Iran J Public Health, Vol. 53, No.9, Sep. 2024, pp.2140-2149

Original Article

Auto-Immune Diseases, Head and Neck Trauma, and Smoking Are Strong Predictors of Multiple Sclerosis

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(Received 04 Oct 2023; accepted 15 Jan 2024)

Abstract

Background: Several health, environmental, and lifestyle-related factors have been separately linked to multiple sclerosis (MS) by different studies. However, these studies did not adequately account for the temporal association of these factors with MS while considering the influence of other variables in the analysis. A comprehensive investigation of these factors remains scarce.

Methods: A hospital-based case-control study was carried out between Jun 2020 to Mar 2021 on 525 cases and 1050 controls frequently matched by age and sex. Cases and controls were selected at the same time and from the same centers (Motahari and Imam Reza referral centers) in Shiraz (the capital of Fars Province). Health, socio-demographic, and lifestyle status during adolescence were studied in this case-control study.

Results: The likelihood of having a history of autoimmune disease(s) ($OR_{yes/no}$=15.67, P<0.001) and family history of MS ($OR_{yes/no}$=11.57, P<0.001) were higher in cases. In addition, the likelihoods of reporting a history of head/neck traumas ($OR_{having\ a\ history/no\ history}$=9.16, P<0.001), smoking ($OR_{regular/other}$ =2.24, P=0.008), and stressful events ($OR_{yes/no}$=1.47, P=0.007) were higher among the case group. On the other hand, the odds of sun exposure ($OR_{most\ the\ time/seldom}$ =0.14, P<0.001), physical activity ($OR_{active/inactive}$=0.45, P<0.001), and good quality sleep (OR=0.93, P<0.001) were significantly lower in the case group.

Conclusion: This study provided a broad picture of the factors associated with MS, most of which were modifiable. Positive alterations to these factors through social and health educational programs are likely to reduce the burden of MS in Iran.

Keywords: Multiple sclerosis; Risk factor; Disease development; Case-control; Epidemiology

Introduction

Multiple sclerosis (MS) is a leading cause of non-traumatic disability among young adults, predominantly females (1). Currently, the global estimated number of prevalent cases of MS is about 2.8 million and the global pattern of disease is increasing (1). Iran is also experiencing a significant increase in the incidence of MS (2).

The marked increase in MS incidence may be explained, at least to some extent, by changes in our social, physical, and biological environment. Ge-

netic factors contribute about 30% of MS susceptibility, and the remaining susceptibility is explained by environmental factors (3). In addition to non-modifiable factors (e.g. sex and genetic background), epidemiological studies linked several modifiable factors to MS including serum level of vitamin D (4), sun exposure habits (5), and smoking (6). However, the role of other factors in MS has been scarcely investigated (7). Despite the fact that several health, environmental, and lifestyle-related factors have been separately linked to multiple sclerosis (MS) by different studies, these studies have not adequately considered the temporal association of these factors with MS while considering the influence of other variables in the analysis. As a result, a comprehensive investigation of these factors remains scarce.

Our study was carried out to measure the roles of personal and environmental factors on the risk of MS, using a large case-control study in Iran.

Materials and Methods

Setting

A hospital-based case-control study was carried out between Jun 2020 to Mar 2021 on 525 cases and 1050 controls frequently matched by age and sex. Cases and controls were selected at the same time and from the same centers (Motahari and Imam Reza referral centers) in Shiraz (the capital of Fars Province), Iran. These medical centers affiliated with Shiraz University of Medical Sciences are the referral centers for the southern part of Iran.

Written consent was obtained from all participants. Our study was approved by the Institutional Review Board at the Shiraz University of Medical Sciences (approval number: 1398.428).

Selection of cases

The case participants were recruited from MS patients who visited the neurology clinics in Imam Reza and Motahari centers from Jun 2020 to Mar 2021. All selected MS patients were diagnosed according to McDonald's 2005, 2010, or 2017 criteria. Patients were included if they were at least 20 yr of age (to avoid reverse causality, patients with disease onset before the age of 20 yr were excluded) and were able to take part in a face-to-face interview. Data were collected from patients during their routine clinic visit waiting time.

Selection of controls

For each case, two healthy controls were selected from the individuals who visited the internal, gynecology, ultrasound, pediatric, and general surgical clinics in the centers. All controls were free of MS at the time of the interview and were frequency-matched with cases by age and sex.

Inclusion and exclusion criteria

Our participant's inclusion criteria were: (1) age between 20 and 60 yr, (2) living in Fars Province at the time of the study, (3) no history of peripheral inflammatory neurological diseases (Guillain-Barre syndrome and chronic inflammatory demyelinating polyneuropathy). Not being willing to participate in the study was the only exclusion criterion.

Data collection

To apply a valid and reliable approach to collect data from the participants, we revised and used the same approach used by previous case-control studies on the same population (8, 9). The questionnaire was originally designed to assess the participant's social, environmental, and behavioral exposures during their normal life (before the symptoms of the study disease started). Structured face-to-face interviews were conducted with the patients and controls by five trained interviewers at the time of routine visits to their physicians. Although it was not feasible to keep the interviewers "blind" to the status of the participants, they were unaware of the study hypothesis. The content validity of the questionnaire was approved by a team of two epidemiologists, a neurologist, and a public health nurse. Moreover, in the pilot phase of the study (conducted on 50 cases and 50 controls), the response rate and the reliability of the questionnaire were tested. Ac-

cordingly, the response rate (all selected individuals participated in the interview) and reliability (Cronbach's alpha =0.82) of the data were approved by the research team.

Socio-demographic factors

The socio-demographic information including sex, birth year, birth order, number of siblings, ethnicity, and relationship of parents were reported by the participants. Participants were also asked about their level of education, job, parental economic status, marital status, and current place of residence.

Factors related to lifestyle

The interested behaviors consisted of self-reported physical activity, daily sunlight exposure, sleep quality, stressful events, history of active and passive smoking, and history of drug abuse. In addition, perceived physical composition during adolescence (thin, normal, or overweight/obese) was reported by the participants. Participants in both groups were asked whether they were breastfed during infancy (never, <4 months, more, and don't know).

In more detail, cases and controls were required to report a rough estimation (seldom, often, and most of the time) of the daytime they usually spent outdoors (playing, sports, walking, or working). Perceived physical activity was measured with a yes/no question "Do you consider yourself a physically active person". Self-reported history of cigarette smoking was also defined (never, occasionally, and regular). Data on exposure to passive smoking during adolescence was obtained, by asking participants if they were routinely exposed to cigarette smoke at home or elsewhere. The history of drug use was asked with a yes/no question.

Sleep quality was reported on a Likert scale from 0 (very bad) to 15 (very good). Moreover, as an objective measure of the occurrence of potentially stressful events, participants were asked to report any highly stressful events (e.g., death of relatives) that occurred during their adolescence which had a notable impact on their emotions (yes/no question).

Medical history

With regard to the participant's medical history, questions were asked about the history of asthma or allergies to anything including animals, foods, and drugs. The presence of other autoimmune disease(s) (including inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, and myasthenia gravis) and migraine in the participants and their families. Familial history of MS was asked too. In addition, history of head/neck traumas, history of tonsillectomy, and received blood and blood products were asked from the participants.

Statistical analysis

An independent *t*-test was used to compare the means of quantitative variables in case and control groups. To compare the distribution of nominal or ordinal variables between the two groups, Chi-square and Fisher exact tests are applied. Adjusted odds ratios were calculated using multiple logistic regressions by controlling for the effect of potential confounding factors to measure the association of the study variables with the risk of developing MS. Due to the small number of several types of pre-existing conditions (presence of another autoimmune disease(s) in the person, familial history of other autoimmune diseases and migraine), the conditions were merged and used as a single variable in the analysis. The final model was defined by the backward and forward variable selection strategy, including covariates with a significant effect on the goodness of fitness of the model. We also tested for any interaction and association between the independent variables. Statistical tests were two-tailed. The statistical power was considered equal to 90% at the stage of calculating the sample size. Statistical analysis was carried out by R for Windows 3.5.3.

Results

Overall, 525 individuals with MS and 1050 controls were interviewed in this study. Of cases 80.8% and of controls 79.1% were female. The mean age of the male cases and controls were 35.9 and 36.7 yr, respectively. The mean age of

female cases was 36.4 compared with 36.2 yr among the controls. These results indicate similarities in the distribution of sex and age in our study (Table 1).

Our study results revealed significant crude associations between parents being related, parental economic status, ethnicity, marital status, body composition during 13-19 yr old, history of drug abuse, experience of stressful event(s), history of asthma/allergy, history of blood and blood products transfusion and history of tonsillectomy, number of siblings, and being breastfed (Table 1). However, these associations were abrogated after adjustment for other variables.

Table 1: Distribution of the age, sex, and potential risk factors among cases and controls

Variables	*Cases (525)*	*Controls (1050)*	*P-Value[1]*
Sex			0.466
Female	424 (80.8)	831 (79.1)	
Male	101 (19.2)	219 (20.9)	
Age groups; number (%)			0.443
20-30 years	127 (24.2)	277 (26.4)	
31-40 years	251 (47.8)	457 (43.5)	
41-50 years	112 (21.3)	237 (22.6)	
51-60 years	35 (6.7)	79 (7.5)	
Parent's relationship			0.022
No	336 (64.2)	611 (58.2)	
Yes	188 (35.8)	439 (41.8)	
Parental economic status			0.003
Poor	79 (15.0)	180 (17.1)	
Moderate	277 (52.8)	617 (58.8)	
High	169 (32.2)	253 (24.1)	
Marital status			<0.001
Married	354 (67.4)	834 (79.4)	
Single	171 (32.6)	216 (20.6)	
Ethnic group			0.002
Fars	450 (85.7)	832 (79.2)	
Others	75 (14.3)	218 (20.8)	
Level of education			<0.001
Up to diploma	246 (46.9)	629 (59.9)	
College	279 (53.1)	421 (40.1)	
Job status			
Housemaker/unemployed	348 (66.3)	701 (66.8)	0.795
Employed	90 (17.1)	167 (15.9)	
Self-employed	87 (16.6)	182 (17.3)	
Sun exposure			<0.001
Seldom	61 (11.6)	15 (1.4)	
Often	365 (79.5)	766 (73.0)	
Most the time	99 (18.9)	269 (25.6)	
Breastfed during childhood			<0.001
Never	83 (15.8)	126 (12.0)	
<4 months	14 (2.7)	12 (1.1)	
More	393 (74.9)	887 (84.5)	
Can't remember	35 (6.7)	25 (2.4)	
Body composition (13-19 years old)			
Thin	233 (44.4)	569 (54.2)	0.001
Normal	220 (41.9)	375 (35.7)	
Overweight/obese	72 (13.7)	106 (10.1)	
Physically active			<0.001
No	252 (48.0)	335 (31.9)	
Yes	273 (52.0)	715 (68.1)	

Table 1: Continued….

History of regular cigarette smoking			0.031
No	488 (93.0)	1004 (95.6)	
Yes	37 (7.0)	46 (4.4)	
History of passive smoking			<0.001
No	249 (47.4)	726 (69.1)	
Yes	276 (52.6)	324 (30.9)	
History of drug abuse			0.012
No	433 (82.5)	916 (87.2)	
Yes	92 (17.5)	134 (12.8)	
Experienced highly stressful event(s)			<0.001
No	239 (45.5)	642 (61.1)	
Yes	286 (54.5)	408 (38.9)	
History of other autoimmune disease(s)[2] and migraine			<0.001
No	229 (43.6)	944 (89.9)	
Yes	296 (56.4)	106 (10.1)	
Familial history[3] of multiple sclerosis			< 0.001
No	485 (92.4)	1041 (99.1)	
Yes	40 (7.6)	9 (0.9)	
Familial history of other autoimmune disease(s)[2] and migraine			<0.001
No	375 (71.4)	868 (82.7)	
Yes	150 (28.6)	182 (17.3)	
History of asthma/allergy			<0.001
No	299 (57.0)	707 (67.3)	
Yes	226 (43.0)	343 (32.7)	
History of head/neck traumas			<0.001
No	432 (82.3)	1031 (98.2)	
Yes	93 (17.7)	19 (1.8)	
History of blood and blood products transfusion			
No	504 (96.0)	1043 (99.3)	<0.001
Yes	21 (4.0)	7 (0.7)	
History of tonsillectomy (before age 20)			
No	469 (89.3)	1009 (96.1)	<0.001
Yes	56 (10.7)	41 (3.9)	
Age; mean (SD)	36.3 (8.2)	36.3 (8.7)	0.990
Number of siblings; mean (SD)	3.7 (2.1)	4.8 (2.5)	<0.001
Birth order; mean (SD)	2.8 (1.9)	3.4 (2.2)	<0.001
Sleep quality; mean (SD)	8.1 (3.7)	9.1 (3.0)	<0.001

1 Based on Chi-square test and independent t-test.
2 Other autoimmune disease(s) including inflammatory bowel disease, systemic lupus. erythematosus, rheumatoid arthritis and myasthenia gravis
3 Familial history (father, mother, sons, daughters, brothers and sisters)

According to the results of multivariate analysis (Table 2), college-educated individuals seemed to have higher odds of developing MS ($OR_{\text{university degree/lower}}$=1.83; 95%CI=1.37 to 2.43). Controls tended to be more physically active than those with MS during adolescence ($OR_{\text{active/inactive}}$=0.45; 95%CI=0.33 to 0.60). We also observed that cases reported more history of cigarette smoking ($OR_{\text{regular/other}}$=2.24; 95%CI=1.22 to 4.07) and history of passive smoking ($OR_{\text{yes/no}}$=2.16, 95%CI=1.62 to 2.87). Moreover, individuals with a history of longer exposure to the sun had significantly lower odds of developing MS ($OR_{\text{most the time/seldom}}$ =0.14; 95%CI=0.07 to 0.30). Similarly, birth order (OR=0.89; 95%CI=0.82 to 0.95) and good quality of sleep (OR=0.93; 95%CI=0.89 to 0.96) were inversely associated with MS. On the other hand, experiencing a highly stressful event(s) ($OR_{\text{yes/no}}$ =1.47; 95%CI=1.11 to 1.96) confers as a risk factor.

Table 2: Adjusted associations of the study variables and multiple sclerosis in Fars Province, Iran

Variables	*Adjusted OR (95% CI)*	*P-value*
History of other autoimmune disease(s)**		
No	Ref*	
Yes	15.67 (11.45, 21.66)	<0.001
Familial history*** of multiple sclerosis		
No	Ref	
Yes	11.57 (4.82, 30.05)	<0.001
History of head/neck traumas		
No	Ref	
Yes	9.16 (5.13, 16.99)	<0.001
Sun exposure		
Seldom	Ref	
Often	0.12 (0.06, 0.24)	<0.001
Most the time	0.14 (0.07, 0.30)	<0.001
Familial history*** of other autoimmune disease(s)**		
No	Ref	
Yes	2.63 (1.89, 3.67)	<0.001
History of regular cigarette smoking		
No	Ref	
Yes	2.24 (1.22, 4.07)	0.008
History of passive smoking		
No	Ref	
Yes	2.16 (1.62, 2.87)	<0.001
Physically active		
No	Ref	
Yes	0.45 (0.33, 0.60)	<0.001
Level of education		
Up to Diploma	Ref	
College	1.83 (1.37, 2.43)	<0.001
Experienced highly stressful event(s)		
No	Ref	
Yes	1.47 (1.11, 1.96)	0.007
Birth order	0.89 (0.82, 0.95)	0.001
Sleep quality	0.93 (0.89, 0.96)	<0.001

* Reference group

** Other autoimmune disease(s) included inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis and myasthenia gravis.

*** Familial history (father, mother, sons, daughters, brothers and sisters)

The full model included parental relationship, number of siblings, breastfed during childhood, parental economic status, job, marital status, body composition, history of drug abuse, history of asthma/allergy, history of blood and blood products transfusion, and history of tonsillectomy as well as final model variables

Regarding medical history of the participants, MS cases had significantly more autoimmune disease(s) and migraine ($OR_{yes/no}$ =15.67; 95%CI=11.45 to 21.66), family history of MS ($OR_{yes/no}$ =11.57; 95%CI=4.82 to 30.05), and family history of other autoimmune disease(s) and migraine ($OR_{yes/no}$ =2.63; 95%CI=1.89 to 3.67). Moreover, individuals with a history of

head/neck trauma had significantly higher odds of developing MS ($OR_{yes/no}$ =9.16; 95%CI=5.13 to 16.99). No significant interaction was observed between the variables included in the final model and the risk of MS.

Discussion

In this case–control study, we revealed that in addition to several environmental exposures, higher education, and lower birth order were associated with increased odds of MS. These factors were rarely studied or did not attain statistical significance in other previously published works (10, 11). Education as a representative of social class, whilst many diseases are associated with low SES, MS, and a few other sets of conditions, are directly linked to high social class (12).

In line with the results of other studies (13-15), active and passive smoking are associated with MS. There are however, few studies, which could not show any type of association between MS and active, and/or passive exposure to tobacco smoke. Some of these studies were subject to methodological issues such as small sample size (10) or overmatching of the smoking behaviors among siblings (16). Furthermore, experimental data suggested that cigarette smoking may play an important role in the development of MS (17). The risk of MS is dose-response makes the association more meaningful. In addition, some believe that the effect of tobacco smoke on MS may depend on genetic background and genetic compositions across different populations (18). For example, smoking is a well-established risk factor for MS in the Caucasian population (19).

Our study suggested that physical activity at younger ages poses a protective effect on MS. The result seems expected as MS is a chronic neurological condition and physical activity seems to play preventive roles in diabetes and depression, two conditions that are associated with several disorders of the nervous system. Physical activity, via affecting visceral adiposity, improving insulin sensitivity, and reducing glucose tolerance plays a key role in reducing inflammation and can act as a beneficial rehabilitation strategy for MS patients to manage the symptoms (20).

Here, we suggested that longer sunlight exposure during adolescence is a powerful protective factor for MS. The association was also seen in other studies (15, 19). With regard to MS, sun exposure has also received great attention as researchers observe geographical and latitude dependency of the spatial distribution and MS incidence (21).

In the present study, familial history of MS and personal/familial history of other autoimmune diseases and migraine were significantly and independently associated with MS. Based on the current literature, both history of MS and other autoimmune diseases among family members is an important risk factor for MS (10, 13, 21). This finding supports the auto-immune nature of MS (22).

Our study also revealed that individuals with a history of head/neck traumas have significantly higher odds of developing MS. An alteration in the blood-brain barrier (BBB) may result in increased BBB permeability and trauma. Particularly mild concussive injury to the head, neck, or upper back may lead to the formation of new lesions or the enlargement and activation of old lesions, those steps that are revealed in the pathogenesis of MS (23).

We reported that those with sleep disorders have a higher risk of MS when compared to those without such a condition. Very few studies investigated this association. A case–control study in Sweden uncovered the association between shift work and increased risk of MS (24). In addition, the oxidative stress induced by sleep deprivation has been related to be associated with the presence of MS acute relapses, exerting a toxic effect on oligodendrocytes (25). The evidence supporting the role of sleep quality in some oligodendrocyte functions (including myelination, and the proliferation of new immature oligodendrocytes) suggests that sleep alterations could influence patients' prognosis with regard to MS. Sleep disorder also might share a common pathophysiologic pathway with MS (primary) or be secondary to MS-related symptoms such as pain, muscle cramps, and nocturia (26). However, in recent

years, strong recommendations to improve the quality of sleep have emerged from several studies demonstrating that sleep quality is key to preserving anatomical and functional integrity of the brain and other organs (27). Overall, most published reports on sleep quality and circadian disruption in MS patients are descriptive in nature and cannot approve a causal link between sleep disruption and the pathogenesis of MS. Therefore, more research is needed to gain a deeper understanding of the effects of sleep disorder and its underlying mechanisms in the pathology of MS.

Our study suggested that the experience of stressful event(s) poses adverse effects on MS development. This is in line with mounting evidence suggesting that stress adversely affects many diseases, especially autoimmune and inflammatory disorders, such as MS (28). One of the proposed possible mechanisms to define the role of stress in MS is that stress activates the hypothalamic–pituitary–adrenal (HPA) axis through the hypothalamic secretion of corticotrophin-releasing hormone (CRH). This will normally suppress immune responses through the release of glucocorticoids from the adrenals (29). In this context, MS is worsened by stress possibly due to a dysfunctional HPA axis because of reduced production of adrenal steroids (30).

Our study has some noticeable strengths. First, using a relatively large sample size; second, although we can't rule out the existence of some selection bias, the study is a hospital-based case-control study and the participation rate was astonishingly high, reducing the possibility of non-response bias. Third, all variables were assessed prior to the date of the first symptom reducing the possibility of reverse causation. However, our work comes with several limitations. It is important to consider the inherent limitations of our study design varying from recall selection bias, and misclassification due to self-reported information. We revised a previously used questionnaire evaluated for bias in retrospectively reported data among cases and controls comparing reported and recorded data. Moreover, based on the nature of the study variables (mostly objective or easily memorable) and the disease (with low mortality), it is unlikely that recall or selection bias fully explains the observed strong associations.

Conclusion

We revealed a significant number of factors associated with MS in a Middle-Eastern region. We introduced (supported) that low sun exposure during adolescence, active and passive smoking, lower birth order, a higher education level, sedentary lifestyle, familial history of MS, personal/familial history of other autoimmune diseases and migraine, history of head/neck trauma, improper sleep quality, and stressful events may increase the risk of MS later in life. Preventing these exposures through educational programs is likely to help in reducing the risk of MS. Future studies, although logistically and methodologically challenging, especially large-scale prospective studies are recommended to clarify the causality of the reported behavioral and environmental factors associated with MS.

Journalism Ethics 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.

Acknowledgements

This work was supported by the Research Council of Shiraz University of Medical Sciences, Shiraz, Iran (Grant Number: 97-01-04-19050).

We would like to thank all of the neurologists, physicians, and study participants for their valuable cooperation in our study.

Conflict of interest

The authors declare that there is no conflict of interest.

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