. Then, 200 patients (79.9%) had T1 lesions, and 45 patients (17.7%) had lesions that captured contrast. In this group, cervical imaging could not be performed for 11 patients, making their data incomplete. The distribution of patient diagnoses according to MS clinical subtypes is shown in Figure 1.

Among the study participants, 139 (55.6%) reported consuming salty foods, whereas 121 (48.4%) smoked. The average vitD level among the participants was 16.3±8.41 ng/mL. Patients with vitD values of <20 ng/mL, considered deficient, which totaled 172 (68.8%). The average body mass index (BMI) of patients was 25.77±4.37 kg/m². Those with a BMI of 30 kg/m², thus classified
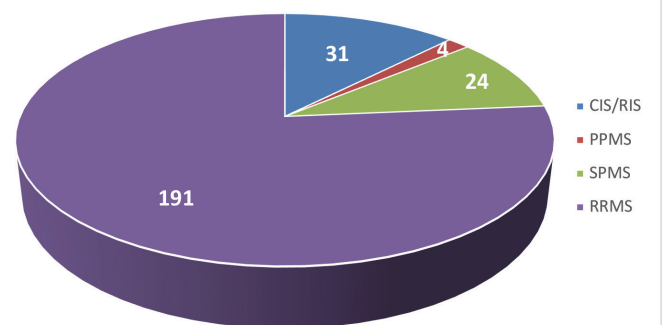

Figure 1. Percentage distribution and number of patients by multiple sclerosis clinical phenotypes

as obese, consisted of 32 (12.8%) years. The average EDSS score of patients was calculated to be 1.88. Further, 45 patients had an EDSS score of ≥4. The average relapse count was 3±2.52.

No significant correlation was identified between salt consumption and both regions were associated with the initial attack symptoms and the lesion location (p-values of 0.235 and 0.190, respectively). Similarly, no significant correlation was found for T1 lesion presence, contrast-enhancing lesion presence, T2 lesion count, cervical lesion count, gender, and MS clinical subtype (with p-values of 0.302, 0.138, 0.173, 0.862, 0.420, and 0.175, respectively). Significant correlations were observed between smoking and both gender and salt consumption (p<0.001 and p=0.006, respectively). About 37.6% and 76.8% of female and male patients smoked (p<0.001). The vitD average for the entire patient group was 16.38±8.41 ng/mL. Compared to the 172 individuals with vitD levels of lower than the cutoff value of 20 ng/mL, 78 individuals exceeded this level. In the correlation analysis between vitD and parametric values, a negative correlation with EDSS (p<0.001) and a positive correlation with BMI (p=0.038) were observed. No correlation was identified with the number of relapses (p=0.066). Correlations were found between the T2 lesion count, cervical lesion count, and vitD values (p=0.006 and p=0.027, respectively). Comparing groups with EDSS scores of ≤4 and ≥4, significant differences in vitD values were found between the two groups (p=0.001). As the T2 lesion count increased, so did the number of patients with vitD levels of <20. Similarly, as the cervical lesion count increased, more patients had vitD levels of <20. The average BMI of the patient group was 25.77±8.30 kg/m². In contrast to the 218 individuals with BMIs of lower than the cutoff value of 30 kg/m², 32 individuals exceeded this level. In the correlation analysis with nonparametric variables, no correlation was identified between BMI and other variables.

Significant differences were observed in the cervical lesion count and MS clinical subtype between groups with vitD levels of <20 and >20 (p<0.001 for both). About 88.9% of those with an EDSS score of >4 had vitD levels of <20 ng/mL, compared to 64.4% of those with EDSS scores of <4.

Discussion

In our study, the demographic, radiological, and laboratory data of 250 patients were followed up in our clinic with environmental factors. The supratentorial region was the most common area involved causing the first attack symptom in patients with MS. Although no significant correlation was found between the lesion site and EDSS, a significant relationship was observed between the number of relapses and EDSS. Moreover, as the number of lesions and their location increased, EDSS also increased.

The most prominent among environmental factors was the negative correlation between patients' vitD levels and EDSS.

No statistically significant relationships were found between environmental factors, such as smoking, salt, and BMI, and EDSS. Although our study identified a relationship between the vitD and disease, a relationship with other environmental factors was not found. In our study, the female-to-male ratio was slightly above expectations. A study conducted throughout Europe found a higher ratio in Italy and Greece than in other countries, suggesting that the female-to-male ratio might be higher in the Mediterranean geography. Moreover, autoimmune diseases are known to be more common in women, and autoimmunity is influenced by genetic and environmental factors. The geography of a country may contribute to this process. Due to the abundance of industrial establishments in the Marmara region where our city is located, environmental factors might play a decisive role in triggering autoimmunity (4).

MS is a chronic disease affecting young adults. It is most commonly seen between ages of 20-40 years. Bencsik et al. (5), have shown that the average age of onset is 28 years. Piperidou et al. (6), found the average age of onset in women to be 27.2 and 30.4 in men. McDonnell and Hawkins (7) have shown the average age of onset for MS to be 31.6 years. In this study, the average age of onset was determined as 33.05 in both sexes: 32.55 in men and 33.23 in women. No significant difference was found between the average ages of onset in patients of both genders (p=0.650). The average ages were also within the expected range.

In our study, the supratentorial region was the most common area causing the initial attack symptom. Patients with involvement in this region mostly presented symptoms, such as weakness, numbness in a part of the body, walking disorder, and lateralizing signs. In a study conducted by Kantarci et al. (8), in 1998, the initial symptoms of patients with MS were sensory in 30.7% of patients, motor in 28.6%, brainstem and cerebellar in 21%, visual disorders in 14.4%, and sphincter disorders in 5.1%. In another study conducted by Yüceyar et al. (9), with 122 patients, sensory symptoms were the most common initial attack symptom in 46%, with 99 patients having monoregional and 22 having polyregional symptoms. In a study by Houzen et al. (10), 48.1% of patients presented with sensory findings, 40.7% with motor findings, and 18.5% with visual impairment. In a study conducted by Tola et al. (11), in Spain, 55% started with sensory symptoms, 49% with pyramidal signs, 31% with brainstem symptoms, 24% with cerebellar symptoms, and 14% with optic neuritis. Our study's findings were consistent with those of the literature. Smoking status was the only parameter in our study that was correlated with salt. Smokers consumed more salt. Out of 25 people who smoked and had an EDSS score of ≥4, 20 preferred salty foods. Although it did not seem statistically significant (p=0.070), a significant arithmetic difference was observed. The primary reason for the statistical insignificance was thought to be the inadequacy of the sample. In a study with

an adequate sample size, we anticipate that the combination of smoking and salt might have a cumulative effect on the EDSS. Both animal and human models demonstrated that high salt intake induces Th17 lymphocytes (12). Th17 lymphocytes have been reported to expose that the high salt intake are associated with proinflammatory cytokines and show high pathogenicity (13). Farez et al. (14) examined 70 RR patients with MS for 2 years; they found that the risk of attack in those with moderate-high salt intake was increased 2.75 times and the risk of new lesion development by 3.4 times compared to those who did not consume as much salt.

Smoking was correlated with the salt intake and, additionally, with gender. As expected, men smoked more than women. In a study conducted by Hernán et al. (15) with 201 patients with MS and 1903 healthy controls, smoking was reported as a risk factor for the development of new MS and for patients with existing RR MS forms to transition to the SP MS form. In a meta-analysis by Hawkes (16) data from six studies were reviewed, showing that the risk of MS increased in those who smoked before the disease. In a study conducted in Norway by Riise et al. (17), MS developed over time in 87 out of 22,312 individuals, and smoking was identified as a risk factor for MS development in this group. Handel et al. (18), emphasized that smoking causes deterioration in patients with MS; however, the cause of progression could not be definitively shown and needed further studies for confirmation. In our study, no statistically significant relationship was observed between smokers and patients with the disease. We had defined smoking status as either currently smoking or those who had smoked in the past and quit. Nonsmoking status was defined as having never smoked. The lack of statistical significance could be due to this categorization, or it could be considered that there were not enough patients with adequate distribution for this parameter. In our study, vitD was evaluated in two different ways. First, parametrically without grouping patients, and later non-parametrically by setting the deficiency limit of 20 ng/mL as the cut-off and evaluating patients in two groups: >20 and <20 ng/mL the cutoff vitD values. A negative correlation with EDSS was observed in both categorical and noncategorical evaluations. In the non-categorical evaluation, in addition to the EDSS, a positive correlation with BMI was observed, while in the categorical evaluation, a correlation with T2 and number of cervical lesion was observed. In a long-term study conducted on 7 million military personnel in the United States, a negative relationship was found between active vitD levels and the risk of MS (19). In a retrospective study conducted in Italy, among patients with the first clinical signs suggestive of MS, those with low vitD levels were found to have a higher risk of developing clinical MS (20). Another study conducted in the United States reported that nurses who received a daily 400 IU vitD supplement had a 40% lower risk of developing MS compared to those who did not (21). A study conducted in Sweden with 192 patients and 92 healthy controls revealed that high vitD levels were reported to reduce the risk of developing MS (22). In a prospective study conducted by Simpson et al. (23), with 145 patients with RR MS between 2002 and 2005, high vitD levels were reported to reduce relapse frequency. Parallel to other studies, our study also found that the vitD level showed a negative correlation with EDSS. Although seasonal differences and whether or not a vitamin supplement was taken were overlooked, such a correlation strengthens the vitD-EDSS relationship. The fact that those with a higher number of T2 and cervical lesions had lower vitD levels once again reveals that having a low vitD level contributes to the disease progression.

Study Limitations

The study's sample size may have limited the ability to detect statistically significant relationships between certain environmental factors and EDSS scores in patients with MS. This study does not address the potential prognostic markers and their impact on long-term outcomes of patients with MS.

Conclusion

In conclusion, this study presents significant findings that help us better understand the course of MD and the factors affecting it. It reveals that the supratentorial region plays a critical role at the disease onset, that there is a clear relationship between the number of relapses and EDSS scores, and particularly that vitD levels are a potential factors in the course of MS. However, the potential effects of other environmental factors on MS have not yet been clarified. This indicates the need for more detailed research in the future to better understand the role of these factors. Additionally, this study has laid a valuable foundation for future research on the pathophysiology and treatment of MS. Based on this study, future research projects should consider further investigation of the impact of various environmental factors including, but not limited to, diet, physical activity, and specific geographic locations on the progression and management of MS.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of the Kocaeli University Faculty of Medicine (protocol no: 2014/264, date: 14.10.2014).

Informed Consent: The study participants were informed about the study, and an informed consent form was signed.

Authorship Contributions

Surgical and Medical Practices: S.D.B., Concept: S.D.B., H.E., Design: S.D.B., H.E., Data Collection or Processing: S.D.B., Analysis or Interpretation: S.D.B., Literature Search: S.D.B., H.E., Writing: S.D.B

Conflict of Interest: No conflict of interest was declared by the authors.

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