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Multiple Sclerosis and Several Demographic Characteristics, Family History of MS, and Month of Birth: A Case-Control Study

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Background: Several factors have been reported as risk factors for multiple sclerosis (MS); however, the main causes of the disease are still unknown. A geographical area with a low MS incidence is Ahvaz, Iran.
Objectives: The objective of this study was to evaluate the association of several demographic characteristics, family history, and birth month with MS in Ahvaz.
Patients and Methods: This was a case-control study including 155 MS cases and 155 controls matched for age, sex, and residential status. The participants were selected randomly, using a systematic method, from the MS patients referred to the MS Society of Khuzestan (Iran). The data collection tool was a standardized questionnaire designed by the authors to assess demographic characteristics. Data were analyzed using descriptive statistics including mean, frequency, and standard deviation and inferential statistical tests including χ^2, Fisher's exact test, and logistic regression using SPSS version 19.
Results: In both cases and controls, no significant associations were found between Arab ethnicity and incidence of MS, marital status and risk of MS in Ahvaz, or more than 15-year residency in Ahvaz, birth in Khuzestan, and month of birth and the risk of MS ($P > 0.05$). However, there was a marginally significant association between living from birth to age 15 years in Ahvaz and MS ($P = 0.05$). Furthermore, there was an association between a family history of MS and the risk of MS in Ahvaz ($P = 0.02$), which was significant in univariate logistic regression ($P = 0.006$).
Conclusions: The findings suggested that according to the ecological conditions of Ahvaz, a family history of MS may increase the risk of developing MS.

Keywords: Case-Control Studies; Multiple Sclerosis; Demography

1. Background

Multiple sclerosis (MS) is a chronic inflammatory condition and the most common disease of the brain and spinal cord among the young (1). Despite extensive research, the exact cause of MS is still unknown. Several factors have been reported as risk factors for MS, but the main causes are still unknown (2). Recent studies have indicated the main cause of MS could be a combination of genetic susceptibility and environmental exposures during pregnancy and early puberty. The occurrence of MS is influenced by vitamin D deficiency, nutrition, season of birth, Epstein-Barr virus infection, and smoking behavior. In addition, these risk factors combined with a genetic predisposition can lead to the development of MS (3-10). Furthermore, studies showed these factors are associated with each other in influencing MS so that individuals exposed to more than one agent have a higher risk of the disease (11). Studies showed that the presence of a specific group of human leukocyte antigens on the cell membrane represents the genetic background of patients with MS that can make the body more prone to activated autoimmune responses in MS (such as viruses) (12).

A study in Canada showed that the risk of MS for the fraternal twin of a sibling with MS is approximately two-fold higher than a non-twin sibling of a person with MS (13). Although genetic predisposition is important in MS, it cannot explain the variations in MS incidence according to geographical differences and migration (14, 15).

There is strong evidence indicating an association between geographical differences and susceptibility to MS. The highest and lowest MS incidence rates are in temperate and warm climate regions, respectively. Several studies suggest that the MS prevalence increases as the distance from the equator increases in the both northern and southern hemispheres (16). One of the main factors influencing this dependence is the protective effect of sunlight (17, 18). For most people, the ultraviolet (UV) radiation of sunlight is

the main source of vitamin D, and in high-altitude regions where the exposure to sunlight is lower, especially during the winter months, low levels of vitamin D are common. In prospective studies, the association between vitamin D deficiency and increased risk of MS has been confirmed (19). Immigration studies indicate that the risk of MS is associated with accommodation during early life (20). This may indicate that environmental factors during pregnancy or birth, or both, may affect the disease (18, 20). A number of studies have examined some demographic characteristics and risk of MS. A study in Brazil showed that marital status is associated with MS (14), although a Canadian study did not show a connection between marital status and MS (21). A number of studies also examined the relationships between MS and ethnicity, place of residence for the first 15 years of life, and marriage (14, 22-24).

The potential factors influencing the risk of MS have been assessed in several prospective and retrospective studies. However, these studies are varied with respect to sample size and ethnic and cultural groups. In addition, the results of these studies are conflicting, although significant relationships have been reported between month of birth and MS incidence (20). Khuzestan province is classified as a geographical area with a low prevalence of MS (24).

2. Objectives

Considering the limitations of the previous studies conducted in this region as well as its special climate, lifestyle, and socioeconomic factors, the present study aimed to evaluate the effects of birth month, genetics, and several demographic characteristics on developing MS in Ahvaz, Iran.

3. Patients and Methods

This was a case-control study. After obtaining permission from the ethics committee of Jundishapur University of Medical Sciences in Ahvaz, a random systematic sampling method was used to select patients who were referred to the MS Society of Khuzestan (Iran). Sample size was calculated based on previous studies according to the following equation:

$$(1)\quad n = \frac{\left(z_{\frac{\alpha}{2}} + z_{\beta}\right)^2 \left(P_1(1-P_1) + P_2(1-P_2)\right)^2}{(P_2 - P_1)} = 155 \text{ and } 1 - \beta = \%80$$

A neurologist selected the participants for the case group from among patients who were previously diagnosed with MS based on the McDonald criteria and who had sufficient mental ability to attend the study, had a medical record in the Khuzestan MS Association, and were residing in Ahvaz. The case group was selected by systematic random sampling with K = 5 and included patients who agreed to participate in the study. In anticipation of participant withdrawals, sampling continued until reaching the determined sample size. A total of 155 patients were enrolled, and 155 participants for the control group were selected from among healthy subjects (without MS) residing in the city of Ahvaz who were matched with patients for age, sex, and residence and who agreed to participate in the study. A standardized questionnaire designed by the authors to examine the demographic characteristics of the participants. Therefore, for validity, after a review of the literature, a questionnaire was constructed, and the completed questionnaires were evaluated by a group of experts. Furthermore, a test-retest method was used to obtain reliability of the questionnaire, and a coefficient of 0.90 indicated the reliability of the scientific instruments. Data were analyzed using descriptive statistics including mean, frequency, and standard deviation and inferential statistical tests including $\chi 2$, Fisher's exact test, and logistic regression using SPSS version 19.

4. Results

In both case and control groups, 128 (82.6%) participants were women and 27 (17.4%) were men. The groups were similar in age (± 2 years) and sex. Table 1 shows the demographic characteristics of the participants in both groups. Table 2 compares the frequency distributions (in percent) and correlations with respect to length of stay, place of birth, residence of first 15 years of life, ethnicity, and marital status in the two groups. The majority of both cases and controls (76.8% and 82.6%, respectively) were of non-Arab ethnicity. Fisher's exact test for correlation of ethnicity with MS in Ahvaz indicated no significant differences between the two groups ($P > 0.05$). The majority of cases and controls were married (67.7% and 61.9%, respectively). No significant differences were found between the groups with respect to marital status ($P > 0.05$, $\chi 2$ test) or residing for more than 15 years in Ahvaz ($P > 0.05$, Fisher's exact test). However, significant differences were found between the groups with respect to living since birth to the age of 15 in Ahvaz ($P = 0.05$, Fisher's exact test), but for birth in Khuzestan province ($P = 0.23$, Fisher's exact test).

Table 1. Demographic Characteristics of Case and Control Groups [a]

	Cases	Controls
Age, y		
Women	33.43 ± 9.08	33.39 ± 9.13
Men	33 ± 8.71	32.33 ± 8.93
Gender		
Female	128 (82.6)	128 (82. 6)
Male	27 (18.4)	27 (18.4)
MS subtypes		
RRMS[1]	141 (91)	-
PPMS[2]	3 (1.9)	-
SPMS[3]	8 (5.2)	-
PRMS[4]	3 (1.9)	-

[a] Abbreviations: MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; PRMS, progressive-relapsing multiple sclerosis; RRMS, remitting relapsing MS; SD: standard deviation; SPMS, secondary progressive MS.

Table 3 shows the association between month of birth and the risk of MS according to the frequency distribution of birth months (divided into quarters) within each group. The second quarter showed the highest frequency for the case and control groups (40.6% and 33.5%, respectively), but no significant differences between the two groups were found with respect to month of birth (P = 0.85, χ^2 test).

Table 4 shows the distribution of family history of MS in the case and control groups. The findings suggest a statistically significant difference between the two groups with respect to family history (P = 0.02, Fisher's exact test). This association was significant according to the univariate logistic regression (P = 0.006).

Table 2. Demographic Comparisons of MS Patients and Controls [a]

Features	P Value	Control Group [b]	Case Group [b]	OR (95% CI)
Ethnicity				
Arab	0.12	27 (17.4)	36 (23.2)	
Non-Arab		128 (82.6)	119 (76.8)	
Marital status				
Single	0.54 [c]	55 (35.5)	46 (29.7)	
Married		96 (61.9)	105 (67.7)	
Other		4 (2.6)	4 (2.6)	
Residency period in Ahvaz				1.33 (0.81 - 2.19)
> 15, y	0.15	116 (74.8)	107 (69)	
< 15, y		39 (25.2)	48 (31)	
Birthplace				0.72 (0.35 - 1.47)
Khuzestan	0.23	140 (90.3)	135 (87.1)	
Other		15 (9.7)	20 (12.9)	
First 15 years of residency				0.62 (0.36 - 1.07)
Ahvaz	0.05	92 (71.9)	74 (61.7)	
Other		36 (28.1)	46 (38.3)	
Total		155 (100)	155 (100)	

[a] Abbreviations: CI, confidence interval; MS, multiple sclerosis; OR, odds ratio.
[b] Values are presented as No. (%).
[c] χ^2 test.

Table 3. Absolute and Relative Frequency Distribution of the Month of Birth in MS Patients and Controls [a]

Features	Control Group [b]	Case Group [b]	P Value
Month of Birth			
First quarter	42 (27.1)	40 (25.8)	
Second quarter	52 (33.5)	63 (40.6)	0.58
Third quarter	25 (16.1)	23 (14.8)	
Fourth quarter	36 (23.2)	29 (18.7)	
Total	155 (100)	155 (100)	

[a] Abbreviation: MS, multiple sclerosis.
[b] Values are presented as No. (%).

Table 4. Absolute and Relative Frequency Distribution of the Family History of MS in Patients and Controls [a]

Variable	Case Group	Control Group	P Value	OR (95% CI)
Family history of MS				2.4 (1.05 - 5.46)
Yes	20 (12.9)	9 (5.8)	0.02 [b]	
No	135 (87.1)	146 (94.2)		
Total	155 (100)	155 (100)		
First-degree relative	6 (30)	1 (11.1)		
Second-degree relative	4 (20)	1 (11.1)		
Other relatives	10 (50)	7 (77.8)		
Total	20 (100)	9 (100)		

[a] Abbreviations: CI, confidence interval; MS, multiple sclerosis; OR, odds ratio.
[b] Fisher's exact test (one-sided).

5. Discussion

Numerous studies have assessed the associations of different ethnicities and races with the risk of MS worldwide (2, 12, 14, 25). Iran has different ethnic groups, each with specific lifestyle and behavioral habits as well as different environmental exposures. Khuzestan province (Iran) is located in southwestern Iran between longitude 47° 41' to 50° 39' E and latitude 29° 58' to 33° 4' N. Ahvaz, the capital city of Khuzestan, is one of eight major cities of the country located geographically 31° 20' N and 48° 40' E on the plains of Khuzestan and 18 m above sea level.

Sharafaddinzadeh et al. (2009) conducted a cross-sectional study and found that the prevalence and incidence of MS in persons of Persian ethnicity were higher than in those of Arab ethnicity. However, the prevalence of advanced stages of MS with brain and motor symptoms is higher among Arab ethnic groups (24). The findings of no significant differences between Arab and non-Arab ethnic groups in the present study imply that there was no significant association of Arab ethnicity with the risk of MS. These discordant results could be related to differences in study methods, random sampling, statistical analysis, and time period of research. A study conducted in Israel showed that the incidence of MS in Muslim Arabs, Druze (a Muslim sect), and Bedouins is less than that in Jewish immigrants from Asia or Africa and Christian Arabs (25).

Silva et al. (2009) showed that being unmarried is associated with a higher risk of MS (14), which is inconsistent with the results of the present study. However, Ghadirian et al. (2001) showed no association of marital status with the risk of MS (21), which is consistent with the results of this study. This lack of association could be related to cultural differences, perhaps because lifestyle and exposure to environmental factors involved in the incidence of MS are different in different cultures. Support from the governments and public health systems in Western and European countries differ from that of third-world countries. Most single people They live with family, which may also affect lifestyle and environmental exposures.

According to Table 2, 69% and 74.8% of individuals in the case and control groups, respectively, resided for more than 15 years in Ahvaz. Although more healthy people than MS patients resided in Ahvaz for more than 15 years, the difference was not statistically significant. A previous study has described the importance of environmental factors: when migration from a low-risk area to a high-risk area occurs over the age of 15 years, the risk of MS will increase in the second area (high-risk area) (7). In this study, owing to geographical factors, the frequency of patients born in Khuzestan in the control group (90.3%) was higher than that in the case group (87.1%), but the difference was not significant.In addition, 61.7% of people in the case group and 71.9% of people in the control group lived in Ahvaz for the first 15 years of their lives. Although the proportion of healthy people with their first 15 years of residency in Ahvaz was higher than that of the MS patients (a statistically significant difference with P = 0.05), logistic regression did not show any significant difference between the two groups for this factor (P = 0.17, OR = 1.54 [0.82–2.88]). There have been no epidemiological studies to assess the effect of the first 15 years of residency in Ahvaz on the risk of MS.

For most people, the sun's UV radiation is the most important source of vitamin D, but at high altitudes where exposure to sunlight, especially during the winter months is low, low levels of vitamin D are common. A prospective study shows an association between vitamin D deficiency and increased risk of MS (19). Although the results of the present study showed no significant differences between the month of birth in MS patients, there was a 7.1% higher proportion of people born in the second quarter (July, August, and September) and a 4.5% lower proportion of people born in the fourth quarter (January, February, and March) in the patient group than in the control group. Studies show that the risk of MS for people born north of the equator is 9.1% higher than expected for people born in April and 8.5% less than expected for people born in October (26).

Variations in the distribution of month of birth in MS patients and the effects of latitude support the influence of UV radiation. In other words, exposure to sunlight during pregnancy may reduce the risk of MS in children. Studies show that in the southern hemisphere, more patients with MS were born in November than in May (20). However, the effect of month of birth is greater in Scotland, with the risk of MS being 31% higher than expected for those born in May and 20% less than expected for those born in November (27). However, a Canadian study shows that the birth month is associated with the risk of MS among people with a family history of MS (20). In other words, the interaction between genes and the environment are associated with the weather, and such an interaction is possible during pregnancy or shortly after birth in people born in the Nordic countries (20).

The highest and lowest temperatures in Ahvaz take place during the second and fourth quarters of the year, respectively. Bagheri et al. (2014) (28) and Alonso et al. (2011) (29) suggested that prolonged exposure to sunlight may be associated with a reduced risk of MS. Most of the previous studies on the effects of birth month on the risk of MS have been conducted in the northern hemisphere (above 50°N), such as in Canada, Scotland, Denmark, and Sweden. These countries receive much lower levels of UV light exposure, compared with Iran, especially Ahvaz.

The results of this study suggest that a family history of MS was associated with the risk of MS in Ahvaz (P = 0.02). This association was also significant according to a logistic regression model. Therefore, a family history of MS may be considered a risk factor for MS in this city (P = 0.006). Several studies have indicated an association between genetic factors and the risk of MS (1, 30, 31). Zor-

zon (2003) suggested that family history is a significant risk factor for MS (32), consistent with the findings of the present study. These results suggest a role for genetic susceptibility in the risk of MS. Furthermore, the study of Ashtari et al. (2011) demonstrated an association between a family history of MS and its risk (7).

According to the special ecological conditions of Khuzestan, Ahvaz is defined as a region with low MS prevalence. However, the findings of this study suggest that a family history of MS (genetic factor) along with the environmental factors are still crucial factors influencing the risk of this disease.

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Authors' Contributions

Study concept and design: Maryam Bagheri. Acquisition of data: Maryam Bagheri. Nasrin Elahi. Analysis and interpretation of data: Maryam Bagheri, Hamed Tabesh. Drafting of the manuscript: Maryam Bagheri, Sadigheh Fayazi. Critical revision of the manuscript for important intellectual content: Maryam Bagheri, Sadigheh Fayazi. Statistical analysis: Maryam Bagheri, Hamed Tabesh. Administrative, technical, and material support: Sadigheh Fayazi, Maryam Bagheri, Nasrin Elahi, Hamed Tabesh, Nastaran Majdi-Nasab. Study supervision: Sadigheh Fayazi, Maryam Bagheri, Nasrin Elahi, Hamed Tabesh, Nastaran Majdi-Nasab.

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