



Multiple Sclerosis Associated Risk Factors: A Case-Control Study

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Abstract

Background: Hamadan Province is one of the high-risk regions in Iran for Multiple sclerosis (MS). A majority of the epidemiological studies conducted in Iran addressing MS are descriptive. This study was conducted to assess MS and its associated risk factors in Hamadan Province, the west of Iran.

Methods: This case-control study compared 100 patients with MS (case group) and 100 patients with acute infectious diseases (control group) from September 2013 to March 2014. A checklist was used to assess the demographic, medical, and family history of the patients. The Friedman-Rosenman questionnaire was also used to assess personality type. Statistical analysis was performed using logistic regression model with Stata 11 software program.

Results: The adjusted odds ratio (OR) estimate of MS was 4.37 (95% CI: 2.33, 8.20) for females compared to males; 0.15 (95% CI: 0.06, 0.43) for people aged above 50 years compared to aged 14 to 29 years; 0.44 (95% CI: 0.21, 0.91) for overweight or obese people compared to normal weights. Crude OR indicated a significant association between the occurrence of MS and exclusive breast feeding, season of birth, and smoking. However, the association was not statistically significant after adjustment for other covariates.

Conclusion: The risk of MS is significantly lower in male gender, obese/overweight, and old people. Furthermore, non-smoking, non-exclusive breast-feeding, and born in autumn may increase the risk of MS but need further investigation. However, long-term large prospective cohort studies are needed to investigate the true effect of the potential risk factors on MS.

Keywords: Multiple sclerosis, Risk factors, Case-control study, Iran

Introduction

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disorder of the brain and spinal cord in which focal lymphocytic infiltration leads to damage to myelin and axons (1). "MS has a multifactorial etiology and is triggered by environmental factors in individuals with complex genetic risk profiles" (2, 3). Disease onset usually occurs in young adults and mostly affects 20 to 40 years old people and is more common in females (4, 5). The

public health system is facing an increasing disease burden (6). Epidemiologic studies have suggested the role of genetic and non-genetic risk factors in the etiology of MS including familial clustering (7), exposure to infectious agents (8), age infection during childhood (8, 9), dietary patterns (10), environment exposures (11), season of the birth (9, 12-14), smoking (15, 16), and psychological stress (17).

Each year, an estimated 2.5 million people are affected worldwide (2). MS prevalence in Iran varies geographically, from 5.3 to 74.28 per 100,000 (4). Epidemiological studies conducted recently in Iran have shown an increasing trend of MS, especially in female gender (4, 18, 19). According to the unpublished estimations reported by Isfahan MS Society using a national query, Hamadan Province with the prevalence of 62.5/100,000 is one of the high-risk regions in Iran for this disease (4). A majority of the epidemiological studies conducted in Iran in connection with MS are descriptive.

The present analytical case-control study was conducted to determine the risk factors of MS in Hamadan Province, the west of Iran.

Methods

The Research Council of Hamadan University of Medical Sciences has approved this study. This case-control study was conducted in Hamadan Province, the west of Iran, from September 2013 to March 2014. The participants were enrolled voluntarily into the study. Since no intervention was performed in this study, only verbal informed consent was taken from the participants.

According to Asadollahi et al. (20), the proportion of women to men in patients with MS compared to controls was 79% and 61%, respectively. Based on these results, we arrived at a sample size of 100 for each group and a total sample size of 200 at 95% significance level and 80% statistical power. Accordingly, 100 patients with confirmed MS were considered as cases group and compared with 100 patients with infectious diseases but without history of neurological disorder, as controls group. Cases and controls were selected at the same time and from the same hospital in order to make the study base of the two groups similar. Cases were selected from the patients who referred to the clinic of neurology of Farshchian Hospital. Controls were selected from the patients who referred to the clinic of infectious diseases of the same Hospital. The cases were enrolled regardless of their age, gender, and the date of disease onset. A case of MS was defined as a patient whose disease was diagnosed by a neurologist and

was confirmed by brain MRI or total spinal MRI. We only enrolled those patients whose disease were diagnosed during the last 10 years, were resident of Hamadan Province, had a complete medical record in Farshchian Hospital, and were under treatment. The patients who were not satisfied to participate in the study or were not accessible were excluded from the study. A control was defined as a subject with infectious disease but free of neurological disorders looking for medical care. The patients with infectious disease who referred from other provinces were excluded.

A structured questionnaire was developed consisting of 40 items to collect data on sociodemographic characteristics and environmental factors. The questionnaire included data on gender, age at diagnosis, occupation, marital status, educational level, weight, height, smoking history, exclusive breast feeding, history of measles, history of MS among the family members, season of the birth, history of disorder of immune system, blood group, and RH factor. Body mass index (BMI), which is the ratio of body weight in kg to height in square meters, was categorized into three classes as individuals with underweight BMI ($BMI < 18.5$), normal individuals ($BMI = 18.5-24.9$), and overweight or obese ($BMI \geq 25$).

In addition to the above questionnaire, the Friedman-Rosenman standard questionnaire was used to determine personality type of the participants. The questionnaire included 25 two-choice (yes/no) questions with a total score of 25. Patients who received a score of ≥ 13 were considered as type 'A' otherwise as type 'B' personality. People with type 'A' behavior pattern are known to have more stress, nervousness and anxiety (21, 22). The reliability of the personality questionnaire was 0.77 using Cronbach's alpha coefficient. Data collection was performed through face-to-face interviews.

Means and standard deviations (SD) were calculated for continuous variables, frequency, and percentage for categorical variables. Adjusted and unadjusted odds ratios (OR) estimates of MS were calculated using the simple and multiple logistic regression through backward model. All analyses were performed at 0.05 significance levels using

Stata 11 (StataCorp, College Station, TX, USA) statistical software.

Results

The median duration of MS diagnosis was four years (with a range of 1 to 27). The distribution of

the characteristics of cases and controls are shown in Table 1. About 79.8% of cases and 47.5% of controls were female ($P=0.001$). The mean (SD) age of the control group was higher than that of the case group; 41.2 (14.7) years versus 36.1 (11.6) years respectively ($P=0.007$).

Table 1: Comparison of the characteristics of the cases and control groups

Characteristics	Cases		Controls		P value
	Number	Percent	Number	Percent	
Gender					0.001
Male	20	20.2	52	52.5	
Female	79	79.8	47	47.5	
Age group (yr)					0.001
14-29	28	28.6	18	18.2	
30-39	36	36.7	36	36.4	
40-49	27	27.5	16	16.2	
≥50	7	7.14	29	29.2	
Marital status					0.074
Married	69	69.0	80	80.0	
Single	25	25.0	19	19.0	
Widow& Divorced	6	6.0	1	1.0	
Educational level					0.215
Primary school	19	19.2	14	14.0	
Secondary school	15	15.1	15	15.0	
High school	29	29.3	43	43.0	
Academic	36	36.4	28	28.0	
Positive family history					0.435
No	89	89.9	92	93.9	
Yes	10	10.1	6	6.1	
Smoking status					0.001
Nonsmoker	92	93.9	73	73.0	
Smoker	6	6.1	27	27.0	
Exclusive breast feeding					0.007
Yes	78	83.9	94	95.9	
No	15	16.1	4	4.1	
History of measles					0.180
No	48	57.1	44	46.8	
Yes	36	42.9	50	53.2	
Season of birth					0.089
Spring	23	23.0	33	33.0	
Summer	27	27.0	31	31.0	
Autumn	29	29.0	15	15.0	
Winter	21	21.0	21	21.0	
Blood group					0.349
AB	5	7.0	14	14.0	
A	21	29.6	22	22.0	
B	20	28.2	24	24.0	
O	25	35.2	40	40.0	
Blood Rh					0.349
Negative	13	17.8	24	24.7	
Positive	60	82.2	73	75.3	
BMI					0.054
Normal weight	26	56.5	39	39.0	
Underweight	3	6.5	3	3.0	
Overweight & obesity	17	37.0	58	58.0	
Type of personality					0.101
B	28	28.6	40	40.0	
A	70	71.4	60	60.0	

In addition, most individuals in the control and case groups were married. However, the number of widowed persons and divorcees in cases were higher than in controls, but the difference was not statistically significant ($P=0.074$). The proportion of smoking status was significantly higher in controls than in cases (27% versus 6.12%; $P<0.001$). Approximately 16.1% of the cases and 4.1% of the controls did not mention a history of exclusive breast-feeding. There was a correlation between

MS and exclusive breast-feeding ($P=0.007$). The distributions of educational level, positive family history, history of measles, season of birth, blood group, blood RH, body mass index, and type of personality were almost the same with no statistically significant difference. The effect of various potential risk factors on MS is given in Table 2 and 3 using crude (Table 1) and adjusted (Table 2) OR.

Table 2: Association between multiple sclerosis and potential risk factors using unadjusted odds ratio

Characteristics	Cases, n=100	Controls, n=100	Unadjusted odds ratio (95% CI)	Pvalue
Gender				
Male	20	52	1.00	-
Female	79	47	4.37 (2.33, 8.20)	0.001
Age group (yr)				
14-29	28	18	1.00	-
30-39	36	36	0.64 (0.30, 1.36)	0.249
40-49	27	16	1.08 (0.46, 2.55)	0.852
≥50	7	29	0.15 (0.06, 0.43)	0.001
Marital status				
Married	69	80	1.00	-
Single	25	19	1.52 (0.77, 3.00)	0.222
Widow& Divorced	6	1	6.95 (0.82, 59.20)	0.076
Educational level				
Primary school	19	14	1.00	-
Secondary school	15	15	0.74 (0.27, 1.99)	0.547
High school	29	43	0.50 (0.21, 1.15)	0.101
Academic	36	28	0.95 (0.40, 2.21)	0.901
Positive family history				
No	89	92	1.00	-
Yes	10	6	1.72 (0.60, 4.94)	0.311
Smoking status				
Nonsmoker	92	73	1.00	-
Smoker	6	27	0.17 (0.07, 0.45)	0.001
Exclusive breast feeding				
Yes	78	94	1.00	-
No	15	4	4.52 (1.44, 14.17)	0.010
History of measles				
No	48	44	1.00	-
Yes	36	50	0.66 (0.37, 1.19)	0.169
Season of birth				
Spring	23	33	1.00	-
Summer	27	31	1.25 (0.59, 2.62)	0.595
Autumn	29	15	2.77 (1.22, 6.30)	0.015
Winter	21	21	1.43 (0.64, 3.21)	0.380
Blood group: AB				
A	21	22	2.67 (0.82, 8.73)	0.103
B	20	24	2.33 (0.72, 7.60)	0.160
O	25	40	1.75 (0.56, 5.45)	0.335
Blood Rh				
Negative	13	24	1.00	-
Positive	60	73	1.52 (0.71, 3.23)	0.280
BMI				
Normal weight	26	39	1.00	-
Underweight	3	3	1.50 (0.28, 8.01)	0.635
Overweight & obesity	17	58	0.44 (0.21, 0.91)	0.028
Type of Personality				
B	28	40	1.00	-
A	70	60	1.67 (0.92, 3.02)	0.092

Based on these results, the adjusted OR estimate of MS in females against males was 4.01 (95% CI: 1.32, 12.14). The adjusted OR estimate of MS for people aged above 50 years against those aged 14 to 29 years was 0.11 (95% CI: 0.01, 1.08). The risk of MS was higher among those individuals with-

out exclusive breast-feeding compared to those patients with exclusive breast-feeding ($P=0.010$), among non-smokers compared to smokers ($P<0.001$) (Table 1), although adjusted analysis of these covariates was not statistically significant.

Table 3: Association between multiple sclerosis and potential risk factors using odds ratio adjusted for all other variables in the table

Characteristics	Cases, n=100	Controls, n=100	Adjusted odds ratio (95% CI)	Pvalue
Gender				
Male	20	52	1.00	-
Female	79	47	4.01 (1.32, 12.14)	0.014
Age group (yr)				
14-29	28	18	1.00	-
30-39	36	36	1.18 (0.33, 4.16)	0.795
40-49	27	16	2.58 (0.64, 10.40)	0.182
≥50	7	29	0.11 (0.01, 1.08)	0.059
Body mass index (kg/m²)				
Normal weight	26	39	1.00	-
Underweight	3	3	0.61 (0.04, 10.02)	0.729
Overweight & obesity	17	58	0.18 (0.06, 0.54)	0.002

Based on our findings, the patients who were born in autumn were significantly at higher risk of MS compared to those patients born in spring ($P=0.015$), however, there was no association between other seasons and MS (Table 1). Compared to individuals with normal weight, the adjusted OR estimates of MS in individuals with underweight was 0.61 (95% CI: 0.04, 10.02) and that of individuals with overweight or obese was 0.18 (95% CI: 0.06, 0.54).

There was no significant association between MS and marital status, educational levels, history of MS among family members, history of measles, blood groups, RH, and types of personality.

Discussion

In this study, we investigated the potential risk factors for MS. It was shown that among 12 factors, female gender, non-smoking, nonexclusive breast feeding, and born in autumn were the strongest risk factors of MS and obese or overweight people and those who aged 50 years or greater were among the protective factors.

According to our findings, women had a higher risk of developing MS than men, other researches confirmed this finding (4, 5, 23). This may be attributed to the difference in the immune status and nervous system between women and men, which may be affected by gonadal hormones, genetic differences, as well as different environmental exposures and lifestyle in the two genders. Usually, the autoimmune diseases, including MS, occur more frequent in women than in men (5, 23).

Age group of 20 to 40 is more likely to be affected by MS (6, 24). Based on our study, patients aged 50 years or more had lower risk of MS in comparison with those aged less than 50. In addition, the risk of MS among widowed people or divorcees was nearly seven times higher than married people, but the association was not statistically significant. This may be the result of chance error due to sparse data in our study, because only 7 out of 200 patients were divorced or widowed.

In some neurological disorders, such as Parkinson and Alzheimer, cigarettes have a protective role (25, 26). However, the association between MS

and smoking is controversial. Silva et al conducted a case control study, performed a multivariate conditional logistic regression, and indicated that smoking was significantly associated with developing MS (16). In addition, Handel et al. updated a meta-analysis for 14 studies containing 3,052 MS patients and 457,619 controls. They applied conservative and non-conservative analysis and indicated that smoking was associated with an increase in MS susceptibility in both model analyses (15). Unlike previous studies, we found an apparent inverse association between smoking and MS so that the chance of MS in nonsmokers was higher than in smokers. Two reasons might cause this unexpected result. First, smoking might have a strong effect for infectious disease in control group (27, 28). Second, the majority of the MS patients were women (79.8% of cases and 47.5% of controls), while the majority of the smokers were men (93.9% of males and 6% of females); so this imbalance between the two groups might have produced a factitious correlation between smoking and MS.

Our findings indicated that the risk of MS in patients born in autumn was more frequent than in spring. The results of previous literature were inconsistent regarding seasonal relationship. Staple et al conducted a similar study in Australia and confirmed our results (13), while, Salzer et al. in Sweden reported inverse association and reported that patients born in spring were at higher risk than those born in autumn (12). On the other hand, Vazirinejad et al. showed no seasonal effect in Iran (9). To answer this controversy, a systematic survey was conducted in 2012 and revealed that MS is more frequent in spring than autumn for people in the northern hemisphere countries such as Sweden, and a reciprocal pattern was found in countries located in the southern hemisphere like Australia (14). Therefore, it seems that the month of birth for areas with low sunlight exposure may be a risk factor for MS but it does not have important effect for areas with high sunlight exposure such as Mediterranean countries. The reason that may explain this association is that deficiency of vitamin D levels through lack of exposure to sun during pregnancy or early life may

influence the risk of developing MS (12, 14). Another important result of this study was that the risk of MS among individuals without exclusive breast-feeding was higher than individuals with exclusive breast-feeding. A case-control study conducted in Berlin confirmed this subject (29).

The results of our study showed that high BMI (overweight or obesity) was a protective factor against MS disease compared to normal patients. In addition, the risk of MS in people with type 'A' personality was higher compared to type 'B' but this was not statistically significant. In Iran from 50 MS patients 65% were personality type 'A' and 35% were type 'B' (21).

According to our results, covariates such as level of education, history of measles, positive family history of MS, blood group and RH had no significant association with MS. Al-Afasy et al conducted a population-based matched case-control study to determine the risk factors for MS in Kuwait in 2012. The study was performed on 101 MS cases and for each case; two population controls were selected who were individually matched for age, gender, and nationality. The multivariable conditional logistic regression model showed that a family history of MS was associated with a significantly increased risk of MS; but there was no significant association between BMI, history of measles, blood group, and RH with developing MS (30). In addition, another case-control study conducted in Rio de Janeiro indicated that blood group and positive family history of MS were significantly associated with MS but there was no association between MS and history of measles and breast-feeding (16). Different modifiable lifestyle such as sunlight exposure and smoking were associated with lower risk of MS in Iran (31).

This study was associated with a number of limitations as follows. (a) Recall bias is an inherent characteristic of case-control studies so we have to eliminate some of the covariates that were strongly influenced by it such as history of immune system and infectious diseases during childhood. (b) Another important limitation of this study was small sample size. MS is a rare disease, thus finding a large number of patients is impossible. We tried to find as much patients as possible. Howev-

er, we could not find more than 100 patients. (c) On the other hand, this study was performed only on outpatients who referred to Farshchian Hospital and did not include unable patients with severe physical condition. Despite its limitations, this study could examine the effect of several potential risk factors on MS. The results of this study help better understanding the predictors of MS in a middle-income country where limited information is available about the risk factor of this disease. These findings may help policymakers who plan preventive program to reduce MS rate and its associated predisposing factors.

Conclusion

The results of this study identified and examined the most common and important potential risk factors for MS in the target population. We concluded that the risk of MS is significantly lower in male gender, obese and overweight, and old people. Furthermore, non-smoking, non-exclusive breast-feeding, born in autumn may increase the risk of MS but need further investigation. Other covariates such as educational level, history of measles, positive family history of MS, blood group, and RH had no association with MS. However, long-term large prospective cohort studies are needed to investigate the true effect of the potential risk factors on MS. Conducting such studies in other regions of country would contribute towards increasing knowledge on the epidemiological profile of MS in Iran.

Ethical Considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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