Research Article

Frequency of Multiple Sclerosis (MS) Among Relatives of MS Patients in Hamadan Society, Iran

Mehrdokht Mazdeh,[1] Mojtaba Khazaei,[1,*] Nasrin Hashemi-Firouzi,[2] and Masoud Ghiasian[1]

[1]Department of Neurology, Hamadan University of Medical Sciences, Hamadan, IR Iran
[2]Neurophysiology Research Center, Hamadan University of Medical Sciences, Hamadan, IR Iran

[*]*Corresponding author*: Mojtaba Khazaei, Department of Neurology, Hamadan University of Medical Sciences, Hamadan, IR Iran. Tel: +98-8118380315, Fax: +98-08138276010, E-mail: Khazaeimojtaba@yahoo.com

Abstract

Background: Multiple sclerosis (MS) is a chronic inflammatory demyelinating and neurodegenerative disease of the central nervous system with unknown causes. In the last decade, the prevalence of MS in Iran has increased.

Objectives: This study evaluated the frequency of familial MS among patients in the Hamadan society for MS.

Patients and Methods: This cross-sectional study was performed on 1202 MS patients in Farshchian hospital, Hamadan, in 2013. All patients were diagnosed with definite MS. A questionnaire was used to gather information; demographic characteristics, medical history, signs and symptoms at onset, course of disease, relatives with MS, and degree and type of relationship were recorded.

Results: The mean age of the patients with familial MS was 28 ± 10.4 years, with higher rates among women (the female to male ratio was 3.2 : 1). Familial MS was found in 8.65% of the patients, and 58.58% of those patients had a first-degree relative with MS. The highest rate for familial MS was observed in sister-sister relations and brother-sister relation. The MS risk changed from 57.69% in first-degree relatives to 35.57% in second-degree relatives and 6.73% in third-degree relatives.

Conclusions: There has been an increase in the rate of the disease in Hamadan province in recent years. It was found that there are lower rates of familial prevalence relative to this sample being studied in Hamadan society. The familial MS is more common among sisters. Further studies on the MS patients in Hamadan will be needed for a better assessment of familial and environmental factors.

Keywords: Multiple Sclerosis, Heredity, Prevalence, Hamadan

1. Background

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) (1). Over two million people suffer from MS across the world (2). It is a heterogeneous disease that is clinically characterized by an extensive variety of neurological symptoms and signs scattered in time and space (3). The separate areas are recognized as inflammation, demyelination, axonal loss, and gliosis (plaques) in the CNS (4). Different factors, such as autoimmune mechanisms, genetic background (5-7), and environmental factors (8-11), have been known to play roles in the occurrence of MS even though the main etiology of this disease is unidentified.

In 2013, the world health organization (WHO) reported that 2.3 million people suffer from MS worldwide (12). Multiple sclerosis has a complex etiology in different geographical regions, occurring between 2 and 150 times per 100,000 people. Kurtzke et al. (13) classified geographical areas into three regions by prevalence: (a) high (> 30 per 100,000), (b) intermediate (5 - 25 per 100,000), and (c) low risk (< 5 per 100,000) (13). For Europe, an increased prevalence of MS was reported, placing it as higher-risk (14). Asia, and many parts of the non-Western world, lies in the low frequency area (15). MS prevalence among Arabs was reported to be between 4 and 8 per 100,000 (16).

There is a wide variation in the prevalence of MS, from 5.3 to 74.28 per 100,000, in different regions of Iran (17-20). However, it has been shown that there has been an increase in the prevalence of MS between 2008 (1) and 2013 (5, 12, 21, 22). It has also been reported that 5% - 13% of MS patients have an affected relative (23-27). This risk is higher in siblings than for parents or children. There are higher clinical concordance rates in monozygotic pairs than in dizygotic pairs (25% vs. 5%) (28, 29). The escalation in MS rates has occurred relatively rapidly over the past century. Higher rates of MS in families may be indicating environmental or genetic-environmental factors due to relatives sharing similar genetics and environmental conditions (30).

Hamadan is located in the west of Iran and is not close to the equator. Hamadan has a cool and dry climate, being in a mainly mountainous region. Hamadan city had a total population of 1,800,000 in 2006. In Hamadan, the vul-

nerability of individuals has enhanced (31, 32). This city is considered to be a low-prevalence region in international classification (33). However, a recent study showed a prevalence of 61 per 100,000 in Iran, which is indicative of an increasing prevalence (20).

2. Objectives

There is little evidence for the risk of MS prevalence in Hamadan province being affected by environmental or familial factors. The aim of this study was to investigate the prevalence of MS among patients' families.

3. Patients and Methods

3.1. Patients

A cross-sectional study was performed on MS patients registered in Hamadan society. A total of 1202 MS patients from Farshchian hospital, Hamadan, Iran (914 females and 288 males, with a mean age of 28 years and an age range of 18 - 40 years) were collected in 2015. Patients reporting MS in their first-, second-, or third-degree relatives were selected. A person's first-degree relative is a parent, sibling, or child, who shares about half of their genes. A person's second-degree relative is an uncle, aunt, nephew, niece, grandparent, grandchild, or half-sibling, who shares approximately one quarter of their genes with the person. A person's third-degree relative is a first cousin, great-grandparent, or great-grandchild, who shares about one eighth of their genes with the person (34, 35).

The diagnosis of MS was made according to the McDonald criteria with lumbar puncture (LP) and cerebrospinal fluid (CSF) analysis plus magnetic resonance imaging (MRI) twice. A questionnaire was also used to gather information. The study was approved by the ethics committee of Hamadan University of Medical Sciences, Hamadan, Iran, and was conducted in accordance with the declaration of Helsinki (36).

3.2. Data Analysis

SPSS software (version 15) was used for analysis. The results were reported as descriptive indices, such as frequency (percentage), numbers, and mean ± standard deviation.

4. Results

The prevalence of MS was 61 patients per 100,000 persons in Hamadan. Familial MS was found in 8.65% of the subjects. From 1202 patients with MS, 103 had a positive family history. The study examined 1202 subjects (839 females and 363 males) with a mean age of 28 years and age range of 18 - 40 years (28 ± 10.4). Forty-four patients involved the familial recurrence rate of disease.

Table 1 shows the number and percentages of families with patients of MS. In 101 patients with familial MS, 8.08% had only one first-, second-, or third-degree relative with MS. Among the patients with familial MS, 23.76% were male and 76.23% were female, with a ratio of 1:3.2. From 60 cases with first-degree familial MS, the rates of incidence were as follows: sister-sister (60%), sister-brother (26.66%), and child-parent (3.33%). The familial risk reduced from 57.69% in first-degree to 35.57% in second-degree relations, which include cousin-aunt, uncle-aunt, and nephew-niece relationships. It dropped to 6.73% in third-degree relatives (cousins).

Table 1. Incidence Risks for Multiple Sclerosis in Families

Families	Number	Percent
Degree of relationship		
First	60	57.69
Second	37	35.57
Third	7	6.73
Type of relationship		
Sister-sister	34	34.61
Sister-brother	16	15.34
Brother-brother	2	1.92
Daughter-mother	2	1.92
Son-mother	2	1.92
Daughter-father	2	1.92

Table 2 presents the characteristics of patients with familial MS. 41% and 31% of the patients showed the symptoms of visual and sensory dysfunctions, respectively, which were at the onset in related patients. The patients suffer from motor disability and sensory impairment (40% and 35%, respectively) as well as visual symptoms reduced to 14%.

5. Discussion

The prevalence of MS in Hamadan province's area, west Iran, was determined to be 61. This revealed that Hamadan province is a high-risk area. Also, the prevalence of familial MS was 8.65% in MS patients. This finding indicated that the incidence rate of familial MS was low in the sample being studied, namely the population in Hamadan society. This result was similar to previous studies where MS

Table 2. Characteristics of Patients With Familial Multiple Sclerosis

Most Common Symptoms	Sensory Disorder	Motor Disorder	Visual Impairment	No Symptoms
At onset in years	31%	19%	41%	0%
At present time	35%	40%	14%	12%

was more common in women than in men (18, 22). In addition, our result confirmed that healthcare and support services have improved compared to past years (including increased numbers of neurologists and MRIs) (12).

Iran is a country with 20.01 - 60 per 100,000, putting it in the medium to high-risk category for MS (12, 33). It should be noted that the prevalence of MS fluctuates from 5.3 to 74 per 100,000 people in different parts of Iran (17). In Isfahan, a central region of Iran, the prevalence of MS is reported to be 43.8 per 100,000 (20). Familial incidence is approximately 11% in Isfahan (37). A prevalence study of MS in east Azerbaijan and north west Iran was determined to be 7,000 with a medium frequency range, and familial MS has been reported to be 7.2% (38). The familial outbreak of MS is varied in countries and geographic areas. In Saudi Arabia, familial MS has been reported in 21% of MS patients (39). There is also an increasing population living longer with MS in the UK (40). In Europe, MS prevalence has a higher rate in northern countries (3, 14). Familial incidence of MS is low in places like Hong Kong (41) and Argentina (42).

The rate of familial MS was higher among sisters and brothers, while children and parents had the lowest percentage; this is consistent with the results of previous studies (3, 10, 32, 43, 44). The risk of autoimmune disease is also higher in first-degree relatives of MS patients (27). Therefore, in accordance with the results of our study, having a sister with MS contributes to the risk of this disease. This study also found that the male to female ratio was 1: 3.2 in familial MS. These are higher rates of males relative to the general population. It has been indicated that MS has a higher frequency in women (8-10, 32, 44, 45). The effects of patient sex on MS prevalence have also been confirmed in previous studies (9, 18, 32, 38, 44-46).

MS is a disabling disorder affecting many people, especially young women (47, 48). It is a CNS disease, which is characterized by multiple regions of demyelization and inflammation along axons with an autoimmune etiology (49). Patients usually develop the first symptoms between the third and fifth decade of life (50, 51). Although the exact cause of the growing incidences of MS is unknown, both genetic and environmental factors are possibilities. The geographic latitude is a remarkable epidemiological cause. In addition, heredity plays a prominent role in the occurrence of the illness in populations (44, 52-54). MS is initi-

ated by environmental factors in persons with genetic-risk profiles (4), and it is the result of an interaction of genetic background and environmental factors (5, 9, 45, 55-57).

It is reported that multiple environmental factors (sunlight/vitamin D3 and metabolism) in conjunction with genetic risk contribute to MS promotion in the molecular mechanism (5, 9, 56-58). Genetics influence the regulation of seasonal vitamin D concentrations in MS twins (10). Measurement of serum levels of vitamin D at the time of diagnosis of MS is critical (32), and vitamin D pathway gene variants to increased risk of MS may be counteracted through appropriate UVB exposure or supplements (9).

Hamadan is located in the west of Iran; it has a cool and dry climate, being in a mountainous region and far from of the equator. Multiple sclerosis is more common in people who live far from the equator (59). Distribution of MS is explained by ultraviolet B radiation exposure (8, 45, 46). MS relates to an interaction between genetic factors and vitamin D deficiency (5, 56, 57, 60). Less exposure to sunlight results in vitamin D production deficiency (61) and low vitamin D levels are a modifiable risk factor (62). The ultraviolet radiation exposure via producing vitamin D exerts a protective effect against developing MS (63). Vitamin D has an immunomodulatory factor in suppressing MS (64). Reduced exposure to sunlight and ultraviolet radiation are causative in this disease (9, 11, 32, 45, 56, 57, 64). Therefore, the higher level of MS risk in Hamadan seems reasonable.

In conclusion, the data from this study showed that the genetic factor is less effective than other factors at predicting MS, and the rate of females relative to the general population is higher in the sample being studied in Hamadan province. Heredity, geographic latitude, and environmental factors resulted in MS pathophysiology. In recent years, increased numbers of neurologists and MRI machines have enhanced health care and support services.

In order to more precisely extrapolate these findings, more studies on MS patients in Hamadan will be needed for a better assessment of familial prevalence and environmental factors.

Acknowledgments

formation of the patients.

Footnotes

References

1. McFarlin DE, McFarland HF. Multiple sclerosis (second of two parts). *N Engl J Med.* 1982;**307**(20):1246–51. doi: 10.1056/NEJM198211113072005. [PubMed: 6290885].

2. Mao P, Reddy PH. Is multiple sclerosis a mitochondrial disease?. *Biochim Biophys Acta.* 2010;**1802**(1):66–79. doi: 10.1016/j.bbadis.2009.07.002. [PubMed: 19607913].

3. Smestad C, Sandvik L, Holmoy T, Harbo HF, Celius EG. Marked differences in prevalence of multiple sclerosis between ethnic groups in Oslo, Norway. *J Neurol.* 2008;**255**(1):49–55. doi: 10.1007/s00415-007-0659-8. [PubMed: 18080855].

4. Compston A, Coles A. Multiple sclerosis. *Lancet.* 2008;**372**(9648):1502–17. doi: 10.1016/S0140-6736(08)61620-7. [PubMed: 18970977].

5. Mkhikian H, Grigorian A, Li CF, Chen HL, Newton B, Zhou RW, et al. Genetics and the environment converge to dysregulate N-glycosylation in multiple sclerosis. *Nat Commun.* 2011;**2**:334. doi: 10.1038/ncomms1333. [PubMed: 21629267].

6. Javan MR, Seyfizadeh N, Aslani S, Farhoodi M, Babaloo Z. Molecular analysis of interleukin-25 exons 1 and 2 and its serum levels in Iranian patients with multiple sclerosis. *Am J Clin Exp Immunol.* 2014;**3**(2):91–6. [PubMed: 25143869].

7. Binzer S, Imrell K, Binzer M, Vang S, Rogvi-Hansen B, Hillert J, et al. Multiple sclerosis in a family on the Faroe Islands. *Acta Neurol Scand.* 2010;**121**(1):16–9. doi: 10.1111/j.1600-0404.2009.01291.x. [PubMed: 19919645].

8. Ramagopalan SV, Handel AE, Giovannoni G, Rutherford Siegel S, Ebers GC, Chaplin G. Relationship of UV exposure to prevalence of multiple sclerosis in England. *Neurology.* 2011;**76**(16):1410–4. doi: 10.1212/WNL.0b013e318216715e. [PubMed: 21502600].

9. Orton SM, Ramagopalan SV, Para AE, Lincoln MR, Handunnetthi L, Chao MJ, et al. Vitamin D metabolic pathway genes and risk of multiple sclerosis in Canadians. *J Neurol Sci.* 2011;**305**(1-2):116–20. doi: 10.1016/j.jns.2011.02.032. [PubMed: 21440908].

10. Orton SM, Morris AP, Herrera BM, Ramagopalan SV, Lincoln MR, Chao MJ, et al. Evidence for genetic regulation of vitamin D status in twins with multiple sclerosis. *Am J Clin Nutr.* 2008;**88**(2):441–7. [PubMed: 18689381].

11. Milo R, Kahana E. Multiple sclerosis: geoepidemiology, genetics and the environment. *Autoimmun Rev.* 2010;**9**(5):A387–94. doi: 10.1016/j.autrev.2009.11.010. [PubMed: 19932200].

12. Browne P, Chandraratna D, Angood C, Tremlett H, Baker C, Taylor BV, et al. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. *Neurology.* 2014;**83**(11):1022–4. doi: 10.1212/WNL.0000000000000768. [PubMed: 25200713].

13. Kurtzke JF. Epidemiologic contributions to multiple sclerosis: an overview. *Neurology.* 1980;**30**(7 Pt 2):61–79. [PubMed: 6993993].

14. Pugliatti M, Rosati G, Carton H, Riise T, Drulovic J, Vecsei L, et al. The epidemiology of multiple sclerosis in Europe. *Eur J Neurol.* 2006;**13**(7):700–22. doi: 10.1111/j.1468-1331.2006.01342.x. [PubMed: 16834700].

15. Mei FJ, Osoegawa M, Ochi H, Minohara M, Nan S, Murai H, et al. Long-term favorable response to interferon beta-1b is linked to cytokine deviation toward the Th2 and Tc2 sides in Japanese patients with multiple sclerosis. *J Neurol Sci.* 2006;**246**(1-2):71–7. doi: 10.1016/j.jns.2006.02.008. [PubMed: 16581087].

16. Pugliatti M, Sotgiu S, Rosati G. The worldwide prevalence of multiple sclerosis. *Clin Neurol Neurosurg.* 2002;**104**(3):182–91. [PubMed: 12127652].

17. Zabihi R, Galehdari H, Shafiee M, Kazeminejad SR, Alavi SM. Analysis of HLA-DQB1*0602 in Multiple Sclerosis Patients in Khuzestan Province, Iran. *Arch Iran Med.* 2015;**18**(10):698–702. doi: 0151810/AIM.0010. [PubMed: 26443252].

18. Tolou-Ghamari Z. Preliminary Study of Differences Between Prevalence of Multiple Sclerosis in Isfahan and its' Rural Provinces. *Arch Neurosci.* 2015;**2**(4).

19. Etemadifar M, Maghzi AH. Sharp increase in the incidence and prevalence of multiple sclerosis in Isfahan, Iran. *Mult Scler.* 2011;**17**(8):1022–7. doi: 10.1177/1352458511401460. [PubMed: 21459809].

20. Etemadifar M, Janghorbani M, Shaygannejad V, Ashtari F. Prevalence of multiple sclerosis in Isfahan, Iran. *Neuroepidemiology.* 2006;**27**(1):39–44. doi: 10.1159/000094235. [PubMed: 16804333].

21. Yousefipour GA, Rasekhi A. Multiple sclerosis: risk factor analysis in Iran. 2002

22. Radmehr M, Meghdadi S, Bahmanzadeh M, Sabbagh S. Prevalence, Demographics and Clinical Characteristics of Multiple Sclerosis in North of Khuzestan Province, Iran. *JJHR.* 2015;**6**(5).

23. Sazdovitch V, Verdier-Taillefer MH, Heinzlef O, Alamowitch S, Roullet E. Familial multiple sclerosis: study of 357 consecutive patients. *Revue neurolog.* 2000;**156**(6-7):638–40.

24. Amela-Peris R, Aladro Y, Conde-Sendin MA, Alemany-Rodriguez MJ, Munoz-Fernandez C, Reyes-Yanez MP, et al. Familial multiple sclerosis in Canary Islands. *Revista de neurologia.* 2003;**39**(10):911–4.

25. Romero-Pinel L, Martinez-Yelamos S, Gubieras L, Matas E, Bau L, Kremenchutzky M, et al. Anticipation of age at onset in familial multiple sclerosis. *Eur J Neurol.* 2010;**17**(4):572–5. doi: 10.1111/j.1468-1331.2009.02870.x. [PubMed: 20002735].

26. Amela-Peris R, Aladro Y, Conde-Sendin MA, Alemany-Rodriguez MJ, Munoz-Fernandez C, Reyes-Yanez MP, et al. [Familial multiple sclerosis in Canary Islands]. *Rev Neurol.* 2004;**39**(10):911–4. [PubMed: 15573304].

27. Laroni A, Calabrese M, Perini P, Albergoni MP, Ranzato F, Tiberio M, et al. Multiple sclerosis and autoimmune diseases: epidemiology and HLA-DR association in North-east Italy. *J Neurol.* 2006;**253**(5):636–9. doi: 10.1007/s00415-006-0084-4. [PubMed: 16502215].

28. Willer CJ, Dyment DA, Risch NJ, Sadovnick AD, Ebers GC, Canadian Collaborative Study G. Twin concordance and sibling recurrence rates in multiple sclerosis. *Proc Natl Acad Sci U S A.* 2003;**100**(22):12877–82. doi: 10.1073/pnas.1932604100. [PubMed: 14569025].

29. Mumford CJ, Wood NW, Kellar-Wood H, Thorpe JW, Miller DH, Compston DA. The British Isles survey of multiple sclerosis in twins. *Neurology.* 1994;**44**(1):11–5. [PubMed: 8290043].

30. Hardy J, Thompson AJ. Dissecting the familial risk of multiple sclerosis. *Ann Neurol.* 2011;**69**(1):11–2. doi: 10.1002/ana.22353. [PubMed: 21280071].

31. Valadbeigi A, Weisi F, Rohbakhsh N, Rezaei M, Heidari A, Rasa A. Central auditory processing and word discrimination in patients with multiple sclerosis. *European Archives of Oto-Rhino-Laryngology.* 2014;**271**(11):2891–6.

32. Mazdeh M, Seifirad S, Kazemi N, Seifrabie MA, Dehghan A, Abbasi H. Comparison of vitamin D3 serum levels in new diagnosed patients with multiple sclerosis versus their healthy relatives. *Acta medica Iranica.* 2013;**51**(5):289–92.

33. Kurtzke JF. Multiple sclerosis in time and space–geographic clues to cause. *J Neurovirol.* 2000;**6 Suppl 2**:S134–40. [PubMed: 10871801].

34. Fraser FC. Genetic counseling. *Am J Hum Genet.* 1974;**26**(5):636–59. [PubMed: 4609197].

35. Harper PS. Practical genetic counselling. 7 ed. CRC Press; 2010.

36. Association WM. Ethical principles for medical research involving human subjects. 79. World medical association declaration of Helsinki; 2001.

37. Toghianifar N, Etemadifar M, Sharifzadeh A, Nasr Z. Characteristics of familial multiple sclerosis in Isfahan, Iran: A cross-sectional study. *Neurology Asia.* 2014;**19**(1).

38. Hashemilar M, Savadi Ouskui D, Farhoudi M, Ayromlou H, Asadollahi A. Multiple sclerosis in East-Azerbaijan, north west Iran. *Neurology Asia.* 2011;**16**(2):127–31.

39. Al Jumah M, Kojan S, Al Khathaami A, Al Abdulkaream I, Al Blawi M, Jawhary A. Familial multiple sclerosis: does consanguinity have a role?. *Mult Scler.* 2011;**17**(4):487–9. doi: 10.1177/1352458510390406. [PubMed: 21177327].

40. Mackenzie IS, Morant SV, Bloomfield GA, MacDonald TM, O'Riordan J. Incidence and prevalence of multiple sclerosis in the UK 1990-2010: a descriptive study in the General Practice Research Database. *J Neurol Neurosurg Psychiatry.* 2014;**85**(1):76–84. doi: 10.1136/jnnp-2013-305450. [PubMed: 24052635].

41. Lau KK, Wong WW, Sheng B, Yu IT, Fung BH, Li HL, et al. The clinical course of multiple sclerosis patients in Hong Kong. *J Neurol Sci.* 2008;**268**(1-2):78–82. doi: 10.1016/j.jns.2007.11.006. [PubMed: 18068191].

42. Farez MF, Balbuena Aguirre ME, Varela F, Kohler AA, Nagel V, Correale J. Low familial risks for multiple sclerosis in Buenos Aires, Argentina. *J Neurol Sci.* 2014;**346**(1-2):268–70. doi: 10.1016/j.jns.2014.09.004. [PubMed: 25245176].

43. Mazdeh M, Afzali S, Jaafari MR. The therapeutic effect of Avonex, Rebif and Betaferon on EDSS and relapse in multiple sclerosis: a comparative study. *Acta Med Iran.* 2010;**48**(2):83–8. [PubMed: 21132998].

44. Majdinasab N, Hosseini Behbahani M, Galehdari H, Mohaghegh M. Association of interleukin 7 receptor gene polymorphism rs6897932 with multiple sclerosis patients in Khuzestan. *Iran J Neurol.* 2014;**13**(3):168–71. [PubMed: 25422737].

45. Orton SM, Wald L, Confavreux C, Vukusic S, Krohn JP, Ramagopalan SV, et al. Association of UV radiation with multiple sclerosis prevalence and sex ratio in France. *Neurology.* 2011;**76**(5):425–31. doi: 10.1212/WNL.0b013e31820a0a9f. [PubMed: 21282589].

46. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA.* 2006;**296**(23):2832–8. doi: 10.1001/jama.296.23.2832. [PubMed: 17179460].

47. Rezaali S, Khalilnezhad A, Naser Moghadasi A, Chaibakhsh S, Sahraian MA. Epidemiology of multiple sclerosis in Qom: Demographic study in Iran. *Iran J Neurol.* 2013;**12**(4):136–43. [PubMed: 24250923].

48. Adams CW, Hallpike JF. The aetiology and pathogenesis of multiple sclerosis. *Guys Hosp Rep.* 1969;**118**(2):263–86. [PubMed: 4896181].

49. Mazzucchelli RI, Riva A, Durum SK. The human IL-7 receptor gene: deletions, polymorphisms and mutations. *Semin Immunol.* 2012;**24**(3):225–30. doi: 10.1016/j.smim.2012.02.007. [PubMed: 22425228].

50. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol.* 1983;**13**(3):227–31. doi: 10.1002/ana.410130302. [PubMed: 6847134].

51. Josey L, Curley M, Jafari Mousavi F, Taylor BV, Lucas R, Coulthard A. Imaging and diagnostic criteria for Multiple Sclerosis: are we there yet?. *J Med Imaging Radiat Oncol.* 2012;**56**(6):588–93. doi: 10.1111/j.1754-9485.2012.02448.x. [PubMed: 23210576].

52. Sawcer S, Compston A. The genetic analysis of multiple sclerosis in Europeans: concepts and design. *J Neuroimmunol.* 2003;**143**(1-2):13–6. [PubMed: 14575908].

53. Sadovnick AD. Differential effects of genetic susceptibility factors in males and females with multiple sclerosis. *Clin Immunol.* 2013;**149**(2):170–5. doi: 10.1016/j.clim.2013.05.002. [PubMed: 23796437].

54. Azarpira N, Borhani Haghighi A, Pourjafar M, Shariat A. Interleukin 10 gene polymorphism in Iranian patients with multiple sclerosis. *Acta Neurol Taiwan.* 2010;**19**(2):107–11. [PubMed: 20714960].

55. Dyment DA, Sadovnick AD, Ebers GC. Genetics of multiple sclerosis. *Hum Mol Genet.* 1997;**6**(10):1693–8. [PubMed: 9300661].

56. Disanto G, Morahan JM, Ramagopalan SV. Multiple sclerosis: risk factors and their interactions. *CNS Neurol Disord Drug Targets.* 2012;**11**(5):545–55. [PubMed: 22583442].

57. Ascherio A. Environmental factors in multiple sclerosis. *Expert Rev Neurother.* 2013;**13**(12 Suppl):3–9. doi: 10.1586/14737175.2013.865866. [PubMed: 24289836].

58. Smolders J, Damoiseaux J, Menheere P, Tervaert JW, Hupperts R. Association study on two vitamin D receptor gene polymorphisms and vitamin D metabolites in multiple sclerosis. *Ann N Y Acad Sci.* 2009;**1173**:515–20. doi: 10.1111/j.1749-6632.2009.04656.x. [PubMed: 19758194].

59. Marrie RA. Environmental risk factors in multiple sclerosis aetiology. *Lancet Neurol.* 2004;**3**(12):709–18. doi: 10.1016/S1474-4422(04)00933-0. [PubMed: 15556803].

60. Lonergan R, Kinsella K, Fitzpatrick P, Brady J, Murray B, Dunne C, et al. Multiple sclerosis prevalence in Ireland: relationship to vitamin D status and HLA genotype. *J Neurol Neurosurg Psychiatry.* 2011;**82**(3):317–22. doi: 10.1136/jnnp.2010.220988. [PubMed: 21248317].

61. Islam T, Gauderman WJ, Cozen W, Mack TM. Childhood sun exposure influences risk of multiple sclerosis in monozygotic twins. *Neurology.* 2007;**69**(4):381–8. doi: 10.1212/01.wnl.0000268266.50850.48. [PubMed: 17646631].

62. Niino M, Miyazaki Y. [Vitamin D in Multiple Sclerosis]. *Brain Nerve.* 2015;**67**(11):1429–33. doi: 10.11477/mf.1416200316. [PubMed: 26560958].

63. Baarnhielm M, Hedstrom AK, Kockum I, Sundqvist E, Gustafsson SA, Hillert J, et al. Sunlight is associated with decreased multiple sclerosis risk: no interaction with human leukocyte antigen-DRB1*15. *Eur J Neurol.* 2012;**19**(7):955–62. doi: 10.1111/j.1468-1331.2011.03650.x. [PubMed: 22289117].

64. Niino M, Miyazaki Y, Fukazawa T, Kikuchi S. [Vitamin D and latitude as environmental factors in multiple sclerosis]. *Nihon Rinsho.* 2014;**72**(11):1924–9. [PubMed: 25518372].