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Der Pharmacia Lettre, 2017, 9 (3):31-39
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Multiple Sclerosis in South Iran: Prevalence and Risk Factors

Susan Sabbagh¹, Maryam Radmehr^{2*}, Hamed Sanjary H³, Mahin Nosratzahi⁴

¹Assistant professor, Department of Anatomical Sciences, Faculty of Medicine, Dezful University of Medical Sciences, Dezful, IR Iran.

²Assistant professor, Nursing and Midwifery Faculty, Dezful Branch, Islamic Azad University, Dezful, IR Iran.

³Medical student, Isfahan University of Medical Sciences, Isfahan, IR Iran

⁴Internist, Zahedan University of Medical Sciences, Zahedan, Iran

*Corresponding author: Maryam Radmehr, Assistant Professor, Nursing and Midwifery Faculty, Dezful Branch, Islamic Azad University, Dezful, IR, Iran, Email: derranneh2005@yahoo.com

Background: Multiple sclerosis (M.S) is the most common cause of neurological disability in young adults but its etiology is still unknown. It occurs due to a combination of both genetic and environmental factors. The objective was to determine the prevalence of M.S in the northern cities of Khuzestan (Iran) and its relation to familial history, smoking, the month of onset, stress, and immigration.

Patient and methods: This study is a one-step descriptive correlation analysis. Data were collected through a questionnaire completed in a face to face conversation setting and further analyzed using SPSS 17 software package. Statistical significance was determined by chi-square test ($p < 0.05$).

Results: The sample size in this study was 142. Prevalence of M.S in the north of Khuzestan in Iran were 15 per 100,000 people. 11% of patients had a positive familial history of M.S. There was a statistically significant correlation between sex and positive family history ($p = 0.03$) and it was higher in men. Familial MS was higher in siblings than parents or children. 93% of patients were non-smoker, beginning of disease in 37.2% of cases was in summer and 70% of patients had no history of immigration. In 68% of patients, the onset of M.S. co-occurs with stress and there was a statistically significant relationship between stress and symptoms at onset.

Conclusion: In recent years, increasing rate of M.S. was observed. The incidence of M.S in men with positive familial history was higher than in women; paternal positive history was four times higher than maternal ones. Further studies are needed to clarify the underlying genetic or environmental factors that explain this association. Extensive research is also required to investigate the possibility of a relationship between stress and disease.

BACKGROUND

M.S. is an inflammatory and autoimmune disorder of the central nervous system, potentially the most common cause of neurological disability in young adults and with the risk of one in 400[1]. Each year, an estimated 2.5 million people are affected worldwide [2].

The incidence of M.S. is raising worldwide, the highest incidence and prevalence reported in Europe and North America [3,4]. The incidence of M.S. in the United Kingdom is 7.2/1,00, 000 in women and 3.1/1,00,000 in men [5]. The prevalence of multiple sclerosis (MS) in Japan was 8.6/100,000 individuals in 2001[6] and in the other countries of Asia, equatorial areas of Africa and the Middle East is low or moderate [7]. The prevalence of MS in Tehran is estimated to be at least 51.9 per 100,000 and it seems that M.S. incidence has reached a medium-to-high risk level in Iran [8]. Disease onset usually occurs in young adults, more commonly in females. It begins between the ages of 20 - 35 years, but can also rarely appear in children and elderly [7]. Multiple sclerosis has a complex etiology and causes are still unknown. Researchers believe that M.S. is a multifactorial disorder, in which environmental factors are hypothesized to interact with genetically susceptible individuals [9]. Many of the known M.S. risk factors are genetic, with particular HLA patterns; and many genes have been identified for predisposition to the disease or severity level within diagnosed populations [10]. These genetic elements account for the higher disease risk in first-degree relatives of people with M.S. [11]. However, many researchers believe that environmental factors such as vitamin D deficiency, obesity, cigarette smoking are also major risk elements [12-14]. In addition, there are reports for associated factors such as severe stress, nutrition, war participation, chemical agents, hormones, head injury, household animals, women with multiple pregnancies, but such results need more investigations worldwide [12,15-17]. Some researchers also believe that immigration from a high-risk to low-risk area after the age of 15 years might be a risk factor of M.S [18]. A case-control study by Yousefi Pour et al. (2002) showed that physical trauma, surgery stress, psycho-behavioral stress, and childbirth may each have cumulative effects on the rate of occurrence of M.S. [19].

Although the reasons why the incidence of the disease is increasing are unknown, there are major implications for health care provision, because lifetime costs of multiple sclerosis exceed £1-2 billion per case in the U.K [20]. It should be noted that the possible risk factors were mostly studied in areas with low prevalence [21]. With respect to different incidence and prevalence pattern of M.S. in various regions of Iran, it is necessary to conduct broad investigations to find out the high-risk places and potential environmental susceptibility factors. A broad and epidemiological study on M.S. will help to determine the high-risk places and recognize the susceptible environmental factors as well as identify the preventive aspects of multiple sclerosis [22].

OBJECTIVES

The purpose of this study was to determine the prevalence of multiple sclerosis in north cities of Khuzestan in Iran and to examine the correlation of positive family history, cigarette smoking, immigration, the month of onset and stress with the occurrence of the disease.

PATIENT AND METHOD

This study is a one-step descriptive correlation. This study was conducted in a total of seven northern cities of Khuzestan Province located in the southwest of Iran. Cases were obtained from neurology clinics, registration records of the M.S. society, and neurology departments of the general hospitals in north cities of Khuzestan. Data were collected by completing a questionnaire face to face. Demographic data include age, sex, date of birth, the number of siblings and children, home address, and smoking status. Clinical information was recorded by a trained general practitioner through an interview with the patient. Data analysis was done using the Statistical Package for Social Sciences, (SPSS 17.0, SPSS Production Facility, Chicago, Illinois, USA). Chi-Square and independent t-test were used for data analysis.

ETHICS

All information about objects of research and confidential identity of patients was given to them and informed consent letter was signed by each patient. To prevent duplications of the data, each patient was assigned a unique ID number. In all stages of the study, the last version of the declaration of Helsinki was followed by the researcher, and the institutional ethics committee approved the use of the clinical information (Code 79/a, date 2012.14.4).

RESULTS

Overall, we found 142 patients with M.S. disorder in the seven cities under investigation of the north of Khuzestan province in Iran, namely, Dezful, Andimeshk, Shush, Shushtar, Masjedsoleiman, Lali, and Gutevand. According to the information obtained, the estimated population of these towns was 957133. The prevalence of multiple sclerosis was thus approximately 15 per 100,000. Data showed that the number of female patients was 96 (67/6%) whereas the number of male patients was 46 (32/4%), and female / male ratio was 2/08:1. Mean age (S.D.) of patients was $33/4 \pm 9/4$ and 70% of them are 20-39 years old. Mean age of patients of both sexes was equal. Almost half of the patients belonged to crowded families with more than 6 children. 11% of patients had a positive familial history of multiple sclerosis which was more common in the male group than women (Figure 1) and there was a statistically significant correlation between sex and positive family history ($p=0/03$) (Table 1).

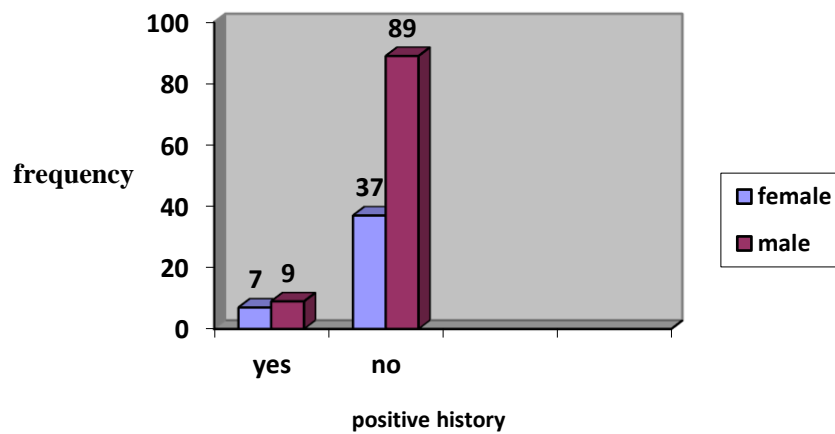


Figure1: Positive Family History in Both Sexes

Table 1: Relationship Between Sex and Family History By Chi- Square Test

	value	df	Asymp.sig(2 sided)
Pearson chi- square	4.686	1	0.03
No. of valid cases	142		

All the patients with positive family history had patients in first-degree relatives; 56.3% had at least one patient in their first-degree relatives, 43.7% had two affected persons and the father was not alone affected. Also, more than 70 percent of the patients had a family history of the disease in siblings than their parents (Table 2). 8% of all patients (68.8% of patients with positive family history), in addition to the history of M.S. in first-degree relatives, had a positive history in second-degree relatives; and this rate was 4 times higher in paternal family compared to maternal ones (Table 3). The findings showed that patients were in different offspring grades and most of the patients with positive family history were fifth offspring or more than this.

93% of patients were non-smokers, 60% of smokers were men and 70% of patients had at least one smoker in their family. Also, our findings showed that the season of onset of M.S. was reported to be summer in 37.2% and winter in 19.7% of cases. In addition, 70% of patients had no history of immigration while 16% showed the history of immigration before an age of 16 and 14% after that. However, the correlation between immigration and age of onset is not statistically significant.

Almost in 68% of M.S. patients, the onset of disease was correlated with stress and 72% of these cases were women (Figure 2). According to the Social Readjustment Rating Scale (SRRS), Holmes and Rahe Stress Scale [23], in 90% of the patients the rate of stress at onset was below 100. In this study, statistically significant correlation was observed between stress and symptoms of M.S. at onset; e.g. main symptom in the first attack was

paresthesia($p=0.008$) and visual impairment ($p=0.003$), but no significant relationship was observed between stress and age of onset.

DISCUSSION

The prevalence of disease in the state of Khuzestan, the southwest of Iran was 15 per 100,000 people and because some cases might not be identified in the study, therefore the prevalence is probably higher estimated. The incidence of M.S. in different population is 1/5-30 per 100,000 people each year, and in some regions, it was reported to be 150-250 [19,21]. Sharafaddinzadeh et al. (2013) reported in a recent study that the prevalence of M.S. in Khuzestan is 18.50 per 100/000 people in [24]. In other studies, in the cities at the center of Iran prevalence of MS was 35/5 per 100/000 people in Isfahan and 20 per 100,000 in the province of Mazandaran in the north of Iran [25,26]. MS is more common in people who live far from equator [27]. Additionally, some researchers reported that decreased sunlight exposure has been linked with a higher risk of M.S. and low intake of vitamin D has been the main biological mechanism used to explain the higher risk among those less exposed to the sun [28-30]. Therefore, it seems that higher risk of M.S. in the center and north than south of Iran (Khuzestan) is reasonable.

Findings of this study showed that 88.7% of patients did not have a positive history of M.S among their families and 11.3% of patients did, 56.3% had one relative with M.S. and 43.7% had two. Although most M.S. cases occur sporadically, a considerable proportion, about 20% of the patients are related by family [31]. Some researchers believe that genetic susceptibility is probably one cause of multiple sclerosis [32,33]. It was suggested that relatives of affected persons have more chance for M.S. In monozygotic and dizygotic twins, the risk of disease in both twins is 35% and 4% respectively. Probably alteration in human antigen leukocyte site of human chromosome of 6, cause a higher risk of disease. The important note here is that environmental factors could influence M.S. risk of monozygotic twins to increase from 100% to 30% [34,35]. Some studies reported about 15-20% of patients have positive family history and its rate in first-degree family relatives is 10-40 folds. In U.S.A., the risk of disease in general population is 0.1% and in children of afflicted persons, it becomes 4% [36]. In Saudi Arabia, familial M.S. has been reported in 21% of M.S. patients [37]. In a study in Isfahan, familial M.S. was found in 11% of patients, 57.7% had a first-degree relative with M.S. and highest rate for familial M.S. was observed in sister-sister relations [38] which are similar to our results. Findings of this study showed that half of the patients had familial M.S. in siblings and 25% of cases had two afflicted persons in their siblings. Also, the incidence of men with positive familial history was higher than women and the positive history in the paternal family was four times greater than the maternal. However, Ale –Yasin et al. (2002) reported that there is no significant difference in the risk of disease between maternal and paternal roots in twins [21]. So, more research is needed, especially in the field of familial and environmental factors and that what different risk factors women have from men other than the genetic.

The present study showed that 93% of patients were non-smokers but 70% had at least one smoker in their family. Pakdaman et al. (2008) reported that only 8.5% of patients were smokers [8]. Schwartz et al. (2013) reported that among 860 patients with multiple sclerosis, 88% were non-smokers [39]. In a case-control study on 100 patients

with M.S. and the same number of patients with acute infection, there was a significant relationship between smoking and incidence of multiple sclerosis. Mikaeloff et al. (2007) observed in a population-based, case-control study that children exposed to smoking parents have a higher M.S. risk [40]. Salzer (2012) reported that the high rate of nicotine in blood is a risk factor in young adults [41]. Although some researchers believed that smoking could increase the risk of multiple sclerosis but there was no clear explanation for it. Therefore, the association between M.S. and smoking remains controversial, so there is a need for more investigation in this area.

Our findings indicated that the onset of M.S. in 37.2% of patients was in summer and only 19% onset was in winter which is the lowest seasonal occurrence. In a study by Damasceno et al. (2012), they found that most exacerbations were in the spring/summer transition, which also showed higher UV radiation index and humidity rate [42]. A study by Meier et al. (2010) showed that disease activity in the M.S. patient was 2-3 times higher in March-August than during the rest of the year and disease intensity was also elevated during the summer season [43]. It seems that seasonal fluctuation with other environmental factors might influence M.S attacks.

In our study, we evaluated the effect of immigration on M.S. 30% of all patients had a history of immigration, about half of which presents disease history before puberty and rest of them have had their immigration after that. 57% of immigrations were inside of province and 43% were out of Khuzestan. Also, there was no significant relationship between immigration and age of onset. It was indicated in some studies that immigration is a risk factor of M.S., so that change of living place (especially from high-risk regions), could influence the rate of M.S. occurrence and the immigrant below 15 may obtain his native characteristics [18,44]. Ascherio (2007) believed that immigration in low age from one area to another place could be a risk factor of M.S. [45]. In this study, 43% of migrations were out of the province and sporadically from Isfahan, Tehran, Ilam, Hamadan, Nishapur, Yazd and Lorestan. Isfahan and Semnan are the most high-risk provinces in Iran [21,25]. Our analysis was not without potential confounders, although findings showed that the sex ratio in MS is varied and recent studies imply that the female/male ratio is decreasing, which needs more studies to access the role of environmental factors [46]. The other finding of this study was the negative role of socio-economics variables.

Our study showed that the onset of 68% of patients was with stress and 90% of them level of stress was below 100. Additionally, there was a statistically significant correlation between stress and signs at onset, considering that in these patients the first symptoms were sensory disorders and visual impairment. In some chronic diseases, the critical point of stress is higher than 300 [23]. In spite of little evidence, severe stress is one of the risk factors of M.S per Marrie [27]. Networks are Medias which apply toward teaching of courses, and for improvement of educational performances of students [47]. One objective of educational planner is to assess the learner specific issues, successful education, and assurance of physical and intellectual health [35]. Patients, their families, and significant others are important for collaborating with physicians, health care providers, health educators [48]. The results of a study by Yousefipour et al. (2002) showed there was a statistically significant correlation between the onset of M.S. and severe anxiety [49]. This study was associated with several limitations as follows: an accurate

number of patients were difficult to obtain because some of the patients follow their treatment in other states but it seems that the number of these patients are insignificant.

CONCLUSION

Higher incidence of M.S. in men with positive familial history rather than women was a novel finding of present study so that paternal positive history was four-fold greater than maternal ones. These findings were not reported in any earlier study and, could be important for the explanation of genetic factors in the etiology of M.S. Further studies are needed to clarify the underlying genetic or environmental factors that explain this association. Moreover, our data indicated that a single estimate of the absolute excess risk was applicable to all first-degree relatives of M.S. patients. Upon confirmation in other settings, this may be of clinical relevance.

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