Turkish Journal of Neurology

Turk J Neurol 2025;31(2):118-127
Doi: 10.55697/tnd.2025.211

ORIGINAL ARTICLE

The effect of demographic features and environmental risk factors on the clinical course in patients with multiple sclerosis

İrem İlgezdi Kaya[1], Bedile İrem Tiftikçioğlu[2], Yaşar Zorlu[3], Levent Öcek[4], Ufuk Şener[4], Figen Tokuçoğlu[5]

[1]Department of Neurology, Gaziantep Dr. Ersin Arslan Training and Research Hospital, Gaziantep, Türkiye
[2]Department of Neurology, İzmir Bakırçay University Faculty of Medicine, İzmir, Türkiye
[3]Department of Neurology, Retired Education Supervisor, İzmir Tepecik Training and Research Hospital, İzmir, Türkiye
[4]Department of Neurology, University of Health Sciences, İzmir Tepecik Training and Research Hospital, İzmir, Türkiye
[5]Department of Neurology, Balıkesir University Faculty of Medicine, Balıkesir, Türkiye

ABSTRACT

Objectives: This study aimed to investigate demographic, clinical, and environmental risk factors in patients with multiple sclerosis (MS) and their relationship with the disease.

Patients and methods: The medical records of 913 patients with MS followed for ≥6 months between January 1996 and December 2015 were retrospectively reviewed, and 221 patients (158 females, 63 males; mean age: 43.4±11.6 years; range, 18 to 73 years) with demographic, clinical, and laboratory data were included.

Results: Relapsing-remitting MS was identified in 75.6% (n=167) of patients, and progressive MS was identified in 24.4% (n=54). The initial Expanded Disability Status Scale (EDSS) scores were lower in the relapsing-remitting MS group compared to the progressive MS group (2.3±1.0 *vs.* 2.6±1.4; p<0.05). Motor symptoms were the initial presenting symptoms in 33.0% of the patients, followed by sensory symptoms and optic neuritis. The transition to the progressive phase was observed to occur at a younger age in patients with an earlier onset age (p<0.001). Motor symptom onset correlated with later disease onset, progression, and higher final EDSS score (p<0.05). Vitamin D deficiency and insufficiency were observed in 18.1% and 73.5% of patients, respectively. Seropositivity for Epstein-Barr virus (EBV) antibodies was high. Vitamin D levels and EBV serology were similar between the groups.

Conclusion: In our patient group, early disease onset correlated with earlier transition to progression phase. Onset with motor symptom correlated with progression and higher disability scores. Vitamin D deficiency and high EBV seropositivity were common but not directly linked to clinical course. These findings potentially reflect MS patient profiles, warranting further epidemiological studies.

Keywords: Disease course, environmental factors, epidemiology, multiple sclerosis, progression.

Multiple sclerosis (MS) is a neurodegenerative and immune-mediated demyelinating disease of the central nervous system.[1] Despite numerous studies conducted to date, its exact cause has not yet been determined.[1-3] Studies have shown that genetic predisposition, geographical location, altitude, environmental factors, exposure to toxic substances, population changes due to migration, race and ethnicity, dietary habits, obesity, serum vitamin D and sex hormone levels, stress, smoking, viral infections such as Epstein-Barr virus (EBV), and bacterial infections such as Mycoplasma pneumoniae, all play a role in influencing the disease. These factors are believed to not only

Correspondence: İrem İlgezdi Kaya, MD. Giresun Üniversitesi Giresun Eğitim ve Araştırma Hastanesi, Nöroloji Kliniği, 28100 Giresun, Türkiye.
E-mail: iremilgezdi@yahoo.com
Received: May 14, 2024 **Accepted:** February 26, 2025 **Published online:** April 17, 2025
Cite this article as: İlgezdi Kaya İ, İrem Tiftikçioğlu B, Zorlu Y, Öcek L, Şener U, Tokuçoğlu F. The effect of demographic features and environmental risk factors on the clinical course in patients with multiple sclerosis. Turk J Neurol 2025;31(2):118-127. doi: 10.55697/tnd.2025.211.

contribute to susceptibility to the disease but also play a role, individually or in combination, in the course of the disease.[1-3]

It is a well-known fact that factors believed to play a role in the etiopathogenesis of MS vary not only among countries but even within regions of the same country. With the increasing number of studies investigating risk factors, it is anticipated that country-specific data will become more pronounced.[4-8] Based on this assumption, we aimed to examine the demographic and environmental factors that may predispose individuals to the disease and their relationship with the clinical course of the disease.

PATIENTS AND METHODS

The medical records of 913 patients who were regularly followed at the İzmir Tepecik Research and Training Hospital, Department of Neurology were retrospectively reviewed between January 1996 and December 2015. Among these patients, 221 (158 females, 63 males; mean age: 43.4±11.6 years; range, 18 to 73 years) who met the following criteria were included in the study: a diagnosis of definite MS according to the revised 2010 McDonald criteria, and availability of complete demographic, clinical, and laboratory data for analysis.[9] Patients with other central nervous system demyelinating diseases or endocrinological diseases that could affect vitamin D levels or potentially lead to obesity were excluded from the study. Patients were classified as having either relapsing-remitting MS (RRMS) or progressive MS (PMS) based on clinical and magnetic resonance imaging (MRI) findings, as well as biological markers recorded during follow-up.[10] Written informed consent was obtained from all participants. The study protocol was approved by the İzmir Tepecik Training and Research Hospital Ethics Committee (Date: 30.06.2015, No: 4). The study was conducted in accordance with the Declaration of Helsinki.

The demographic data such as patients' age, sex, and body mass index (BMI), calculated based on height and weight, were recorded. Information regarding smoking status, family history of autoimmune diseases, age at MS onset, type of initial attack, interval between the initial two attacks, duration of follow-up, initial and final Expanded Disability Status Scale (EDSS) scores, duration of transition to the progressive phase if applicable, serum 25-hydroxyvitamin D (25[OH]D) levels, and EBV serology (anti-viral capsid antigen [VCA] immunoglobulin (Ig)M, anti-VCA IgG, anti-Epstein-Barr nuclear antigen [EBNA] IgG, anti-early antigen [EA] IgG) were recorded. Patients with a history of smoking prior to the diagnosis of MS were included in the smoking group. Family history of autoimmune diseases in first- and second-degree relatives was also assessed.

Patients were grouped into motor, sensory, optic, brainstem, and cerebellar attack types based on the symptoms of first attack, neurological examination, and MRI data. Patients presenting only with Lhermitte's sign at the initial attack were included in the spinal onset group. Neurological functions of patients were assessed using the EDSS. To make disease activity more apparent, patients were evaluated in two groups based on EDSS scores: those with scores <3 and those with scores ≥3.

Serum vitamin D levels had been previously measured between March and April. Serum vitamin D levels were measured using the Cobas 411 analyzer (Roche Diagnostics International Ltd., Rotkreuz. Switzerland) by electrochemiluminescence immunoassay. Vitamin D levels were categorized as <20 ng/mL (deficiency), 20-29 ng/mL (insufficiency), and ≥30 ng/mL (normal). Serum EBV VCA-IgM, VCA-IgG, anti-EBNA, and anti-EA antibody levels were analyzed using the enzyme-linked fluorescence assay (ELFA) method with the Vidas EBV panel and miniVidas device (BioMérieux, Craponne, France). Results were interpreted as seropositive or seronegative based on kit intervals.

Statistical analysis

Statistical analyses were performed using IBM SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Data were expressed as mean ± standard deviation or frequency (n) and percentage (%), as appropriate. Between-group comparisons were made using Student's t-test or the chi-square test, where appropriate. One-way analysis of variance and Tukey's post hoc analysis were applied for multiple group comparisons. For the multivariate analysis, confounding factors identified in univariate analyses were further entered into the logistic regression analysis using the backward stepwise (conditional) method to determine independent predictors of transition to progressive disease state. The Hosmer-Lemeshow goodness-of-fit statistics were used to assess model fit. A significance level of <0.05 was considered statistically significant.

RESULTS

Among the patients, 167 (75.6%) were classified as having RRMS, and 54 (24.4%) were classified as having PMS. The mean age at disease onset for the entire group was 30.8±9.7 years (range: 15 to 62 years). There was no significant difference in age at disease onset between sexes. Patients in the RRMS group were younger both at the time this study was conducted and at disease onset compared to the patients in the PMS group (p<0.001 and p=0.004, respectively). Out of the 54 patients with progressive disease, 37 (68.5%) were female. The mean age at transition to the progressive phase was 41.0±9.4 years (range, 28 to 57 years). The age at transition to progressive phase was not statistically significantly different between females (39.6±9.1 years) and males (44.1±9.8 years; p=0.125). The mean disease duration for all patients was 13.7±8.5 years, and the mean follow-up duration was 7.6±6.2 years (range, 1.7 to 21.6 years). Both the initial and final EDSS scores were significantly lower in the RRMS group compared to the PMS group (p=0.032 and p<0.001, respectively). The interval between the first two attacks was shorter in the RRMS group (2.7±3.6 years) compared to the PMS group (3.3±3.0), but the difference was not statistically significant. There were no significant differences in laboratory findings between the groups. Detailed data are presented in Table 1. The same data were also evaluated considering patient sex. No difference was observed between sexes in the RRMS group. However, in the PMS group, age at disease onset (p=0.033) and BMI (p=0.019) were significantly higher in male patients, while disease duration (p=0.033) and duration of transition to the progressive phase (p=0.003) were significantly higher in female patients (Table 2).

The most common symptoms observed during the initial attack were motor symptoms (n=73; 33%), followed by sensory (n=55; 24.9%) and optic involvement (n=38; 17.2%). Twenty-nine (13.1%)

TABLE 1
Distribution of demographic, disease-related, and laboratory findings according to MS clinical types

	RRMS group (n=167)			PMS group (n=54)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			41.1±11.5			50.4±9.2	**<0.001**
Sex							
Female	121	72.5		37	68.5		0.347
Body mass index (kg/m^2)			24.2±4.4			24.7±4.0	0.429
Smoking	29	17.4		9	16.7		0.545
Concomitant autoimmune disease	11	6.6		4	7.4		0.522
Concomitant autoimmune disease 1st degree relatives	16	9.6		2	3.7		0.136
Concomitant autoimmune disease 2nd degree relatives	9	5.4		1	1.9		0.251
Age at disease onset (year)			29.6±9.5			34.9±9.4	**0.004**
Disease duration (year)			12.7±8.7			16.5±7.2	**0.005**
Follow-up duration (year)			7.1±6.1			8.9±6.6	0.077
Duration between the first two attacks (year)			2.7±3.6			3.3±3.0	0.329
Initial EDSS			2.3±1.0			2.6±1.4	**0.032**
Latest EDSS			2.1±1.1			5.1±2.0	**<0.001**
Age at progression (year)			N/A			41.0±9.4	N/A
Duration to progression (year)			N/A			6.8±6.8	N/A
Vitamin D (ng/mL)			13.8±10.9			19.5±22.3	0.075
Deficiency							
Insufficiency							
Normal							
Anti EBNA IgG titer			6.7±2.8			6.3±3.3	0.389

MS: Multiple sclerosis; RRMS: Relapsing-remitting multiple sclerosis; PMS: Progressive multiple sclerosis; SD: Standard deviation; EDSS: Expanded disability status scale; EBNA: Epstein-Barr virüs nuclear antigen; IgG: Immunglobulin G; N/A: Not available.

TABLE 2
Demographic, disease, and laboratory findings according to MS disease type and sex

	RRMS group (n=167)							PMS group (n=54)						
	Female (n=121)			Male (n=46)				Female (n=37)			Male (n=17)			
	n	%	Mean±SD	n	%	Mean±SD	*p*	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			41.5±11.1			40.2±12.6	0.510			49.2±9.4			52.9±8.2	0.171
Body mass index (kg/m^2)			24.3±4.7			23.9±3.8	0.643			23.9±3.9			26.6±3.7	**0.019**
Smoking	22	18.2		7	15.2		0.420	5	13.5		4	23.5		0.293
Concomitant autoimmune disease	8	6.6		3	6.5		0.644	4	10.8		0	0		0.209
Concomitant autoimmune disease 1st degree relatives	12	9.9		4	8.7		0.536	2	5.4		0	0		0.465
Concomitant autoimmune disease 2nd degree relatives	7	5.8		2	4.3		0.528	1	2.7		0	0		0.685
Age at disease onset (year)			30.1±9.3			28.1±9.8	0.649			32.3±8.1			40.5±9.8	**0.033**
Disease duration (year)			12.5±9.0			13.2±7.8	0.653			17.9±7.3			13.4±6.2	**0.033**
Follow-up duration (year)			7.0±6.1			7.5±6.2	0.618			9.4±6.5			7.7±6.8	0.377
Duration between the first two attacks (year)			2.9±3.7			2.3±3.3	0.360			3.3±3.1			3.5±2.9	0.877
Initial EDSS			2.3±1.0			2.1±1.0	0.093			2.6±1.1			2.8±2.0	0.593
Latest EDSS			2.1±1.1			2.2±1.1	0.471			5.0±2.1			5.3±2.0	0.577
Age at progression (year)			N/A			N/A				39.6±9.1			44.1±9.8	0.124
Duration to progression (year)			N/A			N/A				8.2±7.4			3.5±3.2	**0.003**
Vitamin D (ng/mL)			13.3±11.1			15.0±10.3				22.2±25.8			13.4±8.4	
Deficiency			8.8±4.8			9.6±4.0	0.375			10.6±5.3			8.5±4.6	0.191
Insufficiency			23.5±2.7			23.3±3.2				24.1±3.0			24.2±1.0	
Normal			41.3±13.4			46.6±17.6				601±40.9			N/A	
Anti EBNA IgG +			6.5±3.0			7.5±2.2				6.3±3.2			6.4±3.5	
Positive			6.6±2.8			7.5±2.2	0.050			6.3±3.2			6.9±3.1	0.853
Negative			0.1±0.1			N/A				N/A			0.1*	

MS: Multiple sclerosis; RRMS: Relapsing-remitting multiple sclerosis; PMS: Progressive multiple sclerosis; SD: Standard deviation; EDSS: Expanded disability status scale; EBNA: Epstein-Barr virüs nuclear antigen; IgG: Immunglobulin G; N/A: Not available; * SD is not available due to the number of patients (n=1).

TABLE 3
Clinical characteristics according to disease course in patients with EDSS scores <3 and ≥3, expressed as mean±SD

	EDSS <3 (n=140)													
	RRMS (n=133)							PMS (n=7)						
	Female (n=98)		Male (n=35)		Female *vs.* Male	Total (n=133)		Female (n=6)		Male (n=1)		Female *vs.* Male	Total (n=7)		RRMS *vs.* PMS
	Mean±SD	Min-Max	Mean±SD	Min-Max	*p*	Mean±SD	Min-Max	Mean±SD	Min-Max	Mean±SD	Min-Max	*p*	Mean±SD	Min-Max	*p*
Age	40.0±10.3	19.0-64.0	39.2±12.9	18.0-65.0	0.586	39.8±11.0	18.0-65.0	41.2±9.8	33.0-59.0	40.0*	N/A	0.857	41.0±0.9	33.0-59.0	0.763
Initial EDSS	2.3±1.0	1.0-6.5	2.0±0.8	1.0-4.0	0.094	2.2±0.9	1.0-6.5	2.5±2.0	1.0-6.5	8.5*	N/A	0.286	3.4±2.9	1.0-7.0	0.777
Latest EDSS	1.7±0.6	0.0-2.5	1.7±0.6	0.0-2.5	0.952	1.7±0.6	0.0-2.5	2.3±0.3	2.0-2.5	2.0*	N/A	0.571	2.2±0.3	2.0-2.5	**0.010**
Disease duration (year)	11.3±8.2	2.0-36.0	12.5±7.5	2.0-29.0	0.283	11.6±8.0	2.0-36.0	9.8±4.3	5.0-16.0	13.0*	N/A	0.571	10.3±4.1	5.0-16.0	0.992
Duration to progression (year)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3.6±4.6	0-11.0	2.0*	N/A	1.000	3.3±4.2	0-11.0	N/A

	EDSS ≥3 (n=81)													
	RRMS (n=34)							PMS (n=47)						
	Female (n=23)		Male (n=11)		Female *vs.* Male	Total (n=34)		Female (n=31)		Male (n=16)		Female *vs.* Male	Total (n=47)		RRMS *vs.* PMS
	Mean±SD	Min-Max	Mean±SD	Min-Max	*p*	Mean±SD	Min-Max	Mean±SD	Min-Max	Mean±SD	Min-Max	*p*	Mean±SD	Min-Max	*p*
Age	47.7±12.1	28.0-73.0	43.3±11.7	18.0-59.0	0.561	46.2±12.0	18.0-73.0	50.7±8.7	28.0-64.0	53.7±7.7	39.0-65.0	0.369	51.7±8.4	28.0-65.0	**0.017**
Initial EDSS	2.5±0.9	1.0-4.0	2.3±1.6	1.0-6.0	0.243	2.4±1.2	1.0-6.0	2.6±0.8	1.0-4.0	2.4±1.4	1.0-7.0	0.231	2.5±1.1	1.0-7.0	0.404
Latest EDSS	3.8±0.8	3.0-6.5	3.9±0.8	3.0-6.0	0.383	3.8±0.8	3.0-6.5	5.5±1.8	3.0-9.0	5.5±1.9	3.0-8.5	1.000	5.5±1.8	3.0-9.0	**<0.001**
Disease duration (year)	17.8±10.7	4.0-53.0	15.6±8.7	2.0-29.0	0.717	17.1±10.0	2.0-53.0	19.5±6.7	9.0-37.0	13.4±6.4	2.0-25.0	**0.009**	17.4±7.2	2.0-37.0	0.748
Duration to progression (year)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	9.0±7.6	0-30.0	3.6±3.3	0-10.0	**0.020**	7.3±7.0	0-30.0	N/A
Duration to EDSS 3 (year)	13.5±9.1	0-37.0	11.1±8.6	0-27.0	0.424	12.7±8.9	0-37.0	12.5±8.2	0-36.0	6.3±5.7	1.0-24.0	**0.006**	10.4±8.0	0-36.0	0.199

EDSS: Expanded Disability Status Scale; SD: Standard deviation; RRMS: Relapsing-remitting multiple sclerosis; PMS: Progressive multiple sclerosis; N/A: Not available; * SD is not available due to the number of patients (n=1).

patients presented with brainstem symptoms, 17 (7.7%) with cerebellar symptoms, two with spinal symptoms, and two with mental symptoms. The disease began with involvement of more than one system in five (2.2%) patients. The age at disease onset was significantly higher in patients with motor symptoms at onset compared to those with other initial symptoms ($p<0.05$). Positive correlations were also found between onset with motor symptoms and transition to the progressive phase ($p<0.001$) and higher EDSS scores ($p<0.05$). There were no significant differences between patient groups when considering initial attack symptoms and sex. When patients were divided into 10-year age groups based on age at disease onset, a significant decrease in the duration of transition to the progressive phase was observed with increasing age at disease onset ($p<0.001$). In patient groups with EDSS scores <3 and ≥3, no difference in EDSS scores between sexes was observed in the RRMS group, while in the PMS group, disease duration and duration of transition to the progressive phase were longer in female patients compared to males ($p=0.009$ and $p=0.020$, respectively). As expected, the final EDSS scores were higher in the PMS group compared to the RRMS group (Table 3).

The number of smoking patients was significantly low. Body mass index, calculated considering patients' heights and weights, was evaluated among different groups and by sex, with no significant differences observed. The overall mean BMI was 24.3±4.3 (range: 16.1-40.6). The mean BMI was 24.2±4.5 for females and 24.7±4.0 for males. Patients with earlier disease onset had lower BMI ($p<0.001$) and were younger ($p<0.001$), and they progressed to the progressive phase later. When patients were evaluated in 10-year age groups, BMI was found to significantly increase with age ($p<0.001$). Considering the higher prevalence of obesity in older age in Türkiye, data between the ages of 10 and 20 were emphasized. The relationship between BMI and EDSS, considering the potential effect of BMI on EDSS, was examined, but no correlation was found between BMI and EDSS ($p>0.05$).

Serum vitamin D levels were deficient in 158 (71.5%) patients, insufficient in 39 (17.6%) patients, and within normal limits in 24 (10.9%) patients. When MS groups were examined separately, the mean vitamin D levels were deficient in both groups. There were no significant differences in vitamin D levels between sexes in the groups. Patients who did not describe symptoms of EBV infection had high seropositivity for EBV antibodies, including anti-VCA IgG, anti-EA IgG, and anti-EBNA IgG (mean anti-EBNA IgG: 6.6±3.0 U/mL). There was no difference in anti-EBNA IgG titers between groups. There was no relationship between the elevation of EDSS scores, used as a clinical activity criterion, and anti-EBNA IgG titers. When environmental factors were evaluated in groups created based on EDSS score, there was no difference in smoking history, vitamin D levels, and anti-EBNA antibody titers between the groups with high and low EDSS scores, while a significant but weak correlation was observed between the disease onset age and a high final EDSS score (indicating future high disability; $p=0.015$, $r=0.164$).

Considering birth month and season, the highest birth rate was observed in March and August (n=28, 12.7%, each), while the lowest was in November (n=9, 4.1%). Spring and summer were the seasons with the highest number of births, each with 64 (29.0%) patients, while autumn had the lowest birth rate (15.7%).

Fifteen (6.8%) patients had a concomitant autoimmune disease. Hashimoto's thyroiditis was the most common (2.7%), followed by Graves' disease (1.8%). Psoriasis, rheumatoid arthritis, celiac disease, and ulcerative colitis were recorded as other concomitant autoimmune diseases. The presence of autoimmune diseases was observed in first-degree relatives of 18 (8.1%) patients and in second-degree relatives of 10 (4.5%) patients.

The significant confounding factors found in univariate analyses, including age at disease onset, disease duration, and initial EDSS, and other well-known factors, such as vitamin D

TABLE 4
Predictors of transition to the progressive disease state

	OR	95% CI	*p*
Age at disease onset	0.914	0.876-0.954	**<0.001**
Disease duration	0.921	0.877-0.966	**0.001**
Initial EDSS	0.831	0.586-1.178	0.298
Vitamin D			
Deficiency	0.758	0.305-1.883	0.551
Insufficiency	0.302	0.87-1.046	0.059
Smoking	0.565	0.208-1.532	0.262
Anti EBNA seropositivity	1.232	0.110-13.753	0.865

OR: Odds ratio; CI: Confidence interval; EDSS: Expanded Disability Status Scale; EBNA: Epstein-Barr virus nuclear antigen.

deficiency and insufficiency, tobacco usage, and EBNA seropositivity, were further analyzed with multivariate analysis to determine independent predictive factors for progression. Logistic regression analysis revealed that the age at disease onset and the disease duration were significant predictors of transition to the progressive disease course, independent from initial EDSS scores, vitamin D levels, tobacco usage, and seropositivity of EBNA (Table 4). The Hosmer-Lemeshow goodness-of-fit test yielded a significance value of 0.314, indicating a high predictive value.

DISCUSSION

Multiple sclerosis is a chronic inflammatory demyelinating disease of autoimmune origin characterized by neuroinflammation and neurodegeneration of the central nervous system. It is frequently observed in young adults. The role of genetic and environmental factors in the onset and course of the disease was emphasized in numerous studies.[1-3]

As with many autoimmune inflammatory diseases, MS also shows a predominance in females. According to the 2020 MS Atlas, the estimated female-to-male ratio of MS worldwide is approximately 2, a ratio that was also identified in Türkiye.[11] In our study group, the female-to-male ratio was 2.5 overall and 2.6 in the RRMS group, which is consistent with the literature.

The significant predictors of transition to the progressive disease course were determined to be disease duration and age at disease onset. Remyelination is often observed in the early stages of MS and in younger individuals, but its capacity decreases significantly in time as the disease duration extends towards the progressive phase.[2] In the literature, the average age of onset of MS was reported to be around 20 to 35 years for RRMS and approximately 40 years for primary progressive MS.[2] The average age of disease onset and its distribution according to MS groups in our study were consistent with this study.

In recent years, obesity, particularly during childhood and adolescence, was emphasized as an important risk factor for MS, independent of other factors.[3] Obesity was proposed to trigger low-grade chronic inflammation by stimulating the release of proinflammatory cytokines, such as IL-6, TNF-α, and C-reactive protein, and by attracting immune cells into adipose tissue.[4] Oliveira et al.[12] demonstrated a linear relationship between EDSS scores and BMI in their study investigating disability and insulin resistance in MS patients. However, a similar relationship was not observed in our study group. Epidemiological studies conducted in our country reported a high obesity rate compared to European countries and a similar obesity rate to the USA. A report indicated that the prevalence of obesity in Türkiye doubled between 1990 and 2010 and was estimated to range between 34.4% and 36.0%.[13] Our inability to demonstrate the relationship between obesity and increased disability may be due to the widespread prevalence of obesity in Türkiye.

In a study investigating the relationship between birth month and the risk of MS, it was found that the birth rate of patients with MS was higher in spring months, particularly in those born in March, April, and May, compared to autumn months and summer months. However, it was observed that patients with MS had the lowest birth rate in November.[14] Our study results were also consistent with these findings in the literature.

It is widely accepted that smokers have an increased risk of developing MS compared to nonsmokers. Smoking increases the risk of MS by approximately 1.6-fold.[6] Additionally, it was suggested that smoking triggers the conversion from clinically isolated syndrome (CIS) to MS and the transition from a relapsing course to secondary progressive phase.[3] Healy et al.[15] examined the effect of smoking on disease progression in patients with MS using clinical and MRI characteristics. They observed that patients who were smokers had significantly worse EDSS scores, MS severity score, and brain parenchymal fraction compared to those who never smoked. Another result obtained from that study was that smokers were more prone to progression, and RRMS converted to the progressive phase in a shorter time in these patient. Furthermore, a significant difference was observed in MRI, showing an increase in lesion volume and a decrease in brain parenchymal fraction compared to nonsmokers in T2-weighted images. However, in a study by Koch et al.[16] in 2007, the possible effects of smoking on the transition to progressive phase and the clinical disability (evaluated with EDSS scores) could not be demonstrated. Similarly, in our patient group, there was no correlation between smoking history and EDSS scores, a marker of disability, which may be related to the overall low smoking rate in the group or due to small sample size.

The clinical presentation of MS is heterogeneous, and it varies depending on the location of lesions in the brain or spinal cord. It is known that the most common initial symptoms of MS are sensory, motor symptoms, and visual loss.[2] There are numerous studies investigating the initial presentation of MS symptoms in the literature. An analysis conducted on 14,969 patients from the MSBase cohort reported the distribution of clinical features as follows: sensory, 46%; visual, 27%; pyramidal, 22%; brainstem, 20%; cerebellar, 7%; sphincteric, 3%; and cognitive, 1.4%.[17] Similarly, in an epidemiological study conducted in the Central Black Sea region, the most common initial symptoms were reported as motor (34.5%), sensory (31.9%), and optic neuritis (25.8%).[18] Although there may be minor variations in the ranking of initial symptoms in studies from different countries, motor, sensory, and optic symptoms consistently rank in the top three, which is consistent with our findings.

Approximately 85% of MS patients begin with an acute attack affecting one or more areas, referred to as CIS.[2] Conversion rates to MS vary depending on demographic and clinical characteristics (up to 85% after optic neuritis, up to 61% after transverse myelitis, and up to 60% after brainstem syndromes). However, it was noted that these rates are similar to each other.[19] In various studies conducted over the past decade, patients with oligoclonal band positivity in the cerebrospinal fluid, a high number of T2 lesions, or subclinical evoked potential anomalies were reported to have a higher conversion rate from CIS to clinically definite MS. Accordingly, with the 2023 update to the MS diagnostic criteria, patients with oligoclonal band positivity at the time of the first clinical attack who meet the dissemination in space criterion are now considered to fulfill the dissemination in time criterion and can be diagnosed with MS.[20] The probability of experiencing a second attack is reported to be between 57 to 84% within the first two years,[21,22] and a study conducted in Türkiye reported that this period could be as short as 10 months.[23]

The secondary progression is considered a consequence of the disease course, with reports indicating a transition rate of 10% within 10 years, 50% within 20 years, and 93% within 30 years.[24] The factors identified were associated with an increased risk of transitioning to PMS, including older age at symptom onset, higher EDSS scores at onset, smoking, motor and cerebellar dysfunction, spinal cord lesions, male sex, and increased frequency of relapses within the first two years.[24] However, in our study, we found a significant linear relationship between the onset of motor symptoms and older age at disease onset with the likelihood of progression, but no correlation with the time and age of progression. The earlier onset of progressive phase transition in patients with RRMS may be attributed to an earlier age at disease onset in this group. Contrary to the literature, we observed an earlier progression in females; however, due to the small number of patients in the progressive phase, we refrained from making definitive interpretations.

For many individuals, the primary source of vitamin D is exposure to sunlight, particularly ultraviolet B radiation. The amount of vitamin D in the body is measured by the level of 25(OH)D in the circulation. Vitamin D may enhance pathogen elimination and immune tolerance by acting on innate immune cells, while its effects on acquired immune cells include stimulating differentiation of regulatory T and B cells, reducing the production of proinflammatory cytokines, and increasing the secretion of anti-inflammatory cytokines. Furthermore, in addition to these immunomodulatory effects, direct effects of vitamin D on nerve cells, including promoting oligodendrocyte maturation, were also observed.[3] Although low vitamin D levels are known to increase the risk of MS, it was suggested that low maternal sun exposure during the intrauterine period may also increase the risk of developing MS. This view was associated with increased autoimmune disease activity, clinical severity, and relapse rates in the late winter-early spring period when the lowest vitamin D levels are reached.[25] In one of the pioneering studies establishing the relationship between vitamin D and MS, it was suggested that elevated vitamin D levels before the age of 20 may reduce the risk of developing MS later in life. Subsequent studies supported this view by finding that high ultraviolet B exposure during childhood and sunlight exposure in summer months reduced the risk of MS.[26,27] It was emphasized that insufficient vitamin D intake not only predisposed individuals to MS but also had negative effects on the disease process.[6] Our region, located along the Aegean Sea, experiences sunny weather for a significant portion of the year. Studies conducted in Türkiye with healthy individuals showed that vitamin D levels were largely insufficient and deficient.[28] Sirinocak et al.[29] examined vitamin D

levels in 74 patients with MS and 50 healthy control subjects and demonstrated that both patients and healthy individuals had insufficient and deficient serum vitamin D levels. Due to the significant vitamin D deficiency observed in all our study groups, a specific effect of vitamin D deficiency on progression was not observed. The role of vitamin D in the pathophysiology of MS is multifactorial and likely influenced by many other genetic and environmental factors. Vitamin D deficiency may be associated with dietary habits in our region and vitamin D receptor gene polymorphism.

Among the environmental factors interacting with genetics in the etiopathogenesis of MS, viral triggers have always been prominent. Among these factors, EBV has been one of the most discussed factors interacting with MS. Infection with EBV, which is often asymptomatic during early childhood, can lead to infectious mononucleosis when acquired later in lifetime.[3] In a study where EBV infection was monitored in EBV seronegative individuals, it was shown that the risk of MS increased 32-fold after EBV infection.[7] In seropositivity, the most significant difference is observed in childhood. Seropositivity of EBV was reported in 83% of pediatric patients with MS, while it was reported to be between 50% and 55% in healthy children aged 6 to 17 years. It is known that seropositivity significantly increases after the age of 12, and even in seronegative pediatric patients, exclusion of non-MS diseases is highly recommended.[8,30] In our study, since the patients tested highly positive for anti-VCA IgG, anti-EBNA IgG, and anti-EA IgG, no significant difference in seropositivity was observed between the groups. The high seropositivity we detected in anti-VCA IgG and anti-EBNA IgG in patients with MS is consistent with previous studies.[31]

In conclusion, the demographic, clinical, and laboratory characteristics of MS patients and their effects on the onset and course of the disease were investigated in our study. It was observed that the birth rate in autumn was lower in our patient group. An earlier onset of the disease and a longer time to progression were found in early disease onset. The onset of motor symptoms, older age at disease onset, and higher disability at the last assessment were associated with progression. Low/insufficient levels of vitamin D were detected in all patients, while high positivity for EBV antibodies, including anti-VCA IgG, anti-EBNA IgG, and anti-EA IgG, was found, but their association with disease type and progression could not be demonstrated. Although the number of patients examined was not sufficient, we hope that our findings will shed light on future large-scale studies to be conducted on MS epidemiology in our region.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Concept, design: İ.İ.K., B.İ.T., Y.Z.; Data collection or processing: İ.İ.K., L.Ö.; Analysis or interpretation: B.İ.T.; Literature search, writing: İ.İ.K., B.İ.T.; Supervision and review: U.Ş., F.T., Y.Z.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Ascherio A, Munger KL. Epidemiology of multiple sclerosis: From risk factors to prevention-an update. Semin Neurol 2016;36:103-14. doi: 10.1055/s-0036-1579693.
2. Filippi M, Bar-Or A, Piehl F, Preziosa P, Solari A, Vukusic S, et al. Multiple sclerosis. Nat Rev Dis Primers 2018;4:43. doi: 10.1038/s41572-018-0041-4.
3. Ward M, Goldman MD. Epidemiology and pathophysiology of multiple sclerosis. Continuum (Minneap Minn) 2022;28:988-1005. doi: 10.1212/CON.0000000000001136.
4. Samara A, Cantoni C, Piccio L, Cross AH, Chahin S. Obesity, gut microbiota, and multiple sclerosis: Unraveling the connection. Mult Scler Relat Disord 2023;76:104768. doi: 10.1016/j.msard.2023.104768.
5. Munger KL, Åivo J, Hongell K, Soilu-Hänninen M, Surcel HM, Ascherio A. Vitamin D status during pregnancy and risk of multiple sclerosis in offspring of women in the finnish maternity cohort. JAMA Neurol 2016;73:515-9. doi: 10.1001/jamaneurol.2015.4800.
6. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. Nat Rev Neurol 2017;13:25-36. doi: 10.1038/nrneurol.2016.187.
7. Bjornevik K, Cortese M, Healy BC, Kuhle J, Mina MJ, Leng Y, et al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Science 2022;375:296-301. doi: 10.1126/science.abj8222.
8. Fadda G, Yea C, O'Mahony J, Waters P, Yeh EA, Marrie RA, et al. Epstein-Barr virus strongly associates with pediatric multiple sclerosis, but not myelin oligodendrocyte glycoprotein-antibody-associated disease. Ann Neurol 2024;95:700-5. doi: 10.1002/ana.26890.

9. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292-302. doi: 10.1002/ana.22366.
10. Lublin FD, Coetzee T, Cohen JA, Marrie RA, Thompson AJ; International Advisory Committee on Clinical Trials in MS. The 2013 clinical course descriptors for multiple sclerosis: A clarification. Neurology 2020;94:1088-92. doi: 10.1212/WNL.0000000000009636.
11. Atlas of MS. 3rd ed: The Multiple Sclerosis International Federation; September 2020. Available at: https://www.atlasofms.org/map/global/epidemiology/number-of-people-with-ms.
12. Oliveira SR, Simão AN, Kallaur AP, de Almeida ER, Morimoto HK, Lopes J, et al. Disability in patients with multiple sclerosis: Influence of insulin resistance, adiposity, and oxidative stress. Nutrition 2014;30:268-73. doi: 10.1016/j.nut.2013.08.001.
13. Erem C. Prevalence of overweight and obesity in Turkey. IJC Metabolic & Endocrine; 2015:38-41. doi: 10.1016/j.ijcme.2015.07.002.
14. Pantavou KG, Bagos PG. Season of birth and multiple sclerosis: A systematic review and multivariate meta-analysis. J Neurol 2020;267:2815-22.doi: 10.1007/s00415-019-09346-5.
15. Healy BC, Ali EN, Guttmann CR, Chitnis T, Glanz BI, Buckle G, et al. Smoking and disease progression in multiple sclerosis. Arch Neurol 2009;66:858-64. doi: 10.1001/archneurol.2009.122.
16. Koch M, van Harten A, Uyttenboogaart M, De Keyser J. Cigarette smoking and progression in multiple sclerosis. Neurology 2007;69:1515-20.doi: 10.1212/01.wnl.0000277658.78381.db.
17. Kalincik T, Buzzard K, Jokubaitis V, Trojano M, Duquette P, Izquierdo G, et al. Risk of relapse phenotype recurrence in multiple sclerosis. Mult Scler 2014;20:1511-22. doi: 10.1177/1352458514528762.
18. Akdemir N, Terzi M, Arslan N, Onar M. Prevalence of multiple sclerosis in the Middle Black Sea region of Turkey and demographic characteristics of patients. Noro Psikiyatr Ars 2017;54:11-4. doi: 10.5152/npa.2016.12451.
19. Klineova S, Lublin FD. Clinical course of multiple sclerosis. Cold Spring Harb Perspect Med 2018;8. doi: 10.1101/cshperspect.a028928.
20. Yamout B, Al-Jumah M, Sahraian MA, Almalik Y, Khaburi JA, Shalaby N, et al. Consensus recommendations for diagnosis and treatment of multiple sclerosis: 2023 revision of the MENACTRIMS guidelines. Mult Scler Relat Disord 2024;83:105435. doi: 10.1016/j.msard.2024.105435.
21. D'Alessandro R, Vignatelli L, Lugaresi A, Baldin E, Granella F, Tola MR, et al. Risk of multiple sclerosis following clinically isolated syndrome: a 4-year prospective study. J Neurol 2013;260:1583-93. doi: 10.1007/s00415-013-6838-x.
22. Gaetani L, Fanelli F, Riccucci I, Eusebi P, Sarchielli P, Pozzilli C, et al. High risk of early conversion to multiple sclerosis in clinically isolated syndromes with dissemination in space at baseline. J Neurol Sci 2017;15;379:236-240. doi: 10.1016/j.jns.2017.06.008.
23. Çinar BP, Özakbaş S. Prediction of conversion from clinically isolated syndrome to multiple sclerosis according to baseline characteristics: A prospective study. Noro Psikiyatr Ars 2018;55:15-21. doi: 10.29399/npa.12667.
24. Barzegar M, Najdaghi S, Afshari-Safavi A, Nehzat N, Mirmosayyeb O, Shaygannejad V. Early predictors of conversion to secondary progressive multiple sclerosis. Mult Scler Relat Disord 2021;54:103115.doi: 10.1016/j.msard.2021.103115.
25. Watad A, Azrielant S, Bragazzi NL, Sharif K, David P, Katz I, et al. Seasonality and autoimmune diseases: The contribution of the four seasons to the mosaic of autoimmunity. J Autoimmun 2017;82:13-30. doi: 10.1016/j.jaut.2017.06.001.
26. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA 2006;296:2832-8. doi: 10.1001/jama.296.23.2832.
27. Sebastian P, Cherbuin N, Barcellos LF, Roalstad S, Casper C, Hart J, et al. Association between time spent outdoors and risk of multiple sclerosis. Neurology 2022;98:e267-78. doi: 10.1212/WNL.0000000000013045.
28. Hekimsoy Z, Dinc G, Kafesciler S, Onur E, Guvenc Y, Pala T, et al. Vitamin D status among adults in the Aegean region of Turkey. BMC Public Health 2010;10:782. doi: 10.1186/1471-2458-10-782.
29. Sirinocak PB, Eskut N, Colak A, Sener U, Zorlu Y. Vitamin D, Parathormone, gender, interleucin 10 and tumor necrosis alpha relationship in multiple sclerosis patients. İzmir Eğitim ve Araştırma Hastanesi Tıp Dergisi 2020;24:121-6.
30. Nourbakhsh B, Cordano C, Asteggiano C, Ruprecht K, Otto C, Rutatangwa A, et al. Multiple sclerosis is rare in Epstein-Barr virus-seronegative children with central nervous system inflammatory demyelination. Ann Neurol 2021;89:1234-9. doi: 10.1002/ana.26062.
31. Langer-Gould A, Wu J, Lucas R, Smith J, Gonzales E, Amezcua L, et al. Epstein-Barr virus, cytomegalovirus, and multiple sclerosis susceptibility: A multiethnic study. Neurology 2017;89:1330-7.doi: 10.1212/WNL.0000000000004412.