



Research Paper

Clinical and Imaging Features of Familial and Sporadic Multiple Sclerosis



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Running Title Familial vs Sporadic Multiple Sclerosis
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ABSTRACT

Background: Multiple sclerosis (MS) is a demyelinating neurodegenerative disease affecting the central nervous system (CNS). While most cases are sporadic, familial MS (FMS) constitutes approximately 12.6% of the MS population and is characterized by affected family members. This study aims to investigate the difference between clinical and radiological findings of patients with FMS and sporadic MS (SMS) living in Guilan Province, Iran.

Materials & Methods: In this cross-sectional study, by evaluating their medical records, we examined 113 patients with SMS and 79 patients with FMS who registered in the nationwide MS registry of Iran (NMSRI)-Guilan. The radiologic data were analyzed using OsiriX software, version 12.0.

Results: Compared to the FMS group, the SMS group showed significantly higher age at onset (31.48 ± 9.55 vs 28.92 ± 9.46 , $P=0.034$), higher occurrence of diplopia (29.2% vs 16.4% , $P=0.042$), higher expanded disability status scale (EDSS) score (2.20 ± 2.61 vs 1.09 ± 2.08 , $P=0.002$), more lesions (31.59 ± 25.36 vs 22.83 ± 17.17 , $P=0.017$), higher frequency of lesions in the periventricular region (98.2% vs 89.8% , $P=0.017$) and the lower average size of the smallest lesions (4.65 ± 2.57 vs 8.12 ± 8.58 , $P<0.001$). EDSS score showed significant associations with type of MS (SMS or FMS) ($\beta=0.78$, $P=0.016$), onset age ($\beta=0.09$, $P<0.001$) and disease duration ($\beta=0.13$, $P=0.001$).

Conclusion: FMS differs from SMS with an earlier onset, predominantly relapsing-remitting phenotype, lower diplopia incidence, lower EDSS scores, fewer periventricular lesions and larger smallest lesions.

Keywords: Multiple sclerosis, Magnetic resonance imaging, Relapsing-Remitting, Disability evaluation

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Highlights

- Compared to the familial type, sporadic multiple sclerosis has a greater tendency to affect the periventricular area.
- Familial multiple sclerosis manifests with fewer lesions, but the smallest lesions are larger.
- Sporadic multiple sclerosis typically results in higher expanded disability status scale (EDSS) scores than the familial type.

Introduction

Multiple sclerosis (MS) is a chronic and demyelinating neurodegenerative disease that affects the central nervous system (CNS) and leads to significant disabilities in young adults [1, 2]. Typically, patients undergo a relapsing-remitting course, followed by a progressive phase many years later [3]. Clinical manifestations include motor, sensory, visual and autonomic impairment alongside several other symptoms [3-5]. Magnetic resonance imaging (MRI) is the primary paraclinical diagnostic modality and can show the demyelinated lesions known as plaques [4].

Although the exact cause of MS is unknown, an intricate gene-environment interaction plays a significant role in its pathogenesis [6, 7]. In addition to numerous environmental factors such as Epstein-Barr virus (EBV) infection, smoking, low sunlight exposure, vitamin D deficiency and obesity that are strongly suspected to be associated with MS development [8, 9], a genetic component undoubtedly contributes to the disease. This assumption can be supported by the familial aggregation of MS, varying prevalence rates among different races, and a higher likelihood of affecting monozygotic twins. While a simple inheritance pattern is not expected in MS, human genome studies have identified the considerable role of HLA-DR and 233 significant genetic associations with MS susceptibility [10, 11].

While sporadic MS (SMS) was initially considered the only existing form of the disease, familial MS (FMS) was later presented in 1933 [12]. FMS is characterized by the presence of at least one family member of first-, second-, third-degree, or other relatives of the patient diagnosed with MS [13]. The prevalence of MS varies based on ethnicity and residential region and has globally increased to 2.8 million in 2020, which is 30% higher than that in 2013 [14, 15]. Most MS cases are sporadic, and FMS constitutes nearly 12.6% of the MS population [13].

According to the limited number of studies comparing SMS and FMS, findings suggest a likely difference in the age of onset (AAO) and CNS lesion distribution between these two disease categories [2, 16-18]. However, the precise impact of heredity on the clinical features, development, and prognosis of MS is still unclear [19]. Expanding our knowledge about the unique characteristics of the familial form of MS enlightens the significance of genetic and environmental factors in this disease and improves the diagnostic and therapeutic methods. This study was designed to compare familial and SMS cases to comprehensively understand their variations and implications.

Materials and Methods

Study design

This analytical study employed a cross-sectional design to investigate patients with clinically definite MS registered in the nationwide MS registry of Iran (NMSRI)-Guilan. A definite MS diagnosis was made by an expert neurologist based on the 2017 revised McDonald criteria [20]. The data were collected by a medical student who retrieved information from the medical records of individuals with MS in this registry system. This dataset encompassed an extensive array of demographic and clinical data, including age, gender, onset age, disease clinical course (such as relapsing-remitting MS, primary progressive MS, secondary progressive MS and clinically isolated syndrome), disease duration, number of attacks (defined by neurological symptoms that have persisted for longer than 24 hours within the past 12 months), medical comorbidities, first presentation of the disease, FMS history, utilization of disease-modifying therapies (DMTs), expanded disability status scale (EDSS) score and the most recent brain MRI. If data records were inadequate, patients were contacted via telephone for additional information and if not feasible, they were invited by medical experts for an appointment to provide additional information through physical examination or a review of their medical records.

Study participants

As of early 2023, there were 1134 registered MS patients in NMSRI-Guilan, with 196 patients (17.2%) diagnosed with FMS. Initially, we assessed all FMS patients ($n=196$) along with an equal number of randomly chosen SMS patients ($n=196$). After a comprehensive review of their medical records, 117 FMS and 83 SMS were excluded due to the unavailability of their MRI scans, severe artifacts, disease duration exceeding 15 years, and insufficient patient cooperation. Consequently, 79 FMS and 113 SMS were included in the study. The patient selection process is shown in Figure 1.

The inclusion criteria were as follows: Patients definitively diagnosed with MS according to the 2017 revised McDonald criteria [20] and less than 15 years after the onset of their disease. The exclusion criteria were as follows: inadequate data in medical records, unrecoverable or incomplete MRI sequences or presence of severe artifacts, presence of other neurological disorders impeding MS diagnosis, and a duration of more than 15 years since the onset of their disease.

Patient classification

Sporadic cases of MS pertain to individuals who are the only members in their family diagnosed with the disease. Conversely, at least one first to third-degree relative was also diagnosed with MS in FMS cases. First-degree relatives include parents and siblings, second-degree relatives include uncles and aunts, while third-degree relatives include cousins and others.

Magnetic resonance imaging acquisition and analysis

Subjects in both groups underwent a 1.5 T brain MRI scan using an 18-channel MRI scanner (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany). The imaging protocol comprised T1-weighted images (with echo time [TE]=12 ms and repetition time [TR]=664 ms). Thin-slice images (1 mm) were acquired in axial, sagittal and coronal views. During post-processing analysis, an expert radiologist, utilizing OsiriX software, version 12.0 [21], evaluated the characteristics of brain lesions. The assessment included the location of

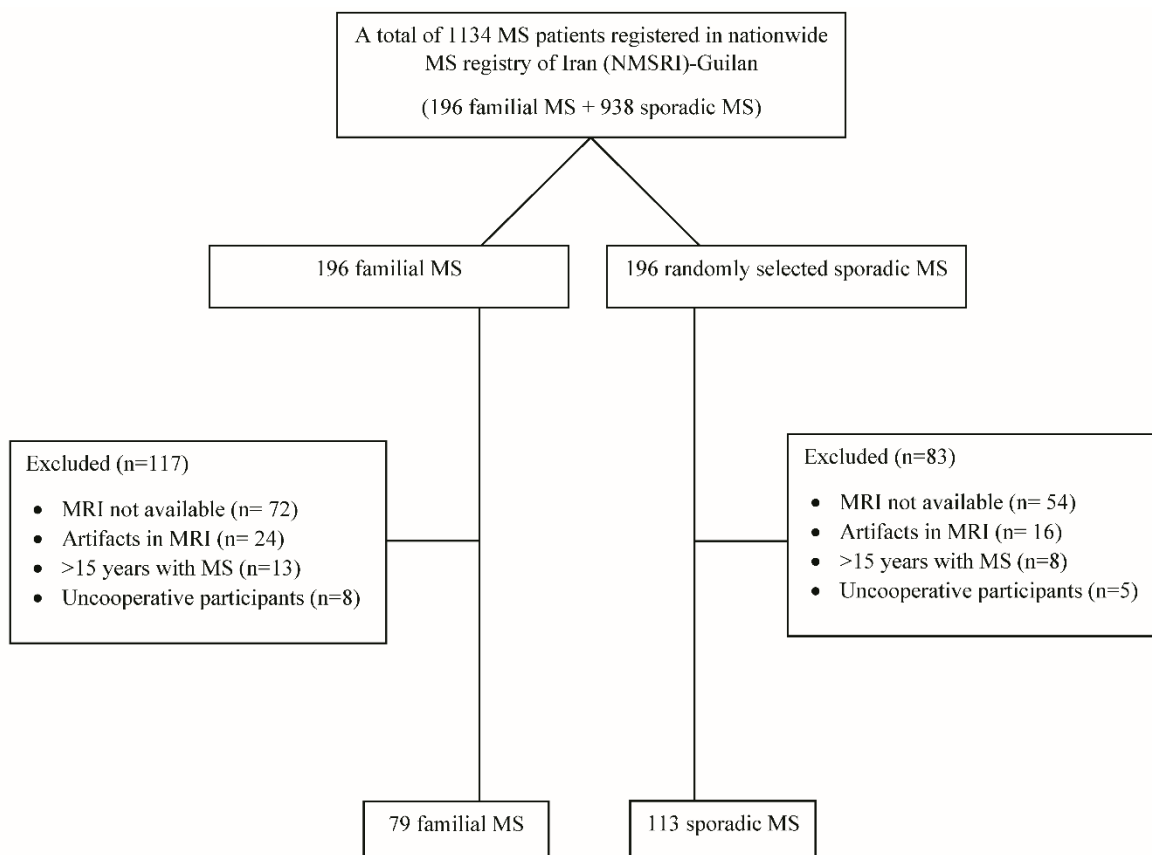


Figure 1. Flow chart of study participants selection from the NMSRI-Guilan

lesions (periventricular, callosal, cervical, infratentorial, juxtacortical, or cortical), the number of lesions, the area of the smallest and largest lesion (mm²) and the presence of black holes. The imaging data were analyzed concerning the number of lesions, explicitly focusing on the axial view and T2-weighted and FLAIR MRI images. Additionally, the location of the lesions was categorized, and the presence or absence of black holes was determined by examining the T1-weighted view.

Statistical analysis

We employed the Mean±SD or the median and interquartile range to depict the quantitative data based on the distribution's normality. Additionally, categorical data was delineated using numerical representations and percentages. For inferential analysis, we initially assessed the normality of quantitative variables using visual methods, specifically the Q-Q chart, skewness, kurtosis, and the Shapiro-Wilk test. To compare quantitative variables across two groups, the independent t-test was utilized if the data exhibited a normal distribution; otherwise, the Mann-Whitney U test was applied. The chi-squared and Fisher exact tests were employed for categorical variables. All analyses were conducted using SPSS software, Version 26.0. The effect size of significant correlations was determined using Spearman's correlation coefficient. Subsequently, significant correlations underwent further evaluation through backward multivariate regression analysis.

Results

This study assessed 192 MS patients consisting of 79 FMS (41.1%) and 113 SMS (58.9%) patients. Patients were approximately matched in terms of DMTs utilization, except for ocrelizumab, which exhibited a statistically significant elevation in the SMS group (Table 1). While the average age of patients between FMS and SMS exhibited a statistically borderline difference (FMS: 34.82±9.40; SMS: 37.71±10.83, P=0.057), a notable statistically significant difference was observed in the onset age between the two groups (FMS: 28.92±9.46; SMS: 31.48±9.55, P=0.034). Moreover, our investigation revealed no statistically significant differences between the two groups concerning gender distribution (P=0.604), disease duration (P=0.738), number of attacks (P=0.42) and medical comorbidities (P=0.237). Table 2 represents the study participants' demographic and clinical characteristics.

Within the FMS group, 21 individuals (26.5%) exhibited a familial predisposition to MS among their first-degree relatives, 23(29.1%) among second-degree relatives, and 35(44.4%) among third-degree relatives (Figure 2).

When comparing the initial disease presentations between the two groups, sensory symptoms emerged as the most common (51.3% in SMS vs 51.9% in FMS, P=0.938). Moreover, among all the other primary mani-

Table 1. Distribution of DMT used among the study population

DMT	No. (%)			P
	Overall (n=192)	SMS (n=113)	FMS (n=79)	
Glutiramer acetate	23(11.98)	11(9.73)	12(15.19)	0.252*
Dimethyl fumarate	53(27.60)	29(25.66)	24(30.38)	0.472*
Fingolimod	12(6.25)	5(4.42)	7(8.86)	0.237**
Interferon β-1a low dose	9(4.69)	3(2.65)	6(7.59)	0.165**
Interferon β-1a high dose	16(8.33)	12(10.62)	4(5.06)	0.170*
Interferon β-1b	3(1.56)	1(0.88)	2(2.53)	0.570**
Teriflunomide	11(5.73)	9(7.96)	2(2.53)	0.129**
Rituximab	40(20.83)	25(22.12)	15(18.99)	0.598*
Natalizumab	8(4.17)	6(5.31)	2(2.53)	0.474**
Ocrelizumab	6(3.13)	6(5.31)	0	0.044***

*Chi-square test, **Fisher exact test, ***Significant results.

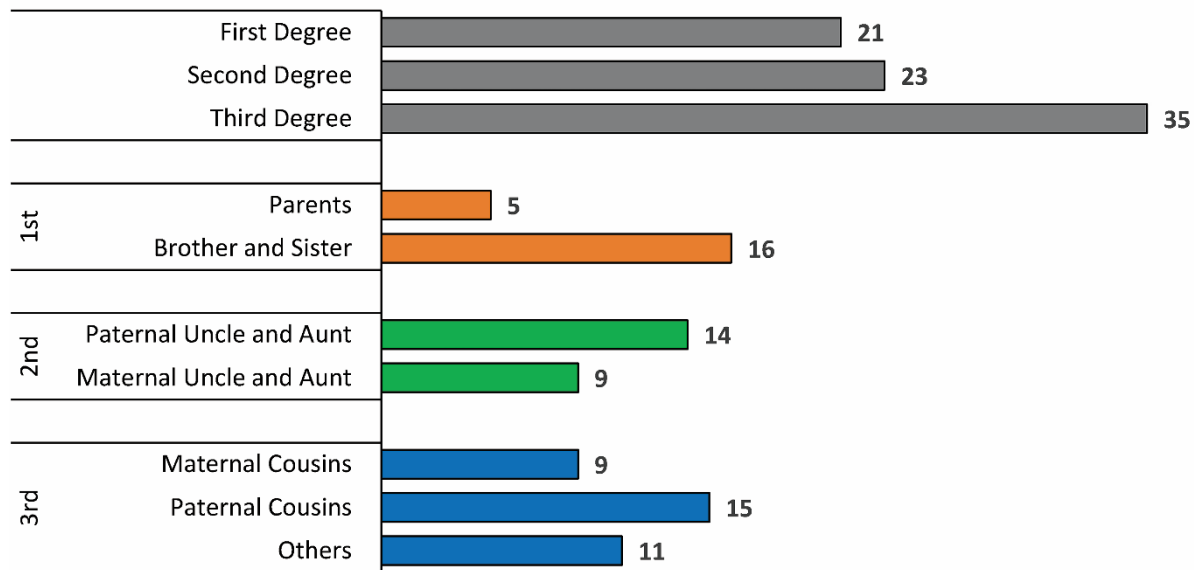


Figure 2. Distribution of familial history of MS among FMS patients



Note: In each row, the data denotes the number of FMS patients with MS among their respective family members.

festations, only diplopia was significantly higher in the SMS group (29.2% in SMS vs 16.4% in FMS, $P=0.042$) (Table 2).

In comparing imaging findings between the two groups, the SMS group exhibited a significantly higher number of lesions (31.59 ± 25.36 , range: 4-170, $P=0.017$) in contrast to the FMS group (22.83 ± 17.17 , range: 2-67, $P=0.017$). Furthermore, a statistically significant difference was observed in the average size of the smallest lesions (FMS: 8.12 ± 8.58 , SMS: 4.65 ± 2.57 mm², $P<0.001$). However, there was no statistically significant difference found in the average size of the largest lesions (FMS: 98.57 ± 80.97 , SMS: 100.84 ± 105.72 mm², $P=0.555$) or in the incidence of black holes (SMS: 25.3% vs FMS: 23.8%, $P=0.822$). Imaging findings of study participants can be found in Table 3.

The frequency of lesions in the periventricular region was significantly higher in the SMS group (98.2%) compared to the FMS group (89.8%, $P=0.017$). However, no statistically significant difference was observed in juxtacortical/cortical ($P=0.27$), infratentorial ($P=0.118$), cervical ($P=0.134$) and callosal ($P=0.178$) regions between the two groups (Table 3).

The average score of EDSS was significantly higher in the SMS group (2.20 ± 2.61) compared to the FMS group (1.09 ± 2.08 , $P=0.002$). Interestingly, most patients in both groups showed mild EDSS scores (SMS: 62.8% vs FMS: 84.8%) (Table 2). Moreover, when comparing

EDSS scores among different degrees of relatives, those in the first degree exhibited significantly higher scores (3.07 ± 2.68) than second-degree (0.34 ± 1.15) and third-degree (0.4 ± 1.24 , $P_{1,2}<0.001$, $P_{1,3}<0.001$, $P_{2,3}=0.993$) relatives (Table 4).

Within the SMS group, a moderate correlation was detected between the EDSS score and various factors, including onset age ($r=0.314$, $P=0.001$), disease duration ($r=0.342$, $P<0.001$), number of lesions ($r=0.305$, $P=0.001$) and the smallest lesion size ($r=-0.208$, $P=0.027$). Conversely, in the FMS group, significant correlations were found between the EDSS score and onset age ($r=0.422$, $P<0.001$), number of attacks ($r=-0.224$, $P=0.047$) and the largest lesion size ($r=0.321$, $P=0.004$) (Table 5).

Multivariate linear regression analysis revealed that, collectively, the type of MS (SMS or FMS), number of lesions, largest lesion size, onset age and disease duration accounted for approximately 26.4% of the variability observed in the EDSS score ($P<0.001$). Notably, the final model underscored significant associations between the type of MS (FMS or SMS) ($\beta=0.78$, $P=0.016$), onset age ($\beta=0.09$, $P<0.001$) and disease duration ($\beta=0.13$, $P=0.001$) with the EDSS score (Table 6).

Table 2. Demographic and clinical characteristics of the study population

Variables		No. (%) / Mean $\pm$ SD			P
		Overall (n=192)	SMS (n=113)	FMS (n=79)	
	Mean age (y)	36.52 $\pm$ 10.34	37.71 $\pm$ 10.83	34.82 $\pm$ 9.40	0.057*
Age (y)	<30	54(28.13)	28(24.78)	26(32.91)	0.152**
	30-40	65(33.85)	35(30.97)	30(37.97)	
	40-50	52(27.08)	34(30.09)	18(22.78)	
	$\geq$ 50	21(10.94)	16(14.16)	5(6.33)	
Gender	Male	64(33.33)	36(31.86)	28(35.44)	0.604**
	Female	128(66.67)	77(68.14)	51(64.56)	
Onset age (y)		30.43 $\pm$ 9.58	31.48 $\pm$ 9.55	28.92 $\pm$ 9.46	0.034 [†] &
Disease duration (y)		7.15 $\pm$ 4.19	7.05 $\pm$ 4.16	7.29 $\pm$ 4.26	0.738 [†]
Medical comorbidities		25(13.02)	12(10.62)	13(16.46)	0.237**
DMT usage		181(94.3)	107(94.7)	74(93.7)	0.765 ^{††}
MS clinical course	RRMS	152(79.17)	82(72.57)	70(88.61)	< 0.001 ^{††} &
	SPMS	26(13.54)	19(16.81)	7(8.86)	
	PPMS	12(6.25)	12(10.62)	0	
	CIS	2(1.04)	0	2(2.53)	
Number of attacks	None	77(40.10)	41(36.28)	36(45.57)	0.420**
	Once	73(38.02)	44(38.94)	29(36.71)	
	Twice	20(10.42)	12(10.62)	8(10.13)	
	Thrice or more	22(11.46)	16(14.16)	6(7.59)	
First presentation	Vision loss	58(30.21)	31(27.43)	27(34.18)	0.317**
	Sensory	99(51.56)	58(51.33)	41(51.90)	0.938**
	Motor	58(30.21)	39(34.51)	19(24.05)	0.120**
	Ataxia	53(27.60)	36(31.86)	17(21.52)	0.115**
	Diplopia	46(23.96)	33(29.20)	13(16.46)	0.042 ^{††} &
	Urinary	19(9.90)	15(13.27)	4(5.06)	0.061**
EDSS score		1.74 $\pm$ 2.46	2.20 $\pm$ 2.61	1.09 $\pm$ 2.08	0.002 [†] &
	Mild	138(71.88)	71(62.83)	67(84.81)	< 0.001 ^{††} &
	Moderate	49(25.52)	40(35.40)	9(11.39)	
	Severe	5(2.60)	2(1.77)	3(3.80)	

Abbreviations: DMT: Disease-modifying therapy; EDSS: Expanded disability status scale; MS: Multiple sclerosis; CIS: Clinically isolated syndrome; RRMS: Relapsing-remitting MS; SPMS: Secondary progressive MS; PPMS: Primary progressive MS. *The independent samples t-test, **Chi-square test, [†]Mann-Whitney U test, ^{††}Fisher exact test, &Significant results.

Table 3. Imaging findings of the study population

Variables		No. (%) / Mean±SD			P
		Overall (n=192)	SMS (n=113)	FMS (n=79)	
Lesion location	Periventricular	182(94.79)	111(98.23)	71(89.87)	0.017***&
	Juxtacortical/ Cortical	189(98.44)	110(97.35)	79(100)	0.270***
	Infratentorial	45(23.33)	31(27.43)	14(17.72)	0.118*
	Cervical	119(61.98)	75(66.37)	44(55.70)	0.134*
	Callosal	128(66.67)	71(62.83)	57(72.15)	0.178*
Number of lesions		27.99±22.72	31.59±25.36	22.83±17.17	0.017***&
Smallest lesion size (mm²)		6.08 ± 6.07	4.65±2.57	8.12±8.58	<0.001***&
Largest lesion size (mm²)		99.91±96.08	100.84±105.72	98.57±80.97	0.555**
Black hole		47(24.48)	27(23.89)	20(25.32)	0.822*

*Chi-square test, **Mann-Whitney U test, ***Fisher exact test, &Significant results.



Discussion

This investigation sought to delineate demographic, clinical, and imaging distinctions among individuals with sporadic and familial forms of MS. The SMS cohort exhibited significantly higher AAO, higher incidence of diplopia as the initial manifestation, higher EDSS scores, higher number of total lesions, higher number of lesions

in the periventricular region, and lower average size of the smallest lesions relative to the FMS cohort. Moreover, the EDSS score was higher in the SMS group and demonstrated significant associations with MS subtype (SMS or FMS), onset age and disease duration.

In the present investigation, the FMS group exhibited a lower AAO, aligning with the findings reported by

Table 4. Comparing average EDSS scores across various familial relationships

Variable	Familial History (Mean $\pm$ SD)			P
	1 st Degree	2 nd Degree	3 rd Degree	
EDSS score	3.07 $\pm$ 2.68	0.34 $\pm$ 1.15	0.41.24	P _{total} <0.001* P _{1,2} <0.001** P _{1,3} <0.001** P _{2,3} =0.993**

EDSS: Expanded disability status scale.



*One-way ANOVA test, **Post Hoc Tukey HSD test.

Table 5. The spearman correlation between EDSS score and independent variables among study groups

MS Types	Onset Age	Disease Duration	Number of Attacks	Number of Lesions	Largest Lesion Size	Smallest Lesion Size
EDSS score	Coefficient	0.314	0.342	0.179	0.305	0.116
	P	0.001	<0.001	0.058	0.001	0.220
	Coefficient	0.422	0.066	-0.224	0.032	0.321
	P	<0.001	0.562	0.047	0.780	0.004

EDSS: Expanded disability status scale; MS: Multiple sclerosis.



Table 6. Backward multivariate linear regression of independent variables

Model	Unstandardized Coefficients		P	95% CI for B	
	B	Std. Error		Lower Bound	Upper Bound
1 st	Constant	-2.137	0.696	0.002	- 3.510 -0.765
	MS type (sporadic/familial)	0.593	0.336	0.079	- 0.070 1.255
	Gender	-0.422	0.335	0.210	- 1.083 0.240
	Number of lesions	0.012	0.008	0.144	- 0.004 0.029
	Smallest lesion size	-0.025	0.027	0.352	- 0.078 0.028
	Largest lesion size	0.004	0.002	0.035	0 0.008
	Medical comorbidities	-0.211	0.479	0.660	-1.156 0.734
	Onset age	0.090	0.017	< 0.001	0.058 0.123
	Disease duration	0.106	0.040	0.008	0.028 0.184
	Number of attacks	0.150	0.103	0.150	- 0.054 0.354
Final	Constant	-2.343	0.662	0.001	-3.650 -1.036
	MS type (sporadic/familial)	0.777	0.321	0.016	0.144 1.411
	Number of lesions	0.014	0.008	0.089	-0.002 0.030
	Largest lesion size	0.004	0.002	0.053	0 0.007
	Onset age	0.089	0.016	<0.001	0.057 0.122
	Disease duration	0.130	0.037	0.001	0.057 0.204

EDSS: Expanded disability status scale; MS: Multiple sclerosis.

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Dependent variable: EDSS score; Adjusted R square=0.264, F=14.69, P<0.001.

Salehi et al. [22] and Katsavos et al. [16]. Notably, Katsavos et al. discerned a reduced AAO in FMS patients with the affected first-degree relatives. In contrast, those with third-degree relatives showed no such distinction [16]. Conversely, several other investigations failed to observe a significant distinction in the AAO between individuals with FMS and SMS [2, 17, 19, 23-25]. This outcome might be because MS is a complex disease with both genetic and environmental factors contributing to its onset and progression. FMS suggests a stronger genetic component, possibly leading to an earlier disease onset. On the other hand, SMS may have a later onset because it could be more influenced by environmental factors, which may take longer to exert their effects. Furthermore, genetic predisposition in FMS may interact with environmental factors at an earlier age, leading to an earlier onset of the disease.

No significant difference in disease duration was observed between the two groups, aligning with findings from other research studies [2, 17, 19].

Furthermore, our study found no difference in gender distribution between familial and sporadic types of MS. This observation aligns with findings from prior research [2, 16, 17, 26]. It was established that MS results from the interplay between genetic and environmental factors. Although females are relatively more susceptible to MS than males, this holds for both sporadic and familial cases; hence, the gender distribution remains parallel in both scenarios.

Regarding the frequency of attacks, most patients in both groups encountered one or fewer attacks. However, the observed difference between the two groups was not statistically significant, consistent with the findings of Moghadam et al. [2]. In contrast, Andrijauskis et al. [19]

reported a higher annual attack rate in FMS compared to SMS, with 1.4 attacks vs 0.8 attacks ($P < 0.05$).

In our investigation, certain patients presented with concurrent medical comorbidities such as hypertension, diabetes, respiratory disorders, thyroid disorders, migraine, and seizures. However, no significant difference was observed between the two study groups, aligning with the conclusions drawn by Moghadam et al. [2] and Mokhtari et al. [25]. Given the complex interplay between genetic, environmental, and lifestyle factors that contribute to the pathogenesis of MS, it is plausible that these same factors may also impact the co-occurrence of other medical comorbidities. Therefore, further investigation is warranted to understand these associations comprehensively.

We observed a higher incidence of diplopia among SMS patients as the first presentation of the disease, consistent with findings by Katsavos et al. [16] and Faraji et al. [23]. Nevertheless, Mokhtari et al. [25] reported no significant difference between the two groups regarding visual symptoms as the initial manifestation of the disease.

In this study, we observed significantly higher EDSS scores in the SMS group, contrary to prior research outcomes. Moghadam et al. [2] and Katsavos et al. [16] reported no substantial difference in EDSS scores between the two groups. In contrast, Andrijauskis et al. [19] and Faraji et al. [23] identified lower EDSS scores in SMS patients. Furthermore, we observed a higher EDSS score in FMS patients with first-degree relatives affected by MS. Conversely, Tipirneni et al. [17] found no significant variations in EDSS scores based on the degrees of familial relationships (first, second and third degrees).

Our investigation revealed that the FMS patients exhibited fewer lesions and a higher average size of the smallest lesion than the SMS group. Nonetheless, there was no statistically significant difference between the two groups' average size of the largest lesion and the occurrence of black holes. Tipirneni et al. [17] reported a greater average T1-lesion volume in the FMS group.

Furthermore, we observed a notable increase in lesions within the periventricular region among SMS patients, aligning with the results reported by Moghadam et al. [2]. Interestingly, they also noted significantly more lesions within the callosal region among FMS patients. Katsavos et al. [16] reported higher lesions in the subcortical and cervical regions for SMS and FMS patients, respectively. Additionally, Andrijauskis et al. [19] iden-

tified a significant rise in lesions within the cerebellum and brainstem, specifically among FMS patients.

Conclusion

In conclusion, FMS exhibits distinct characteristics from SMS across various facets, such as an earlier onset age, a predominance of RRMS phenotype, lower rate of diplopia, lower EDSS scores, lower lesion frequency in the periventricular area, fewer overall lesion numbers, and a higher average size of the smallest lesions.

Study limitations

The present investigation encountered certain limitations. Unfortunately, many patients in NMSRI-Guilan lacked MRI scans, and many available MRIs had severe artifacts, leading to their exclusion and thus reducing the sample size. This limitation raises concerns about the finality of our findings and may affect their generalizability to the broader MS patient population. The cross-sectional nature of our design offers a snapshot of a specific moment, preventing the establishment of definitive cause-and-effect relationships and failing to capture changes over time. Uncontrolled variables, such as lifestyle factors and healthcare accessibility, could introduce confounding elements into our results. Additionally, the reliance on self-reported data to categorize patients as FMS introduces the possibility of bias. Participant responses may be influenced by inaccurate recall or intentional alteration. Lastly, the study's confinement to a specific geographical location (Guilan Province, Iran) suggests caution in extrapolating the results to populations with distinct cultural, social, or environmental conditions. As a result, there is a need for more extensive multinational investigations that incorporate the assessment of genetic predisposition among participants to ensure the generalizability of the findings.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of [Guilan University of Medical Sciences](#) (Code: IR.GUMS.REC.1401.380). The researchers adhered to the ethical principles of the Declaration of Helsinki. Additionally, signed informed consent was acquired from each participant, along with approval from the chairman of the MS Society of Guilan province for data extraction.

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Authors contributions

Conceptualization: Alia Saberi, Amirreza Ghayeghran, and Mohammad Ali Sahraian; Methodology: Sharareh Eskandari; Formal analysis: Sharareh Eskandari; Supervision: Alia Saberi and Amirreza Ghayeghran; Writing the original draft: Kamal Amir Ashjei Asalemi, Nima Broomand Lomer, Kasra Sarlak, and Negin Ashoori; Investigation: Kamal Amir Ashjei Asalemi; Writing, review, editing and final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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