Original Article

Demographic and Clinical Characteristics of Familial and Sporadic Multiple Sclerosis Patients

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Abstract:

Background: Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, immune-mediated disease of the central nervous system. It is still unestablished whether heredity correlates with the disease's progression and severity. **Methods:** This study includes the patients with MS seen in the MS clinic of Kashani Hospital, affiliated with Isfahan University of Medical Sciences, from January 2019 to January 2020. We gathered data regarding the demographic and clinical characteristics, such as type of disease and family history of MS. Patients were grouped based on having relatives with MS. We compared demographic and clinical characteristics between those with a family history of MS (familial MS: FMS) and those without a family history of MS (sporadic MS: SMS). **Results:** We included 2,929 MS patients, 523 (17.2%) with FMS and 2,406 (82.8%) with SMS. Patients with FMS were found to have active lesions in the thoracic spine more frequently than those with SMS (P = 0.022). We also found differences in the distribution of gender (P = 0.036) and the frequency of having active brain lesions (P = .024) among patients with FMS and SMS. No difference was found between the demographic/clinical characteristics and the number of affected relatives in the family. **Conclusions:** Significant differences were found among different groups of patients in terms of demographical and clinical characteristics.

Keywords: *Familial multiple sclerosis, magnetic resonance imaging, multiple sclerosis*

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, immune-mediated disease of the central nervous system, which causes demyelination and may contribute to neurodegeneration.[1,2] MS is estimated to affect approximately 2.5 million people worldwide,[3] 1 per 1,000 individuals in the United States[4] and 1.62 per 1,000 individuals in Iran.[5] The prevalence of MS is believed to be rising in several regions around the world.[6] MS affects young people and women more frequently and is known as one of the common causes of disability.[7,8]

Although most MS cases are sporadic, studies have shown that nearly 20% of patients with MS have a family history of MS,[9,10] pointing to a possible contribution of genetic factors in the disease development. So far, more than 100 genes have been suggested to be associated with MS. Recent studies have shown different alleles that are seen more often in patients with MS, including HLA-DR2, HLA-DRw6, HLA-DR3, HLA-DR2, and HLA-DRB1*15. On the other hand, some genes are shown to have a protective effect against MS or found less often in patients with MS, including DR4 and HLA-DR9.[11-16]

Familial MS (FMS) is defined as having at least one first-degree, second-degree, or third-degree relative diagnosed with MS.[17] The prevalence of FMS is higher in the areas with a higher prevalence of MS. FMS incidence is found to be higher among first-degree and second-degree relatives.[18] For instance, if first-degree relatives have MS, the relative risk of developing MS is found to be 9.2 higher than the general population, and this risk is up to 3.2 times higher for individuals with a second-degree relative with MS.[19] Additionally, FMS is more prevalent among twins, with 31-fold increased risk of developing MS in the other twins.[20]

It is still unestablished whether heredity affects the progression and severity of the disease. Although some studies noted that heredity increases the likelihood of disease progression (but not the severity),[21] there

How to cite this article: Mokhtari S, Houshi S, Mirmosayyeb O, Barzegar M, Afshari-Safavi A, Ghasemi M, *et al*. Demographic and clinical characteristics of familial and sporadic multiple sclerosis patients. Int J Prev Med 2023;14:86.

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Access this article online

Website: www.ijpvmjournal.net/www.ijpm.ir

DOI: 10.4103/ijpvm.ijpvm_187_22

Quick Response Code:

are still insufficient data to determine whether FMS has a different disease course compared to sporadic MS (SMS). This study aims to look into this question by evaluating patients with FMS and their disease course.

Materials and Methods

This study deploys a cross-sectional design using the MS database of the MS clinic in Kashani Hospital, affiliated with Isfahan University of Medical Sciences. We included patients who visited the clinic from January 2019 to January 2020 and were diagnosed with MS. The patients were diagnosed with MS by two neurologists based on the 2017 revised McDonald criteria.[22] The regional bioethics committee of Isfahan University of Medical Sciences approved the study, and all participants signed a written informed consent prior to their enrollment in the study.

We gathered data regarding the demographic and clinical characteristics of study participants, including age, sex, alcohol consumption, smoking, occupation, level of education, disease‐modifying drugs, course and type of disease (e.g., relapsing‐remitting MS, progressive MS, clinically isolated syndrome), current and early symptoms (e.g., visual, sensory, motor, brainstem, and cerebellar), physical comorbidity, psychological comorbidity, other autoimmune diseases, active brain lesion, active cervical lesion, active thoracic spine lesion, brain atrophy, longitudinally extensive transverse myelitis, consanguinity, and family history of MS. We used 1.5 T magnetic resonance imaging (MRI) to report brain and spinal findings. Active lesions were discovered through the initial MRI of patients, and an MRI-based method was used to evaluate brain atrophy.[23] Moreover, we evaluated the level of disability in all study participants using the extended disability status scale (EDSS). EDSS is an approach to quantify disability in MS and to monitor gradual changes in the course of disability.[24] The score ranges from 0 to 10, with higher values representing higher levels of disability. To find cases with FMS, we looked for the status of MS in the first-degree, second-degree, and third-degree relatives. In this study, first-degree relatives are parents, siblings, and offspring; second-degree relatives are grandparents, uncles, aunts, and grandchildren; and third-degree relatives are nephews and offspring of grandchildren. We divided patients into two groups with and without a family history of MS to compare demographic and clinical characteristics between them. Different comparisons are made: the comparison between FMS and SMS, the comparison based on the degree of relatives, the comparison based on the number of MS patients in the family, and the comparison between MS patients and their relatives who are MS patients to highlight the factors that significantly contribute to the disease.

Descriptive statistics are reported as mean and standard deviation for continuous variables with a normal distribution, median and interquartile range for variables with non-normal distribution, and frequency (percentage) for categorical variables. We used the independent sample *t*-test, the nonparametric Mann-Whitney test, and the Kruskal-Wallis test to compare variables of interest between two groups. Additionally, for the categorical variables, we used the Chi-square test. In this study, we set the level of significance at 0.05 while performing two-tailed tests. All statistical analysis procedures were performed using IBM SPSS Statistics (version 18).[25]

Results

Our final sample consisted of 2,929 patients with MS, including 523 (17.9%) cases with FMS and 2,406 (82.8%) cases with SMS. Table 1 shows the comparison of demographic and clinical characteristics between patients with FMS and SMS. We found no statistically significant difference in the average age of patients with FMS (38.41 ± 9.55) and SMS (38.18 ± 9.80; $P = 0.628$). Similarly, we found no statistically significant difference between the two groups regarding gender ($P = 0.283$), first measured EDSS score ($P = .508$), and MS type ($P = .142$).

Sensory symptoms were the most common symptoms among both groups (35.7% of patients with FMS 32.0% of those with SMS). Visual symptoms were the second most common symptoms among both groups (27.5% of cases with FMS and 30.1% of those with SMS). There was no statistically significant difference between the two groups in terms of the first symptoms ($P = 0.692$). Moreover, 39.0% of patients with FMS and 37.7% of patients with SMS had physical comorbidities ($P = 0.584$). There was no statistically significant difference in the number of cases with active brain lesions and cervical lesions between the two groups ($P = .104$ and $P = .728$, respectively). However, the number of cases with thoracic spine lesions was higher among patients with FMS (0.8%) compared to patients with SMS (0.1%) ($P = .022$).

Table 2 shows the breakdown of FMS cases with regards to the degree of relatives with MS in comparison to patients with SMS. Overall, there were 159, 83, 220, and 61 patients with first-degree, second-degree, third-degree, and multiple-degree FMS, respectively. There were more women among patients with a second-degree relative with MS compared to other groups of FMS ($P = 0.036$). Moreover, fewer patients with a third-degree relative with MS had active brain lesions ($P = 0.024$). We found no difference regarding other clinical and demographic features between various groups of patients with FMS.

Table 3 presents the demographic and clinical characteristics of patients with FMS broken down by the number of relatives with MS. We grouped patients with FMS into three groups: patients with one affected relative, patients with two affected relatives, and patients with three or more affected relatives. We found no statistically significant difference in the demographic/clinical characteristics between these groups.

Table 1: Demographic and clinical characteristics of familial MS compared to sporadic MS patients

	Variable	Overall (*n*=2,929)	Familial (*n*=523)	Sporadic (*n*=2,709)	*P*
Age		38.22 (9.75)	38.41 (9.55)	38.18 (9.80)	0.628
Age of onset		30.33 (9.06)	29.84 (8.86)	30.44 (9.11)	0.172
First EDSS		2 (1.5)	2 (1)	2 (1.5)	0.508
Current EDSS		1 (2)	1 (2)	1 (2)	0.424
Sex	Male	604 (20.6)	117 (22.4)	487 (20.2)	0.283
	Female	2,325 (79.4)	406 (77.6)	1,919 (79.8)	
Smoke	No	248 (8.7)	45 (8.7)	203 (8.7)	0.999
	Yes	2,611 (91.3)	473 (91.3)	2,138 (91.3)	
MS type	RRMS	2,072 (70.7)	381 (72.8)	1,691 (70.3)	0.142
	PMS	496 (16.9)	91 (17.4)	405 (16.8)	
	CIS	361 (12.3)	51 (9.8)	310 (12.9)	
First symptom	Visual	782 (29.6)	137 (27.5)	645 (30.1)	0.692
	Sensory	864 (32.7)	178 (35.7)	686 (32)	
	Motor	431 (16.3)	80 (16)	351 (16.4)	
	Brainstem	310 (11.7)	59 (11.8)	251 (11.7)	
	Cerebellar	152 (5.8)	28 (5.6)	124 (5.8)	
	Other	103 (3.9)	17 (3.4)	86 (4)	
Physical comorbidities	No	1,819 (62.1)	319 (61)	1,500 (62.3)	0.584
	Yes	1,110 (37.9)	204 (39)	906 (37.7)	
Psychological comorbidities	No	2,432 (83)	434 (83)	1,998 (83)	0.999
	Yes	497 (17)	89 (17)	408 (17)	
Autoimmune disease	No	2,872 (98.1)	514 (98.3)	2,358 (98)	0.861
	Yes	57 (1.9)	9 (1.7)	48 (2)	
Active brain lesion	No	1,992 (85.1)	389 (87.6)	1,603 (84.5)	0.104
	Yes	348 (14.9)	55 (12.4)	293 (15.5)	
Active cervical lesion	No	1,863 (93.8)	372 (93.5)	1,491 (93.9)	0.728
	Yes	123 (6.2)	26 (6.5)	97 (6.1)	
Active thoracic spine lesion	No	2,922 (99.8)	519 (99.2)	2,403 (99.9)	0.022
	Yes	7 (0.2)	4 (0.8)	3 (0.1)	
Atrophy	No	1,691 (72.5)	314 (70.7)	1,377 (72.9)	0.376
	Yes	643 (27.5)	130 (29.3)	513 (27.1)	
LETM	No	1,743 (88.3)	345 (88.5)	1,398 (88.2)	0.93
	Yes	232 (11.7)	45 (11.5)	187 (11.8)	
Consanguinity	No	2,188 (74.7)	388 (74.2)	1,800 (74.8)	0.781
	Yes	741 (25.3)	135 (25.8)	606 (25.2)	

SD, Standard Deviation; IQR, Inter Quartile Range (third quartile to first quartile)

Finally, we performed an analysis to compare the demographic and clinical characteristics of patients with MS and their affected relatives [Table 4]. We divided patients into three groups based on the degree of relatives affected with MS. Among patients with a second-degree relative with MS, current EDSS scores were higher among the relatives (P = 0.036). Moreover, among patients with a third-degree relative with MS, the distribution of the first clinical symptom was different between patients with MS and their relatives (P = 0.015).

Discussion

In the present study, we looked for differences in clinical and demographic characteristics of patients with FMS and those with SMS.

In our group of patients with MS, nearly 18% had FMS. Previous studies in Isfahan, Iran, have reported the frequency of FMS from 10% to 20.1%.[9,26,27] Moreover, among the 2,516 patients with MS in Saudi Arabia, 12.8% had a familial history of MS.[28] In a larger study in Tehran, Iran, of 21,580 cases with MS, 13.04% were FMS.[29] Furthermore, a recent study in Northwest Iran reported 13.9% of patients with MS had a family history of MS.[30] While there are some inconsistencies in the frequency of FMS reported in different studies, the numbers are in a close range. The observed differences could be due to different sampling methods and study designs.

We found no difference in the age of onset between patients with FMS and SMS. A study conducted in Abu Dhabi showed that the age at disease onset is not associated with the FMS.[31] Additionally, similar results were found among Lithuanian patients.[17] Conversely, the age at onset was slightly higher among patients with SMS in a large study on 21,580 patients with MS conducted in Tehran, Iran.[29]

Table 2: Demographic and clinical characteristics of familial MS categorized based on the degree of familial MS

Variable		Degree of relationship					*P*
		Overall (*n*=523)	1st degree (*n*=159)	2nd degree (*n*=83)	3rd degree (*n*=220)	Multiple (*n*=61)	
Age		39.4 (9.5)	41.3 (9.8)	39.07 (11.3)	38.7 (8.5)	37.7 (9.3)	0.025
Age of onset		29.8 (8.7)	31.1 (9.6)	29.4 (9.3)	29.4 (8.3)	29.0 (8.1)	0.198
First EDSS		2 (1)	2 (1)	2 (2)	2 (1)	2 (2)	0.721
Current EDSS		1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	0.962
Sex	Male	117 (22.4)	38 (23.9)	9 (10.8)	52 (23.6)	18 (29.5)	0.036
	Female	406 (77.6)	121 (76.1)	74 (89.2)	168 (76.4)	43 (70.5)	
Smoke	Yes	45 (8.7)	15 (9.6)	5 (6)	17 (7.8)	8 (13.1)	0.458
	No	473 (91.3)	142 (90.4)	78 (94)	200 (92.2)	53 (86.9)	
MS type	RRMS	381 (72.8)	117 (73.6)	56 (67.5)	161 (73.2)	47 (77)	0.923
	PMS	91 (17.4)	27 (17)	15 (18.1)	39 (17.7)	10 (16.4)	
	CIS	51 (9.8)	15 (9.4)	12 (14.5)	20 (9.1)	4 (6.6)	
First symptom	Visual	137 (27.5)	46 (29.9)	22 (28.2)	57 (27.3)	12 (20.7)	0.238
	Sensory	178 (35.7)	49 (31.8)	24 (30.8)	78 (37.3)	27 (46.6)	
	Motor	80 (16)	29 (18.8)	11 (14.1)	37 (17.7)	3 (5.2)	
	Brainstem	59 (11.8)	16 (10.4)	15 (19.2)	20 (9.6)	8 (13.8)	
	Cerebellar	28 (5.6)	9 (5.8)	3 (3.8)	12 (5.7)	4 (6.9)	
	Other	17 (3.4)	5 (3.2)	3 (3.8)	5 (2.4)	4 (6.9)	
Physical comorbidities	No	319 (61)	90 (56.6)	46 (55.4)	140 (63.6)	43 (70.5)	0.149
	Yes	204 (39)	69 (43.3)	37 (44.6)	80 (36.4)	18 (29.5)	
Psychological comorbidities	No	434 (83)	124 (78)	67 (80.7)	188 (85.5)	55 (90.2)	0.098
	Yes	89 (17)	35 (22)	16 (19.3)	32 (14.5)	6 (9.8)	
Autoimmune disease	No	514 (98.3)	155 (97.5)	82 (98.8)	216 (98.2)	61 (100)	0.614
	Yes	9 (1.7)	4 (2.5)	1 (1.2)	4 (1.8)	0 (0)	
Active brain lesion	No	389 (87.6)	113 (82.5)	57 (82.6)	171 (91.4)	48 (94.1)	0.024
	Yes	55 (12.4)	24 (17.5)	12 (17.4)	16 (8.6)	3 (5.9)	
Active cervical lesion	No	372 (93.5)	111 (93.3)	53 (91.4)	162 (94.7)	46 (92)	0.789
	Yes	26 (6.5)	8 (6.7)	5 (8.6)	9 (5.3)	4 (8)	
Active thoracic spine lesion	No	519 (99.2)	158 (99.4)	82 (98.8)	218 (99.1)	61 (100)	0.854
	Yes	4 (0.8)	1 (0.6)	1 (1.2)	2 (0.9)	0 (0)	
Atrophy	No	314 (70.7)	94 (68.6)	50 (71.4)	133 (71.5)	37 (72.5)	0.93
	Yes	130 (29.3)	43 (31.4)	20 (28.6)	53 (28.5)	14 (27.5)	
LETM	No	345 (88.5)	100 (88.5)	54 (91.5)	150 (88.8)	41 (83.7)	0.646
	Yes	45 (11.5)	13 (11.5)	5 (8.5)	19 (11.2)	8 (16.3)	
Consanguinity	No	388 (74.2)	116 (73)	58 (69.9)	169 (76.8)	45 (73.8)	0.63
	Yes	135 (25.8)	43 (27)	25 (30.1)	51 (23.2)	16 (26.2)	

SD, Standard Deviation; IQR, Inter Quartile Range (third quartile to first quartile)

The observed difference could be due to the much larger sample size in the study conducted in Tehran, although another study showed that the age at disease onset does not contribute to FMS in older patients, while it contributes to FMS in younger patients.[32]

We found no sufficient evidence indicating that the two groups are different regarding the EDSS scores. Similar results were reported among 318 patients with MS with 22% of FMS prevalence.[33] On the contrary, in a study among 104 patients with MS, EDSS scores both at the time of diagnosis and the present time were higher among individuals with FMS.[17] Moreover, the distribution of gender was found to have no association with the type of MS (familial/sporadic) in our study. This finding is in accordance with previous studies.[34,35]

We found no difference in the first symptom between patients with FMS and SMS. Similarly, among 384 patients with MS in Greece, findings indicated that the type of MS is not different between cases with FMS and SMS.[36] Additionally, a study in Argentina showed that among a total of 1,333 patients with MS, the type of MS is distributed among cases with FMS and SMS in a similar manner.[32] Our findings are consistent with the previous studies in terms of the first symptom.

Our results showed that there are no differences in physical comorbidities, psychological comorbidities, autoimmune diseases, active brain lesions, and active cervical lesions between the two groups of FMS and SMS. Similar findings were reported in a study done in Greece except for the frequency of active cervical lesions among cases

Table 3: Demographic and clinical characteristics of familial MS, categorized based on the number of affected relatives in the family

	Variable	Number of affected relatives in the family			*P*
		1 (*n*=378)	2 (*n*=113)	≥3 (*n*=32)	
Age		39.7 (9.8)	38.41 (8.9)	39.3 (9.2)	0.44
Age of onset		29.9 (9.0)	29.5 (8.72)	30.5 (8.21)	0.823
First EDSS		2 (1)	2 (1.5)	2 (1.3)	0.749
Current EDSS		1 (2)	1 (2.5)	1.5 (2)	0.497
Sex	Male	78 (20.6)	29 (25.7)	10 (31.3)	0.245
	Female	300 (79.4)	84 (74.3)	22 (68.8)	
Smoke	Yes	30 (8)	9 (8)	6 (18.8)	0.113
	No	344 (92)	103 (92)	26 (81.3)	
MS type	RRMS	274 (72.5)	82 (72.6)	25 (78.1)	0.817
	PMS	64 (16.9)	22 (19.5)	5 (15.6)	
	CIS	40 (10.6)	9 (8)	2 (6.3)	
First symptom	Visual	103 (28.5)	28 (25.7)	6 (20.7)	0.309
	Sensory	124 (34.3)	40 (36.7)	14 (48.3)	
	Motor	58 (16.1)	21 (19.3)	1 (3.4)	
	Brainstem	46 (12.7)	8 (7.3)	5 (17.2)	
	Cerebellar	18 (5)	7 (6.4)	3 (10.3)	
	Other	12 (3.3)	5 (4.6)	0 (0)	
Physical comorbidities	No	221 (58.5)	76 (67.3)	22 (68.8)	0.158
	Yes	157 (41.5)	37 (32.7)	10 (31.3)	
Psychological comorbidities	No	311 (82.3)	98 (86.7)	25 (78.1)	0.409
	Yes	67 (17.7)	15 (13.3)	7 (21.9)	
Autoimmune disease	No	369 (97.6)	113 (100)	32 (100)	0.173
	Yes	9 (2.4)	0 (0)	0 (0)	
Active brain lesion	No	277 (86)	85 (91.4)	27 (93.1)	0.249
	Yes	45 (14)	8 (8.6)	2 (6.9)	
Active cervical lesion	No	263 (93.6)	83 (93.3)	26 (92.9)	0.985
	Yes	18 (6.4)	6 (6.7)	2 (7.1)	
Active thoracic spine lesion	No	375 (99.2)	112 (99.1)	32 (100)	0.873
	Yes	3 (0.8)	1 (0.9)	0 (0)	
Atrophy	No	231 (71.5)	64 (69.6)	19 (65.5)	0.764
	Yes	92 (28.5)	28 (30.4)	10 (34.5)	
LETM	No	249 (90.2)	72 (83.7)	24 (85.7)	0.231
	Yes	27 (9.8)	14 (16.3)	4 (14.3)	
Consanguinity	No	282 (74.6)	80 (70.8)	26 (81.3)	0.462
	Yes	96 (25.4)	33 (29.2)	6 (18.8)	

SD, Standard Deviation; IQR, Inter Quartile Range (third quartile to first quartile)

with FMS with a first-degree relative.[36] Brain lesions are reported to be more common among patients with FMS when first-degree FMS is concerned.[17] Additionally, in our study, unlike previous studies, active thoracic spine lesions were more frequent among patients with FMS. Regarding consanguinity, a study showed that it is more frequent among patients with FMS.[28] However, our observations are more aligned with the study by Ceccarelli *et al*.,[31] in which the frequency of consanguinity was similar among cases with FMS and SMS.

In a case-control study by Katsavos *et al*. in 2018, 102 patients with FMS and 282 with SMS were compared for age of onset, with FMS cases showing a significantly younger age of onset. Furthermore, the distribution of MRI lesions between FMS and SMS patients differed significantly between the two groups. In the former group, there were fewer subcortical lesions, perhaps fewer brainstem lesions, and more cervical cord lesions than those in the latter group (the latter corresponded to the degree of Genetic burden (GB), which could be expressed as the proximity of the relative affected).[36]

With respect to the degrees of relatives with MS, our observations aligned with the literature in certain areas, while different outcomes were observed in other areas. Specifically, we found that age at onset is not associated with the degree of FMS. Our findings are different from those of previous studies reported by Steenhof *et al*.[34] Conversely, researchers reported that the gender of patients is not correlated with

Table 4: Comparison between demographic and clinical characteristics of patients and those of patients' relatives

Variables	Sub-Variable	First Degree			Second Degree			Third Degree		
		Family (*n*=200)	Patients (*n*=160)	*P*	Family (*n*=93)	Patients (*n*=84)	*P*	Family (*n*=307)	Patients (*n*=221)	*P*
Age		42.54 (10.53)	39.12 (9.78)	0.002	45.70 (11.93)	36.62 (11.21)	0.001	40.12 (10.35)	36.59 (8.56)	0.001
Age of onset		31.60 (9.48)	31.08 (9.57)	0.62	31.03 (9.95)	29.37 (9.34)	0.282	28.86 (8.64)	29.38 (8.27)	0.508
Current EDSS		0 (3.5)	1 (2)	0.2	2 (7)	1 (2)	0.036	0 (5)	1 (2)	0.996
Sex	Male	49 (27.2)	38 (23.8)	0.534	15 (16.9)	9 (10.7)	0.277	71 (24.9)	53 (24)	0.835
	Female	131 (72.8)	122 (76.3)		74 (83.1)	75 (89.3)		214 (75.1)	168 (76)	
First symptom	Visual	44 (28.9)	46 (29.7)	0.418	17 (25)	22 (28.2)	0.483	54 (32.7)	58 (27.6)	0.015
	Sensory	54 (35.5)	49 (31.6)		22 (32.4)	24 (30.8)		38 (23)	78 (37.1)	
	Motor	28 (18.4)	29 (18.7)		17 (25)	11 (14.1)		28 (17)	37 (17.6)	
	Brainstem	21 (13.8)	17 (11)		8 (11.8)	15 (19.2)		33 (20)	20 (9.5)	
	Cerebellar	3 (2)	9 (5.8)		1 (1.5)	3 (3.8)		9 (5.5)	12 (5.7)	
	Other	2 (1.3)	5 (3.2)		3 (4.4)	3 (3.8)		3 (1.8)	5 (2.4)	

the degree of FMS,[36] while we found more female cases among patients with FMS with a second-degree relative. Additionally, we found that physical comorbidities and active brain lesions are seen more frequently among patients with FMS with first-degree or second-degree relatives. However, other researchers indicated no association between active brain/cerebellar lesion and the degree of FMS, although they reported a correlation between the active cervical lesion and the degree of FMS.[36]

In the analysis of the number of affected relatives in the family, we found no correlation between this number and the demographic and clinical characteristics of patients with FMS. Finally, we investigated the differences between FMS patients' demographic and clinical characteristics and those of their families. Concerning the first-degree relatives, the demographic and clinical characteristics of patients with MS were observed not to be different from those of their first-degree relatives. Comparing the demographic and clinical characteristics of the second-degree relatives with those of the patients resulted in discovering statistically significant differences between them in terms of the current EDSS score. The same comparison between the third-degree relatives and the patients revealed that statistically, significantly different first symptoms appear in patients than in their third-degree relatives.

This study contains certain limitations. First, our sample was selected from the central part of Iran, limiting the generalizability of the results to other populations. Additionally, the clinical features we recorded were not containing all the features reported previously in the literature. A more rigorous data gathering can improve the results. However, in spite of the limitations, this study performed a comprehensive set of analyses on a relatively large sample of patients with MS.

Conclusion

Patients with FMS tend to have different MS types compared to patients with SMS. Additionally, these individuals have a significantly lower prevalence of active thoracic spine lesions. Comparison of patients with different degrees of FMS revealed that the degree of FMS has an association with the gender of patients, physical comorbidities, and active brain lesions. Furthermore, comparing the demographic and clinical characteristics of the second-degree relatives with those of the patients resulted in discovering a statistically significant difference between them in terms of the current EDSS score.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Received: 27 May 22 **Accepted:** 17 May 23
Published: 22 Jun 23

References

1. Mirmosayyeb O, Brand S, Barzegar M, Afshari-Safavi A, Nehzat N, Shaygannejad V, *et al*. Clinical characteristics and disability progression of early- and late-onset multiple sclerosis compared to adult-onset multiple sclerosis. J Clin Med 2020;9:1326.
2. Mirmosayyeb O, Barzegar M, Nehzat N, Najdaghi S, Ansari B, Shaygannejad V. Association of helicobacter pylori with multiple sclerosis: Protective or risk factor?. Curr J Neurol 2020;19:59-66.
3. Moss BP, Rensel MR, Hersh CM. Wellness and the role of comorbidities in multiple sclerosis. Neurotherapeutics 2017;14:999-1017.
4. Kalron A, Aloni R, Givon U, Menascu S. Fear of falling, not falls, impacts leisure-time physical activity in people with multiple sclerosis. Gait Posture 2018;65:33-8.
5. Nasiri M, Maroufi H, Sahraian MA, Eskandarieh S. Prevalence of multiple sclerosis and its risks in Tehran, Iran, in 2019. Neurol Sci 2021;42:2575-6.
6. Heydarpour P, Khoshkish S, Abtahi S, Moradi-Lakeh M, Sahraian MA. Multiple sclerosis epidemiology in middle east and north Africa: A systematic review and meta-analysis. Neuroepidemiology 2015;44:232-44.
7. Karussis D. The diagnosis of multiple sclerosis and the various related demyelinating syndromes: A critical review. J Autoimmun

2014;48-49:134-42.
8. Westerlind H, Boström I, Stawiarz L, Landtblom AM, Almqvist C, Hillert J. New data identify an increasing sex ratio of multiple sclerosis in Sweden. Mult Scler 2014;20:1578-83.
9. Ashtari F, Shaygannejad V, Heidari F, Akbari M. Prevalence of familial multiple sclerosis in Isfahan, Iran. J Isfahan Med Sch 2011;29.
10. Ramagopalan SV, Sadovnick AD. Epidemiology of multiple sclerosis. Neurol Clin 2011;29:207-17.
11. Seboun E, Oksenberg JR, Rombos A, Usuku K, Goodkin DE, Lincoln RR, *et al*. Linkage analysis of candidate myelin genes in familial multiple sclerosis. Neurogenetics 1999;2:155-62.
12. McDonnell GV, Mawhinney H, Graham CA, Hawkins SA, Middleton D. A study of the HLA-DR region in clinical subgroups of multiple sclerosis and its influence on prognosis. J Neurol Sci 1999;165:77-83.
13. Qiu W, James I, Carroll WM, Mastaglia FL, Kermode AG. HLA-DR allele polymorphism and multiple sclerosis in Chinese populations: A meta-analysis. Mult Scler 2011;17:382-8.
14. Duquette P, Décary F, Pleines J, Boivin D, Lamoureux G, Cosgrove JB, *et al*. Clinical sub-groups of multiple sclerosis in relation to HLA: DR alleles as possible markers of disease progression. Can J Neurol Sci 1985;12:106-10.
15. van Luijn MM, Kreft KL, Jongsma ML, Mes SW, Wierenga-Wolf AF, van Meurs M, *et al*. Multiple sclerosis-associated CLEC16A controls HLA class II expression via late endosome biogenesis. Brain 2015;138:1531-47.
16. Balnyte R, Rastenyte D, Vaitkus A, Mickeviciene D, Skrodeniene E, Vitkauskiene A, *et al*. The importance of HLA DRB1 gene allele to clinical features and disability in patients with multiple sclerosis in Lithuania. BMC Neurol 2013;13:77.
17. Andrijauskis D, Balnyte R, Keturkaite I, Vaitkus A. Clinical and diagnostic features of patients with familial multiple sclerosis. Med Hypotheses 2019;131:109310.
18. Nielsen NM, Westergaard T, Rostgaard K, Frisch M, Hjalgrim H, Wohlfahrt J, *et al*. Familial risk of multiple sclerosis: A nationwide cohort study. Am J Epidemiol 2005;162:774-8.
19. Herrera BM, Ramagopalan SV, Lincoln MR, Orton SM, Chao MJ, Sadovnick AD, *et al*. Parent-of-origin effects in MS: Observations from avuncular pairs. Neurology 2008;71:799-803.
20. Roxburgh RH, Seaman SR, Masterman T, Hensiek AE, Sawcer SJ, Vukusic S, *et al*. Multiple sclerosis severity score: Using disability and disease duration to rate disease severity. Neurology 2005;64:1144-51.
21. Koch M, Zhao Y, Yee I, Guimond C, Kingwell E, Rieckmann P, *et al*. Disease onset in familial and sporadic primary progressive multiple sclerosis. Mult Scler 2010;16:694-700.
22. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, *et al*. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292-302.
23. De Stefano N, Battaglini M, Smith SM. Measuring brain atrophy in multiple sclerosis. J Neuroimaging 2007;17 Suppl 1:10S-15S.
24. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 1983;33:1444-52.
25. Verma JP, Data analysis in management with SPSS software. Springer Science & Business Media, 2012.
26. Saadatnia M, Etemadifar M, Maghzi AH. Multiple sclerosis in Isfahan, Iran. Int Rev Neurobiol 2007;79:357-75.
27. Toghianifar N, Etemadifar M, Sharifzadeh A, Nasr Z. Characteristics of familial multiple sclerosis in Isfahan, Iran: A cross-sectional study. Neurol Asia 2014;19.
28. AlJumah M, Otaibi HA, Al Towaijri G, Hassan A, Kareem A, Kalakatawi M, *et al*. Familial aggregation of multiple sclerosis: Results from the national registry of the disease in Saudi Arabia. Mult Scler J Exp Transl Clin 2020;6:2055217320960499.
29. Salehi Z, Almasi-Hashiani A, Sahraian MA, Eskandarieh S. Epidemiology of familial multiple sclerosis: A population-based study in Tehran during 1999-2018. Mult Scler Relat Disord 2020;43:102178.
30. Talebi M, Sadigh-Eteghad S, Sahraian MA, Fahidi A. Age and sex adjusted prevalence and annual incidence of multiple sclerosis in East-Azerbaijan, Iran. Mult Scler Relat Disord 2021;50:102839.
31. Ceccarelli A, Mifsud VA, Dogar A. Demographic and clinical characteristics of familial and sporadic multiple sclerosis: A single center exploratory study from Abu Dhabi. J Clin Neurosci 2020;76:145-7.
32. Rojas JI, Patrucco L, MIguez J, Sinay V, Cassara FP, Cáceres F, *et al*. Disease onset in familial and sporadic multiple sclerosis in Argentina. Mult Scler Relat Disord 2016;6:54-6.
33. Regal AR, Garcia LA, Dopazo MS, Jorrín M del CA. Familial multiple sclerosis: An epidemiological study in Pontevedra, Spain. (P2.396). AAN Enterprises, 2018;90.
34. Steenhof M, Stenager E, Nielsen NM, Kyvik K, Möller S, Hertz JM. Familial multiple sclerosis patients have a shorter delay in diagnosis than sporadic cases. Mult Scler Relat Disord 2019;32:97-102.
35. Ebers GC, Koopman WJ, Hader W, Sadovnick AD, Kremenchutzky M, Mandalfino P, *et al*. The natural history of multiple sclerosis: A geographically based study: 8. Brain 2000;123 Pt 3:641-9.
36. Katsavos S, Artemiadis A, Davaki P, Stamboulis E, Kilindireas K, Anagnostouli M. Familial multiple sclerosis in greece: Distinct clinical and imaging characteristics in comparison with the sporadic disease. Clin Neurol Neurosurg 2018;173:144-9.