



Clinical Study

Risk factors for increased multiple sclerosis susceptibility in the Iranian population

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ABSTRACT

Multiple sclerosis (MS) is a complex autoimmune disease with increasing prevalence. Many factors have been assessed in relation to its development and its worldwide geographical and racial distribution. Therefore, we decided to conduct a nationwide case-control matched study to estimate the possible influence of putative risk factors on MS status in an Iranian MS population. Between January 2008 and September 2013, 1403 patients diagnosed with MS according to the Poser or McDonald criteria and 883 controls were studied. Of all patients, there were 921 women and 296 men (ratio 3.1:1) with a mean age of 32.6 ± 8.7 years. In the multivariate model adjusted for sex and age (± 2 years), we found associated risk factors of MS to be: history of any allergic condition (Odds ratio (OR): 1.92, 95% Confidence interval (CI): 1.55–2.47, $p < 0.001$), and smoking (OR: 1.93, 95% CI: 1.31–2.73, $p < 0.001$). Sunlight exposure ≥ 3 hours was found to be associated with a reduced risk of MS (OR: 0.23, 95% CI: 0.15–0.31, $p < 0.001$). As expected, cases were more likely to have a positive family history of MS than controls (OR: 1.91, 95% CI: 1.33–2.75, $p < 0.001$). A significant association was found between family history of other autoimmune diseases and MS risk (OR: 1.57, 95% CI: 1.18–2.09, $p = 0.002$). These results support the hypothesis that sun exposure is associated with a decreased risk of MS while smoking, autoimmune family history, MS family history, and personal allergy history are risk factors for MS susceptibility.

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1. Introduction

Multiple sclerosis (MS), an autoimmune inflammatory demyelinating disease of the central nervous system, was clinically described at the beginning of the 19th century [1]. MS is hypothesized to be a complex disorder that is unlikely to result from a single causative event; it is believed that several environmental factors act simultaneously on a genetically susceptible individual to cause the disease [2]. Among the non-genetic factors, lack of sunlight exposure (mediating vitamin D synthesis), exposure to infectious agents, smoking, immunization, hormonal factors, nutritional habits, and psychological stress are the most frequently reported risk factors involved in the etiology of MS [3].

There are variable patterns of MS incidence and prevalence in different ethnic and geographical regions [4]. Despite these

variations, there is a general rise in incidence of the disease in regions closer to the equator [5]. According to the Kurtzke classification, Iran has been traditionally considered as an area with a low prevalence of MS, and located in a low-risk zone for MS [6]. However, previous studies on the prevalence of MS in Iran have revealed different results and reported higher and increasing rates, especially in large cities [7,8]. This remarkable rise puts Iran amongst the regions with the highest prevalence of MS in Asia and Oceania, mostly due to changes in environmental factors [9].

MS is a chronic disease with a significant economic and social burden leading to severe disability and dependence. Therefore, a comprehensive evaluation of risk factors is required, including information from large population studies, to provide a clue to the disease etiology and to design prevention plans. Most of the recent research has evaluated the prevalence of MS in the Iranian population without further assessment of the association between various risk factors and occurrence of MS [7,10,11]. Moreover, previous reports from Iran were confined to certain large cities

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and thus were not representative of all geographical regions and ethnicities in Iran.

To our knowledge, no similar case-control studies including such a large and diverse sample size have been reported in the literature. In light of the scarcity of research on risk factors for MS patients in Iran, this multicenter study was carried out to investigate possible associations between the incidence of MS and individual risk factors and environmental exposures.

2. Methods

2.1. Study design

A large scale case-control analysis of MS was conducted on patients from 27 cities across Iran over a study period of 5 years between January 2008 and September 2013. Iran is a country with the total population of 76 million inhabitants, comprised of many races, several religions and various ethnic backgrounds. It has a subtropical climate and a broad mountain range and desert. It is located in the southwestern region of Asia, between latitudes 24° and 40° North and longitudes 44° and 64° East.

The present study was conducted in compliance with the Declaration of Helsinki [12]. The protocol was approved by the regional committees for research ethics of medical universities, and the entire study protocol was reviewed and approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences. Written informed consent was obtained from all study participants.

2.2. Case definition and ascertainment

Patients, who were being seen for regular follow-up at MS clinics of university affiliated hospitals were approached to participate in the study. The participating patients were required to be aged 15 years or older at the time of their first-ever neurological episode. We included patients with relapsing-remitting, secondary progressive, primary progressive and progressive relapsing MS at different stages of the disease. Overall, 75 patients refused to participate. Finally, 1403 MS patients were included, corresponding to 95% of the initial sample population.

The diagnosis was based on clinical findings, brain and spinal cord MRI results, cerebrospinal fluid (CSF) analysis, sensory evoked potential, and somatosensory evoked potential results. All patients underwent MRI of the brain and/or spinal cord as part of clinical care, including pre- and post intravenous gadolinium scans. Ultimately, only patients with clinically definite MS fulfilling the Poser [13] or McDonald criteria [14] diagnosed by expert neurologists were included. Disability status was defined by the Expanded Disability Status Scale (EDSS) score at the time of recruitment.

2.3. Control definition

Controls were drawn from hospital staff matched on age (± 2 years), sex, and birthplace. The controls had no history of MS or clinical presentation of any neurological or autoimmune disorder and were similar to patients regarding their residential area and ethnicity. Fifty-six subjects refused to participate, thus the control group comprised 883 subjects. Eligible controls were recruited for 63% of patients.

2.4. Covariate assessment

We evaluated environmental and familial risk factors in 1403 MS patients and 883 controls. Information on socio-demographics,

ethnicity, medical history (including allergy history, vaccination, surgical interventions, pregnancy, and traumatic brain injury) and familial history (first-degree relatives) of MS and autoimmune diseases (type 1 diabetes, rheumatic disorders, systemic lupus erythematosus, psoriasis, Graves' disease, Hashimoto's thyroiditis and inflammatory bowel disease) were obtained using a structured questionnaire in a face-to-face interview. In addition, the questionnaire investigated environmental exposures, with items concerning daily sunlight exposure (hour/day) and smoking. Participants were asked about the amount of time they would typically have spent in the sun per day over their lifetime prior to onset of MS. Smokers were defined as patients who were smokers prior to disease onset; individuals who had quit smoking or who had never smoked were considered as non-smokers. With respect to allergy history, the patients and controls were questioned about reactions to various allergens (foods, drugs, pollens, house dust, animal dander, other) or relevant clinical manifestations (conjunctivitis, rhinitis, urticaria, asthma, other). The definition of traumatic brain injury included head trauma severe enough to cause skull fracture, loss of consciousness, or post-traumatic amnesia within a 1 year period prior to onset of MS.

Other relevant information collected and considered in the analysis included first neurological episode compatible with MS disease (time of onset), CSF investigations, MRI and neurophysiologic assessments confirmed by review of medical records.

The standardized questionnaire was carried out by two neurologists. The interviewers were not aware of the study purpose or design. A similar questionnaire was utilized for both patients and controls in the same method in order to prevent interview bias. Exposure to environmental risk factors refers to the time before disease onset in MS patients and during a similar time period in controls.

2.5. Statistical analysis

Adjusted odds ratio (OR) associated with each potential risk factor and the 95% confidence interval (CI) were calculated. To test the association, binomial logistic regression analysis was utilized by applying MS as the dependent variable and the environmental, personal, or familial variables as the predictors, both adjusted for age, sex, ethnicity, city of residence, educational level and adjusted for all other risk factors (overall adjustment). Comparisons of baseline variables between the groups were conducted by two sample Student's *t*-test or chi-squared test, as appropriate.

All *p* values were based on two-tailed tests. We considered a probability value ≤ 0.05 to be statistically significant. Data were analyzed using the Statistical Package for the Social Sciences (SPSS Inc., version 22.0, Chicago, IL, USA).

3. Results

Overall, 95% of eligible MS patients and 94% of eligible healthy controls agreed to participate in the study. One hundred and eighty-six MS patients and 96 controls were excluded because of missing risk factor information. All MS patients fulfilled the McDonald criteria and more than 90% of the diagnoses were supported by positive MRI results. There were no significant differences between patients and controls with respect to age, sex, ethnicity, and educational level. Socio-demographic and clinical features are shown in Table 1. Among MS patients, there were 921 women and 296 men (ratio 3.1:1) with a mean age of 32.6 years \pm standard deviation [SD] 8.7 years (range 15–59). The mean age at onset was 26.3 \pm SD 7.9 years and the mean duration from the initial appearance of symptoms indicative of MS to the diagnosis was 2.8 \pm SD 1.4 years. Most of the included patients

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