Palestinian Medical and Pharmaceutical Journal (PMPJ). 2023; 8(1): 7-16

Familial versus sporadic multiple sclerosis in Palestine: a retrospective cross-sectional pilot study

Asil Jbara[1], Ibaa Saidi[1], Manal Ishtayah[1], Mustafa Ghanim[1,], Nihad Al-Othman[1] & Maha Rabayaa[1]*

[1] Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, Palestine.

*Corresponding author: mustafa.ghanim@najah.edu

Received: (11/10/2021), Accepted: (6/12/2021). DOI: https://doi.org/10.59049/2790-0231.1138

ABSTRACT

Background: Multiple sclerosis (MS) is a prevalent multifactorial neurological condition caused by hereditary and environmental factors. No research in Palestine has focused on family instances and the likely influence of paternal consanguinity (PC). In this study, researchers evaluated numerous risk variables, clinical course, early symptoms, and disability prevalence in familial MS (FMS) cases and sporadic MS (SMS) cases in the Palestinian community. ***Methods*:** A suitable sample of 90 SMS and 31 FMS patients was used in a retrospective cross-sectional analysis. Neurology clinics provided the data. Data were examined using IBM SPSS 22 to compare FMS with SMS in numerous risk factors, clinical course, early symptoms, and disability prevalence. ***Results****:* The research included 90 SMS instances and 31 FMS cases. Males developed FMS at a higher rate (45.2 %) than females (35 %) in the SMS group. In contrast, more females (64.4 %) had SMS than men (54.8 %) in the FMS group. However, ladies were more likely than men to have any MS. Parental consanguinity was identified in around 40% of the SMS and FMS groups. The mean age of onset was the same in both groups (28.5 in SMS and 27.26 in FMS), and practically all patients in both groups had recurrent MS episodes. There is no statistically significant difference between SMS and FMS regarding risk factors and lifestyle variables. Only within the SMS was the occurrence of autoimmune disorders mentioned. Within the two groups, the relapsing-remitting clinical course predominates. The proportion of first presenting symptoms and impairments did not differ substantially between the SMS and FMS. ***Conclusion:*** There were no significant variations between SMS and FMS regarding demographics, risk factors, disability, clinical course, and PC.

Keywords: Multiple Sclerosis, Consanguinity, Sporadic.

INTRODUCTION

Multiple sclerosis (MS) is considered the most frequent demyelinating disease. It is characterized by multifocal inflammatory lesions infiltrated with lymphocytes and inflammatory cytokines. Inflammation damages oligodendrocytes and induces nerve axon demyelination. Nerve axons seem to remain intact, at least in the early stages of the disease (1, 2). Due to these changes, nerve impulse transmission is disrupted (3). However, some lesions may be regenerated by the active oligodendrocytes progenitor cells (2).

MS affects women more frequently than men, with a sex ratio of 2.5:1 (4). Interestingly, the peak age of onset is about five years earlier in women. Although MS is the most prevalent demyelinating disease, it varies by geographic area, ranging from high levels of 120 per 100,000 in North America and Europe (5) to low rates, of 2 per 100,000, in Eastern Asia and sub-Saharan Africa (6). In the Arab world, the prevalence ranges from 2 to 42 per 100,000 population (7). The global prevalence of familial MS is approximately 12.6%. However, the risk is increased with MS risk factors (8).

Based on the clinical phenotype, MS is generally classified into four categories, including progressive relapsing (PRMS), primary progressive (PPMS), relapsing-remitting (RRMS), and secondary progressive multiple sclerosis (SPMS) (4, 9). The clinical manifestations of MS are variable and unpredictable, particularly concerning the development of disabilities, including sensory dysfunction (numbness, tingling, burning, itching), walking abnormalities (caused by fatigue, imbalance, tremor, and spasticity), vision defects (diplopia, blurred,

and abnormal eye movement), intestinal and urinary system malfunction (bladder dysfunction and constipation), cognitive and emotional disturbances (depression and learning difficulties), dizziness and vertigo sexual problems, dysphagia, and dysarthria (10). A precise diagnostic strategy for MS relies of MS on Mcdonald's criteria; detection of the spatial and temporal dissemination of focal neurological deficits and exclusion of essential differential diagnoses (10). Some indications and symptoms are more prevalent during the early stages of the disease. The initial presenting symptoms of MS differ significantly from one patient to another. Optic neuritis is the most frequent manifestation of MS, which develops due to the optic nerve's involvement, resulting in a mostly unilaterally visual acuity deficit (11).

The ultimate cause of MS is unclear and poorly understood. However, MS is considered a multifactorial disease where several genetic predispositions and environmental factors increase the risk of having MS. (12). The genetic burden has been extensively studied, and more than 200 genetic loci and major histocompatibility complex (MHC) polymorphisms have been identified as factors that affect the risk of the disease. The progression and clinical characteristics of MS (13) documented potential environmental risk factors for MS include exposure to infectious viruses such as human herpesvirus type 6, Epstein Barr virus (EBV), and bacteria such as mycoplasma pneumonia (14), smoking (15), vitamin insufficiency (16), diet, and exposure to UV radiation (17). These risk factors are supposed to cause MS by different mechanisms.

Although many studies on MS, its etiology, pathogenesis, clinical presentation, and treatment are not entirely understood. Only scarce studies focused on the familial cases of MS and the possible role of consanguinity specifically in the Arab world, none here in Palestine. Therefore, this study aimed to assess the proportion of FMS cases, compare FMS to SMS in terms of risk factors, clinical presentation, and demographic characteristics, estimate the proportion of PC among MS patients, and compare MS patients with PC to MS patients with no PC.

METHODS

Study design and study sample

A retrospective cross-sectional pilot study was conducted to compare FMS to SMS regarding risk factors, clinical presentation, and PC. A convenience nonprobability sample of MS patients who agreed to participate and meet the inclusion criteria was enrolled in the study. One hundred twenty-one cases of MS patients were obtained from seven private clinics in the Friends Society of MS patients in Palestine and The Ministry of Health's primary health care centers.

Inclusion and Exclusion criteria

The inclusion criteria include patients diagnosed with MS by a neurologist at the included health centers. Patients with a neurologic disease other than MS, current severe relapse of the disease, or declined initiation or continuation were excluded from the study.

Ethical consideration

The ethical approval for the current study was obtained from the Institutional Review Board (IRB) at An-Najah National University in Nablus city. Informed consent was obtained from each patient. Patient privacy and data confidentiality were maintained throughout the study. Consent entails obtaining permission to collect information from the patient's records, and any missing data was received directly from the patients. Patients' participation in this trial was entirely voluntary.

Data collection

Data were obtained from the patient's records at the clinics or self-administered through interviews with them after they were approved to participate. The questions and records were set to cover all data regarding demographic factors including gender, marital status, age of onset and recurrence, lifestyle characteristics including smoking, alcohol intake, body weight, migration history, viral infection and vaccination, autoimmune disease comorbidities, adherence to medications, and parent consanguinity. The data include the clinical course of the disease, initial symptoms, and the presence of the disability. The importance of this data relies on what is

reported in the literature regarding the variables associated with MS.

Statistical Analysis

The IBM Statistical Package of Social Sciences (IBM SPSS) 22 was used for data analysis to summarize parental consanguinity and MS-related independent variables. A Chi-square test was used to compare the FMS with the SMS; a p-value of less than 0.05 was considered significant.

RESULTS

Demographic Characteristics

Of the 121 patients enrolled in the study, 90 have SMS, and 31 have FMS. More females than males are in either form of MS; females represent 64.4% (n=58) of the SMS and 54.8% (n=17) of the FMS. Parental consanguinity was observed in more than one-third of patients in both groups (40% of SMS (n=36) and 41.9% of FMS (n=13)). The mean age of onset was nearly the same among both groups, SMS's mean age of onset was 28.5 years, and FMS was 27.26 years. As for the recurrence of attacks, the familial group all had recurrent attacks (100%, n=31)) and the sporadic group nearly all (95.6 %, n=86). For more details, the demographic characteristics of both groups of MS patients are summarized in (Table 1).

Table (1): Demographic characteristics of the total multiple sclerosis population, classified by sporadic or familial status.

Variable		Sporadic% (n)	Familial % (n)	*p*-value
Total number		90	31	-
Gender	Male	35.6% (32)	45.2% (14)	0.342
	Female	64.4% (58)	54.8% (17)	
Sex ratio (M/F)		0.55	0.82	
Marital status	Single	17.8% (16)	16.1% (5)	0.834
	Married	82.2% (74)	83.9% (26)	
Age of disease onset (mean)		28.50	27.26	-
Recurrence attack		95.6% (86)	100% (31)	0.233

Risk factors and lifestyle characteristics

As summarized in (Table 2), nearly 30% of patients in both groups were smokers, and almost all patients were nonalcoholic before diagnosis. Most patients in both groups were average body weight according to their BMI and had no migration history outside Palestine before diagnosis. Almost 31.1% (n=28) of SMS and 29% (n=9) of FMS cases were infected with a virus such as varicella, hepatitis B, or EBV. Most patients were vaccinated according to the scheduled vaccination program in Palestine. More adherence to medication was observed among FMS patients compared to SMS. Autoimmune diseases were observed within the SMS group (3.3% of patients, n=3). No significant difference between both groups regarding risk factors (p-value > 0.05).

Table (2): Risk factors and lifestyle characteristics in the multiple sclerosis population, classified by sporadic or familial status.

	Sporadic, % (n)	Familial, % (n)	*p*-value
Smoker	30% (27)	32.3% (10)	0.814
Alcoholic	2.2% (2)	0% (0)	0.403
Weight			
Underweight	6.7% (6)	0% (0)	0.359

	Sporadic, % (n)	Familial, % (n)	*p*-value
Normal weight	48.9% (44)	58.1% (18)	
Overweight	34.4% (31)	35.5% (11)	
Obese	4.4% (4)	6.5% (2)	
Morbid obesity	5.6% (5)	0% (0)	
Migration history			
No migration	68.9% (62)	77.4% (24)	
Migration to Europe or the USA	8.9% (8)	3.2% (1)	0.657
Migration to Gulf countries or Arabian country	21.1% (19)	19.4% (6)	
Migration to Russia	1.1% (1)	0% (0)	
Viral infection	31.1% (28)	29% (9)	0.828
Viral vaccination	91% (82)	90.3% (28)	0.909
Associated autoimmune diseases	3.3% (3)	0% (0)	0.737
Adherence to medication	52.2% 47)	71% (22)	0.069
Paternal consanguinity (PC)	40% (36)	41.9% (13)	0.826

Clinical course

Most of the FMS and SMS cases in our study had RRMS clinical course (56.7% (n=51) for SMS and 45.2% (n=14) for FMS), the SPMS was the lowest percentage among SMS cases, while it was PPMS among FMS cases. The variability of the clinical course between the two groups was not significant (p-value > 0.05), as it is shown in (Table 3).

Table (3): Clinical course of familial and sporadic multiple sclerosis groups.

Clinical course	Sporadic, % (n)	Familial % (n)	*p*-value
Relapsing-remitting	56.7% (51)	45.2% (14)	0.235
Primary progressive	25.6% (23)	22.6% (7)	
Secondary progressive	17.8% (16)	32.3% (10)	

Initial presentation

The variation of the initial presenting symptoms between the familial and the sporadic MS patients was not significant. The weakness in one or more extremities was the most common in both groups (Table 4).

Table (4): Initial presenting symptoms of familial and sporadic multiple sclerosis groups.

	Sporadic, % (n)	Familial, % (n)	*p*-value
Vision loss	14.4% (13)	19.4% (6)	
Double vision	6.7% (6)	3.2% (1)	
Weakness in one or more extremities	16.7% (15)	22.6% (7)	
A disrupted sensation of one or more extremities	12.2% (11)	12.9% (4)	
Change in balance	7.8% (7)	0% (0)	
Spasm in one or more extremities	2.2% (2)	0% (0)	
Brief shock or tingling with neck movement	1.1% (1)	0% (0)	0.688
Vertigo (spinning dizziness)	1.1% (1)	6.5% (2)	
Dysarthria	2.2% (2)	0% (0)	
Tonic-clonic seizure	1.1% (1)	0% (0)	
Facial palsy	1.1% (1)	0% (0)	
Color blindness	1.1% (1)	0% (0)	
mixed	32.2% (29)	35.5% (11)	

Prevalence of disability in familial and sporadic MS

The familial group has a slightly higher prevalence of defecation problems, dysphagia, memory problems, speech problems, and vision disabilities. Most disabilities (defecation problems, dysphagia, memory loss, and urination difficulties) were developed within or after 10 years of diagnosis but were not commonly initial symptoms. Movement restrictions are the most common disabilities among both groups, while the least common ones are speech and hearing disabilities, with a prevalence of 0% for hearing problems in both groups. There was no significant difference between the FMS and SMS regarding disability prevalence (Table 5).

Table (5): Prevalence of disability among familial and sporadic MS.

Disability	Onset	Sporadic, % (n)	Familial, % (n)	*p*-value
Defecation problems	At onset	2.2% (2)	9.7% (3)	0.080
	Within 10 years	11.1% (10)	23.3% (7)	
	After 10 years	16.7% (15)	12.9% (4)	
Dysphagia	At onset	2.2% (2)	9.7% (3)	0.189
	Within 10 years	6.7% (6)	12.9% (4)	
	After 10 years	17.8% (16)	12.9% (4)	
Memory Problems	At onset	1.1% (1)	3.2% (1)	0.712
	Within 10 years	13.3% (12)	19.4% (6)	
	After 10 years	25.6% (23)	22.6% (7)	
Movement Restrictions	At onset	23.3% (21)	25.8% (8)	0.858
	Within 10 years	15.6% (14)	19.4% (6)	
	After 10 years	26.7% (24)	19.4% (6)	
Speech Disabilities	At onset	3.3% (3)	0.0% (0)	0.054
	Within 10 years	1.1% (1)	9.7% (3)	
	After 10 years	2.2% (2)	6.5% (2)	
Urination Difficulties	At onset	5.6% (5)	12.9% (4)	0.672
	Within 10 years	22.2% (20)	16.1% (5)	
	After 10 years	15.6% (14)	16.1% (5)	
	On Foleys	5.6% (5)	3.2% (1)	
Vision Disabilities	At onset	12.2% (11)	9.7% (3)	0.266
	Within 10 years	3.3% (3)	12.9% (4)	
	After 10 years	4.4% (4)	3.2% (1)	
Hearing Problems	At onset/within/after 10 years	0.0% (0)	0.0% (0)	

DISCUSSION

The current study is one of the few types of research concerning MS in Palestine. In our retrospective study, we covered 121 patients, among which 31 patients (25.6%) had a family history of MS and were classified as FMS cases; the others had SMS. The percentage of FMS in the studied sample is considered high compared to the percentage found among MS patients in Iran (11.2%) (18), the UK (11.0%) (19), and Denmark (7.1%) (20), but it is nearly similar to the percentage reported in Abu Dhabi (24.5%) (7). This variation could be attributed to environmental and genetic variability between Arab and Western areas. The estimated mean age of diagnosis in our study was approximately 28.5 years old in the sporadic group and 27 years old in the familial group, which comes in line with other studies that were conducted in the Arab world, with the age of

onset of MS being in the third decade (19-21). This study found that MS is more prevalent in females than males (64.4% of sporadic MS patients and 54.8% of FMS). This agrees with previous studies of MS in Jordan, Dubai, and Kuwait, showing a female predominance (21-23). Despite the similarity in demographic features among different groups, the relatively increased male-to-female ratio in the group containing the most heavily loaded families is consistent with previous suggestions that this should be anticipated in polygenic disorders (21). The threshold for the more resistant sex (males in the case of multiple sclerosis) should be lowered due to the elevated rate of susceptibility factors in families identified by having more affected relatives. Comparatively little congruence in clinical phenotype within families was found, as previously reported (24-26). There was no significant difference between the FMS and SMS in the demographic characteristics, similar to the results reported in Abu Dhabi (27). The underlying cause of MS is an interaction between genetic and environmental factors such as vitamin D deficiency, smoking, obesity, and infection, which are likely to play a role in disease development. (1). Additionally, several gene loci that are associated with MS could be reinforced by PC (28). In our study, we found that FMS patients had a PC of 41.9% (13 out of 31), which was not significantly different from the PC (40%) observed among the SMS group (36 out of 90); both numbers are not far from the general population consanguinity rates. In Saudia Arabia, 37.6% of FMS Saudi patients reported PC (29). In contrast to our study, PC was significantly higher in FMS than non-FMS among Saudi patients (30). This variability in results may be attributed to the difference in the sample size. On the other hand, a cross-sectional study examining the effect of PC on the causality of MS found that the risk of MS among offspring of consanguineous unions seems lower than that of offspring of unrelated parents (31).

Smoking, Epstein-Barr virus (EBV) infection, and vitamin D deficiency have been previously environmental solid risk factors for MS (32). We found that 30% of sporadic MS and 32.3 % of the FMS were smokers before diagnosis. Our results are consistent with a study in Beirut, which showed that around (39%) of MS patients were smokers (33). All patients were nonalcoholic before diagnosis; most patients in both groups were in their average body weight and had no history of migration outside Palestine before diagnosis. Almost 30% of patients in both groups were infected with varicella, hepatitis B, or EBV. However, most patients were vaccinated as children as the vaccination program schedule in Palestine (34), which did not show any preference of risk factors in either group. The risk factors, including smoking, alcohol intake, weight, viral infection and vaccination, autoimmune diseases, and migration history, were insignificant between the FMS and SMS groups.

The MS clinical course begins as relapsing-remitting in most patients, most of which change to progressive disease (35). In our study, the RRMS clinical course was predominant in both groups. However, it is slightly higher among SMS. The SPMS was slightly higher among FMS. These findings are not similar to a study in Denmark, where RRMS and SPMS were more common among familial MS cases than sporadic MS cases (20).

We studied the initial presentation of familial and sporadic multiple sclerosis cases. In our study, the most common presenting symptom was weakness in one or more extremities (16.7% of the presenting symptoms in SMS and 22.6% in FMS) without a substantial difference. It nearly approximated the percentage found in MS patients in Jordan (30.8%). FMS's optic neuritis and sensory symptoms were more common (26, 36). In our study, optic neuritis was the second most common initial presenting symptom, with a higher incidence in FMS (19.4%) than in SMS (14.4%). Its disrupted sensation was the third most common among FMS (12.6%), comparable with the SMS percentage (12.2%). The studied initial presenting symptoms were not varied significantly between the two groups, similar to what was observed in the UAE (27) and Iraq (36).

We studied over disease course disabilities in familial and sporadic multiple sclerosis. The most common disabilities in the studied sample were movement restriction,

memory loss, urination, and defecation problems. Others had reported fatigue, spasticity, and voiding disorder as the most frequent disabilities (37), and another study had reported disabilities in cognition, energy, and manual dexterities as more common disabilities (38). The increases in movement disability with time are concurrent with other studies that show that MS patients have a pronounced increase in movement restriction disability across 10 years (39). Overall, there was no significant variation between FMS and SMS in complications of the disease, which is consistent with what was reported previously (24).

STRENGTHS AND LIMITATIONS OF THE STUDY

A significant limitation to our study was that we faced an obstacle in reaching the patients due to the lack of previous data as there were insufficient medical centers specialized in receiving MS patients. Moreover, as the study was retrospective, limiting the study in controlling exposure or outcome, we had to rely on others for accurate recordkeeping. No research groups are working on MS in Palestine. The complexity of MS and its widely variable clinical presentation is challenging. MS patients' mood swings and severity of MS relapses may reduce the number of participants limiting the size sample despite many MS patients in Palestine.

The study had two main aspects of strength. It was the first study addressing familial MS in Palestine, among the few international research comparing familial MS with non-FMS characteristics. Second, in Palestinian societies where consanguinity is widespread, we expect our project to be of high yield for genetic awareness and counseling in Palestine.

CONCLUSIONS

In Palestine, the frequency of sporadic MS is greater than that of familial MS. The paternal consanguinity of familial and sporadic MS patients is virtually identical. There are no significant differences between the two groups regarding demography, risk factors, and impairment. Both ethnicities share other disease trends.

Ethical approval and consent to participate

This article contains human participants, and the IRB granted the ethical approval at An-Najah National University, Nablus, Palestine.

Availability of data and materials

All required data are included in this paper

Authors' contribution

Asil Jbara 1: Conceptualization, data curation, writing-original draft. **Ibaa Saidi 2**: Conceptualization, data curation, writing-original draft. **Manal Ishtayah 3**: Conceptualization, data curation, writing-original draft. **Mustafa Ghanim 4**: Conceptualization, project administration, supervision, data curation, writing-original draft, editing. **Nihad Al-Othman 5**: Supervision, data curation, validation, data analysis, methodology, writing-original draft. **Maha Rabayaa 6**: Writing and editing, formatting, and results interpretation. This work was extracted from the graduation projects of medical students.

Competing interest

The authors state no conflict of interest.

FUNDING

The study receives no funding.

ACKNOWLEDGMENTS

The authors would like to thank the Faculty of Medicine and Health Sciences and its members in NNU for their cooperation in achieving this work. Also, the authors thank the Clinical Research Center (Dr. Sa'ed Zyoud) of An-Najah National University Hospital for their wise pieces of advice.

REFERENCES

1) Dobson, R. (2019). Giovannoni G. Multiple sclerosis–a review. E*uropean journal of neurology*. 26(1). 27-40.

2) Lassmann, H. (2018). Multiple sclerosis pathology. *Cold Spring Harbor perspectives in medicine*. 8(3). a028936.

3) Compston, A. (2008). Coles A. Multiple sclerosis. (1474-547X (Electronic)).

4) Hauser SL GD. (2008). Harrison's Principles of Internal Medicine. 17th ed.

II. ed. New York: McGraw-Hill Medical; 11 p.

5) Khan, F. Turner-Stokes, L. Fau - Ng, L. Ng, L. Fau - Kilpatrick, T. & Kilpatrick, T. (2008). Multidisciplinary rehabilitation for adults with multiple sclerosis. (1468-330X (Electronic)).

6) Leray, E. Moreau, T. Fromont, A. & Edan, G. (2015). Epidemiology of multiple sclerosis. (0035-3787 (Print)).

7) Benamer, HT. Ahmed, ES. Al-Din, AS. & Grosset, DG. (2009). Frequency and clinical patterns of multiple sclerosis in Arab countries: a systematic review. *Journal of the neurological sciences*. 278(1-2). 1-4.

8) Harirchian, MH. Fatehi, F. Sarraf, P. Honarvar, NM. & Bitarafan S. (2018). Worldwide prevalence of familial multiple sclerosis: A systematic review and meta-analysis. *Multiple sclerosis and related disorders*. 20:43-7.

9) Oh, J. Vidal-Jordana, A. & Montalban, X. (2018). Multiple sclerosis: clinical aspects. *Current opinion in neurology*. 31(6). 752-9.

10) Gelfand, JM. (2014). Multiple sclerosis: diagnosis, differential diagnosis, and clinical presentation. (0072-9752 (Print)).

11) Hojjati, SMM. Zarghami, A. Hojjati, SA. & Baes, M. (2015). Optic neuritis, the most common initial presenting manifestation of multiple sclerosis in northern Iran. *Caspian journal of internal medicine*. 6(3). 151-5.

12) Hatch, MN. Schaumburg, Cs. Fau - Lane, TE. Lane, Te. Fau - Keirstead, HS. & Keirstead, HS. (2009). Endogenous remyelination is induced by transplant rejection in a viral model of multiple sclerosis. (1872-8421 (Electronic)).

13) Katsavos, S. Artemiadis, A. Davaki, P. Stamboulis, E. Kilindireas, K. & Anagnostouli, M. (20180. Familial multiple sclerosis in Greece: Distinct clinical and imaging characteristics in comparison with the sporadic disease. *Clinical neurology and neurosurgery*. 173. 144-9.

14) Fujinami, RS. von Herrath, Mg. Fau - Christen, U. Christen, U. Fau - Whitton, JL. & Whitton, JL. (2006). Molecular mimicry, bystander activation, or viral persistence: *infections and autoimmune disease*. (0893-8512 (Print)).

15) O'Gorman, C. Bukhari, W. Todd, A. Freeman, S. & Broadley, SA. (2014). Smoking increases the risk of multiple sclerosis in Queensland, Australia. (1532-2653 (Electronic)).

16) Speer, G. (2013). [Impact of vitamin D in neurological diseases and neurorehabilitation: from dementia to multiple sclerosis. Part I: the role of vitamin D in the prevention and treatment of multiple sclerosis]. (0019-1442 (Print)).

17) Sloka, S. Silva, C. Fau - Pryse-Phillips, W. Pryse-Phillips, W. Fau - Patten, S. Patten, S. Fau - Metz, L. Metz, L. Fau - Yong, VW. & Yong, VW. (2011). A quantitative analysis of suspected environmental causes of MS. (0317-1671 (Print)).

18) Rezaali, S. Khalilnezhad, A. Naser Moghadasi, A. Chaibakhsh, S. & Sahraian, MA. (2013). Epidemiology of multiple sclerosis in Qom: Demographic study in Iran. *Iranian Journal of Neurology*. 12(4). 136-43.

19) Sahraian, MA. Khorramnia, S. Ebrahim, MM. Moinfar, Z. Lotfi, J. & Pakdaman, H. (2010). Multiple sclerosis in Iran: a demographic study of 8,000 patients and changes over time. European neurology. 64(6). 331-6.

20) Steenhof, M. Nielsen, NM. Stenager, E. Kyvik, K. Möller, S. & Hertz, JM. (2019). Distribution of disease courses in familial vs sporadic multiple sclerosis. *Acta Neurologica Scandinavica*. 139(3). 231-7.

21) al-Din, AS. el-Khateeb, M. Kurdi, A. Mubaidin, A. Wriekat, A. al-Shehab, A. Khalil, R. (1995). Multiple sclerosis in Arabs in Jordan. *Journal of the neurological sciences*. 131(2). 144-9.

22) Inshasi, J. Thakre, M. (2011). Prevalence of multiple sclerosis in Dubai, United Arab Emirates. *The International journal of neuroscience*. 121(7). 393-8.

23) Al-Din, AS. (1986). Multiple sclerosis in Kuwait: clinical and epidemiological study. *Journal of neurology, neurosurgery, and psychiatry*. 49(8). 928-31.

24) Weinshenker BG, Bulman D, Carriere W, Baskerville J, Ebers GC. A comparison of sporadic and familial multiple sclerosis. Neurology. 1990;40(9):1354-.

25) Sadovnick, AD. Ebers, Gc. Fau - Dyment, DA. Dyment, Da. Fau - Risch, NJ. Risch, NJ. (1996). Evidence for genetic basis of multiple sclerosis. *The Canadian Collaborative Study Group*. (0140-6736 (Print)).

26) Sadovnick, AD. Wingerchuk, DM. Ebers, GC. Rice, GPA. Baskerville, J. Kremenchutzky, M. Koopman, WJ. Hader, W. Mandalfino P. (2000). The natural history of multiple sclerosis: a geographically based study: 8: Familial multiple sclerosis. Brain. 123(3). 641-9.

27) Ceccarelli, A. Mifsud, VA. Dogar, A. (2020). Demographic and clinical characteristics of familial and sporadic multiple sclerosis: A single center exploratory study from Abu Dhabi. *Journal of Clinical Neuroscience.* 76. 145-7.

28) Roberts, D. Vogler, G. (1991). Consanguinity and multiple sclerosis in Orkney. *Genetic epidemiology*. 8(3). 147-51.

29) Jumah, MA. Kojan, S. Khathaami, AA. Abdulkareem, IA. Blawi, MA. Jawhary, A. (2011). Familial multiple sclerosis: does consanguinity have a role? *Multiple Sclerosis Journal*. 17(4). 487-9.

30) AlJumah, M. Otaibi, HA. Al Towaijri, G. Hassan, A. Kareem, A. Kalakatawi, M. Alrajeh, S. Al Mejally, M. Algahtani, H. Almubarak, A. & Alawi, S. (2020 Oct). Familial aggregation of multiple sclerosis: results from the national registry of the disease in Saudi Arabia. *Multiple Sclerosis Journal–Experimental, Translational and Clinical.* 6(4). 2055217320960499. https://doi.org/10.1177/2055217320960499.

31) Tadmouri, GO. Nair, P. Obeid, T. Al Ali, MT. Al Khaja, N. Hamamy, HA. (2009). Consanguinity and reproductive health among Arabs. *Reproductive health*. 6. 17-

32) Ramagopalan, SV. Dobson, R. Meier, UC. & Giovannoni, G. (2010). Multiple sclerosis: risk factors, prodromes, and potential causal pathways. *The Lancet Neurology*. 9(7). 727-39.

33) Mouhieddine, TH. Darwish, H. Fawaz, L. Yamout, B. Tamim, H. & Khoury, SJ. (2015). Risk factors for multiple sclerosis and associations with anti-EBV antibody titers. *Clinical Immunology*. 158(1). 59-66.

34) Parnell, GP. & Booth, DR. (2017). The Multiple Sclerosis (MS) Genetic Risk Factors Indicate both Acquired and Innate Immune Cell Subsets Contribute to MS Pathogenesis and Identify Novel Therapeutic Opportunities. *Frontiers in immunology*. 8. 425-.

35) Confavreux, C. Vukusic, S. (2014). The clinical course of multiple sclerosis. *Handbook of clinical neurology*. 122. 343-69.

36) Al-hamadani, HA. Marah, HA. & Al-Saffar, F. (2012). Comparison of familial and sporadic multiple sclerosis in Iraqi patients. *Journal of the Faculty of Medicine Baghdad*. 54(1). 1-6.

37) Rommer PS, Eichstädt K, Ellenberger D, Flachenecker P, Friede T, Haas J, Kleinschnitz C, Pöhlau D, Rienhoff O, Stahmann A, Zettl UK. (2019). Symptomatology and symptomatic treatment in multiple sclerosis: Results from a nationwide MS registry. *Multiple Sclerosis Journal*. 25(12). 1641-52.

38) Johansson S, Ytterberg C, Claesson IM, Lindberg J, Hillert J, Andersson M, Widén Holmqvist L, von Koch L. (2007). High concurrent presence of

disability in multiple sclerosis. Journal of neurology. 254(6). 767-73.

39) Conradsson, D. Ytterberg, C. von Koch, L. Johansson, S. Changes in disability in people with multiple sclerosis: a 10-year prospective study. (1432-1459 (Electronic)).