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Familial aggregation of multiple sclerosis: Results from the national registry of the disease in Saudi Arabia

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Abstract

Background: Multiple Sclerosis (MS) is a chronic CNS inflammatory disease commonly affecting young adults. Both genetics and environmental factors have been reported to have a role in pathophysiology of the disease.

Objective: This article aims to report familial nature and aspects of MS in Saudi Arabia.

Method: The study utilized data collected by the National Saudi MS Registry between 2015 and 2018; especially data relevant to the familial history of MS. SPSS 22 was used for all analysis and reporting. Statistical significance was set at p-value < 0.05.

Results: The registry included 20 hospitals and a total of 2516 patients from the different regions of Saudi Arabia with median age 32.00 (Range: 11–63) and 66.5% being female. About 12.8% of all registered patients reported a family history of MS (95%CI: 11.2-13.9). Reported parental consanguinity was significantly higher among patients with family history (FMS) (56.3%) compared to non-FMS patients (27.9%). 42.53% of FMS patients reported having siblings affected with MS (95%CI: 37.01–48.21), with more female siblings affected than males (63.4% vs 36.6% respectively).

Conclusion: Our Findings suggested that FMS was less prevalent than what was reported previously; however, parental consanguinity was significantly more prevalent among FMS patients than non-FMS. Our findings were in line with those reported in recent studies in the region, but lower than those reported by western countries indicating that increasing prevalence of MS in Saudi Arabia could be multifactorial and other environmental factors should be considered for understanding this recent rise in the prevalence of MS in Saudi Arabia.

Keywords: Multiple sclerosis, familial MS, FMS, parental consanguinity, Saudi Arabia

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Background

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) affecting young adults. Both genetics and environmental factors have been reported to have a role in the pathophysiology of the disease. Evidence supports both individual and cumulative effects of environmental and genetic factors.[1,2] Due to variations in these factors, differences can also be seen in prevalence and natural history among people from different geographic locations or different ethnicities.[3,4] With the advancement in research, common genetic variants related to the immune system have been identified in certain individuals, which therefore implicates the autoimmune nature of the disease disturbing the regulatory mechanism rather than the

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coding error.[1] In the past, studies on genetic science have reported strong evidence linking MS and variation in the genes encoding human leucocyte antigens (HLAs) contained within the major histocompatibility complex, and since then familial aggregation, high prevalence among twins, increased probability among relatives and siblings of MS patients have been reported by different studies.[1,4–6] According to several family studies, 15–20% of MS patients have one or more affected relatives.[3,4]

Family studies and twin studies have shown that there is a strong genetic component underlying the etiology of multiple sclerosis. The prevalence of this disease among first-degree relatives of affected individuals is 20 to 40 times higher than the overall population prevalence. Among identical twins, the chances of MS are approximately 200–300 times greater than that of the general population if one is affected.[5–7] The higher concordance rate for monozygotic twins (25–34%) than for dizygotic twins (2–5%) indicates a high heritability.[8,9] A recent systematic review of 184 articles from 1954–2016 estimated the prevalence of familial MS at 12.6% within a total sample size of 14,619 MS patients globally (CI: 9.6–15.9).[4] These studies identified a strong connection of MS with genetic predisposition and therefore, in order to understand the exact mechanism of the disease and create a better management plan for it, both environmental factors and genetic predisposition should be taken into consideration.

The Middle East and far eastern populations have reported a higher prevalence of autosomal recessive diseases. These communities have high rates of consanguineous marriages and have larger families.[10] According to the 2013 MS Atlas,[11] Middle Eastern and North African countries are located in a low- to moderate-risk zone for MS; however, recent studies have reported increased prevalence in these countries especially among women.[12–16] This increased prevalence, not only imposes a huge burden on the healthcare systems, but also negatively affects the quality of life of impacted patients and their families. Thus, it is important to study the multiple domains and underlying risk factors that are associated with the rising prevalence of MS, and that in turn could benefit the healthcare planning and policymaking.[17] Moreover, current trends are highlighting the major impact of familial aggregation and studying inheritance patterns, which would add to the understanding of the interaction between genes and environmental factors. This in turn could be beneficial for planning future strategies particularly for high-risk groups. Thus, through this article we aim to report familial aspects of MS in Saudi Arabia.

Method

In 2015, the National MS registry was launched in Saudi Arabia. The registry was a hospital-based study with an objective to collect data about all MS patients with confirmed diagnosis according to the 2010 McDonald Criteria from all parts of the Kingdom. All the participating sites from the five major regions; central, eastern, western, northern and southern region of Saudi Arabia obtained IRB/EC approval for participating in the registry. Data was collected from 20 participating hospitals across the Kingdom.

Statistical analysis

Statistical analysis of the data collected until 2018 was performed using SPSS version 22.0. The following is a general description of the statistical methods used for analysis of the collected data collected. Continuous and discreet quantitative variables (age, time duration, etc.) were summarized in terms of descriptive statistics such as mean (Standard Deviation) and Median (Inter Quartile Range) as per normality test. Categorical variables were described as the total number and relative percentage of patients per response category. To evaluate the association between different categorical variables, bivariate analyses were also performed. Chi square and Fisher exact test were reported for categorical variables. Statistical significance was set at p-value <0.05. P values were adjusted by using Alexander Copper method. Logistic regression was used to report the predictors of positive family history. Variables with p-value of 0.25 and less at univariate were entered into multivariate model. Odds ratio with 95% confidence interval were reported.

Results

As of 2018, a total of 2516 patients were registered in the MS Registry in the different regions of Saudi Arabia with median age 32.00 (Range: 11–63) and 66.5% being female. As indicated in Table 1, out of the 2507 MS patients who responded to the Family History question, 12.8% (95%CI: 11.2%–13.9%) had a positive family history of MS. The proportion of individuals who reported a family history of MS varied significantly between the regions, ranging from 8.1% in the southern region to 16.2% in the central region with adjusted p-value of 0.009. Parental consanguinity (PC) was reported by 31.8% of all cases in all regions. History of parental consanguinity varied between the regions and this

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was statistically significant (Adjusted p value: 0.003). The majority of those who reported PC were not first-degree relatives (63.10%). Of the total number of patients, 6.3% reported affected siblings.

Among patients with familial MS, 42.53% reported having at least one sibling affected (95%CI: 37.01-48.21). When compared, female siblings were more affected than male siblings were (63.4% (n = 85) and 36.6% (n = 49)) respectively.

The differences in characteristics among patients with and without family history of MS are shown in Table 2, where Group 1 are patients with positive family history (who reported at least one family member affected with MS) and Group 2 are patients with no family history (who did not report any family member affected with MS). It was noted that there was no difference in gender nor age between the two groups. Between the two groups, 66.1% of patients in Group 1 reported completion of university education, and 33.0% of patients among group 2 reported completion of high school; the difference seen in education level between the 2 groups was not significant with adjusted p value 0.063. Occupational history and marital status did not differ between the two groups as well, with adjusted p-value 0.963 and >0.999 respectively. Mean age of 1st attack was also not significantly different between the 2 groups with adjusted p value 0.387. On the other hand, parental Consanguinity was significantly higher in Group 1 (56.3%) than Group 2 (27.9%) with adjusted p value 0.009. (Table 2)

Results of multivariate analysis showed that individuals with parental consanguinity had higher odds of having positive family history of MS compared to those with no parental consanguinity when adjusted for marital status, education and concomitant diseases with OR 3.30(95%CI: 2.57-4.23). (Table 3)

Discussion

Multiple sclerosis (MS) is a common chronic autoimmune disease that affects the central nervous system (CNS) of young adults. In the recent years, studies have reported increasing prevalence of MS in Saudi Arabia and therefore it became important to generate a disease registry for gathering systematic and timely secondary data related to patients with MS in the different regions of the Kingdom. Globally, registries play an important role in informing the current policies and strategies after looking into disease prevalence, associated factors, and trends in healthcare service provision and utilization. In 2015, a national MS registry was launched in Saudi Arabia with an objective to register all MS patients with confirmed diagnosis according to the 2010 McDonald Criteria. Our study used data collected through the registry to report prevalence of family history of the disease in the Kingdom.

Looking at the demographic findings, we observed that the female to male ratio was about 2:1.This female predominance is consistent with other universal well-established registries.[18–20] The overall percentage of MS patients with family history was 12.8% of which 6.3% had at least one sibling affected. The percentage of MS patients with family history is comparable to figures in the region as well as figures in the west (13.32% in Kuwait, 15–20% in regions such as Europe, Canada, and North America).[19,21]

Table 1. Distribution of familial characteristics across the regions.

Variable	Total n (%)	Western region	Central region	Eastern region	Southern region	Northern region	P value[a]
Family history of MS (n = 2465[b])							
Yes	315 (12.8)	106 (10.8)	136 (16.2)	47 (13.1)	14 (8.1)	12 (11.2)	0.009
No	2150 (87.2)	878 (89.2)	706 (83.8)	313 (86.9)	158 (91.9)	95 (88.8)	
Parental consanguinity (n = 2259[b])							0.003
Yes	719 (31.8)	199 (22.4)	359 (43.8)	68 (24.5)	54 (32.1)	39 (36.8)	
No	1540 (68.2)	690 (77.6)	460 (56.2)	209 (75.5)	114 (67.9)	67 (63.2)	
Siblings with MS (n = 2143[b])							0.068
Yes	134 (6.3)	44 (5.0)	59 (8.1)	22 (7.7)	7 (4.4)	2 (2.0)	
No	2009 (93.7)	828 (95.0)	667 (91.9)	265 (92.3)	152 (95.6)	97 (98.0)	

[a]Adjusted P values (Alexander Copper method used).
[b]indicates the total number of patients who responded to the corresponding question.

Table 2. Characteristics of MS patients with positive family history.

Variable	Group 1[a] n = 315 (%)	Group 2[b] n = 2150 (%)	P value[c]
Gender			>0.999
Male	107 (34.0)	710 (33.0)	
Female	208 (66.0)	1440 (67.0)	
Age			>0.999
<40	246 (78.1)	1663 (77.4)	
>40	69 (21.9)	486 (22.6)	
Education			0.063
None	2 (0.6)	29 (1.4)	
Primary	27 (8.6)	205 (9.5)	
Secondary	77 (24.6)	709 (33.0)	
University	207 (66.1)	1204 (56.1)	
Mean age at 1st attack	26.81 (8.98)	27.90 (8.77)	0.387
Consanguinity			
Yes	175 (56.3)	543 (27.9)	0.009

[a]Group 1 (With family history).
[b]Group 2 (No family history).
[c]Adjusted P values (Alexander Copper method used).

Table 3. Predictors of positive family history of MS.

Variables	Odds ratio (95% CI)	Adjusted odds ratio (95%CI)
Age		
<40	1.04 (0.78–1.36)	–
>40	Ref	
Marital status		
Single	1.25 (1.01–1.64)	1.27 (0.98–1.64)
Widow	1.18 (0.63–2.21)	1.23 (0.64–2.39)
Married	Ref	
Education		
High and above	2.49 (0.59–10.52)	2.92 (0.67–12.71)
Primary	1.65 (0.388–7.01)	1.85 (0.42–8.10)
None	Ref	
Parental consanguinity		
Yes	3.32 (2.60–4.24)	3.30 (2.57–4.23)
No	Ref	
Concomitant disease		
Yes	1.51 (1.13–2.01)	1.28 (0.94–1.74)
No	Ref	

The prevalence of familial MS (FMS) differed significantly among the regions, with the highest prevalence of family history reported in the central region. Likewise, parental consanguinity was also highly prevalent in the central region compared to the other regions. Mean age of 1st attack was lower among patients' group with positive family history, but the difference was not statistically significant.

Compared to a previous study conducted in Saudi Arabia in 2010, where 21% of the MS patients reported familial history,[6] our data showed only 12.8% of patients reported any familial history. This suggests that the increasing prevalence of MS in Saudi Arabia is not related to the familial history. Recent epidemiological studies suggest a trend of an overall increase in disease prevalence and incidence

in the same populations worldwide. This may be attributed to a number of factors, possibly caused by the broad availability of MRI scans and the introduction of new diagnostic criteria in 1983 and 2001, 2005, 2010, & 2017 and their impact on early identification and diagnosis of MS cases.[22,23] In addition, the access to more effective immunotherapies, may have improved life expectancy of affected patients and thus have contributed to increased MS prevalence.[24]

Similar to family history, parental consanguinity (PC) was reported by 37% of MS patients in the 2010 study conducted in Saudi Arabia,[6] in contrast to the finding of our current study, where 31% of MS patients reported parental consanguinity.

A number of recent studies in the region reported similar findings of low prevalence of familial MS. For example, a study conducted in Saudi Arabia in 2018 by Halawani et al. found that 6.2% of MS cases included in the study reported a positive family history of MS,[25] and another study conducted in 2016 found 11.1% of cases with a positive family history.[26] Low prevalence of familial MS among MS patients was also reported in a third study conducted in Qatar by Deleu et al. (2013). On the other hand, there are inconclusive findings from the literature regarding parental consanguinity. Few studies reported an association with familial MS while others did not.[6,27] Nonetheless, parental consanguinity in our study was significantly higher among the group of patients with positive family history (56.3%) compared to the group with negative family history (27.9%). These findings were consistent with other MS studies, which found that familial MS (FMS) patients were more likely than non-FMS patients to report PC, suggesting a potential role of consanguinity in familial MS.[6] In addition, among those with siblings affected, female siblings were found to be more affected than male siblings were. This was also in line with other studies, some of which used data from nationwide registries, suggesting that for siblings, the highest risk was found for sisters of patients with multiple sclerosis. The overall highest age-adjusted risk was for sisters of an affected brother.[28]

The Central region reported a relatively higher prevalence of familial history, parental consanguinity, and number of siblings affected compared to other regions in the Kingdom, indicating that familial factors may be related to increased prevalence in some of the regions in Saudi Arabia. However, in the past few years, consolidation of the evidence for environmental risk factors, identification of new genetic factors, and increased appreciation of the importance of gene–environment interactions have led to a greater consensus that MS is a multifactorial disease and cannot be linked to a single causative factor.[29] A number of recent studies and systemic reviews found strong evidence of associations between decreased sunlight exposure, low vitamin D, history of smoking, adolescent obesity, and the development of MS.[26] A study conducted in Kuwait showed that Bedouin ethnicity and increased daily exposure to sunlight both decreased the risk of MS, while a family history of MS and presence of comorbidities increased the risk of MS.[30]

Therefore, all factors, including the various environmental risk factors that were reported to be associated with higher prevalence of MS in Saudi Arabia should be considered while reporting the increasing prevalence of MS.[25] undefined

Findings of this study should be concluded with caution as this registry was able to collect data from 20 hospitals out of a total of 127 hospitals treating MS population across the Kingdom, covering only 15.7% of all hospitals; therefore, findings of this study cannot be generalized. However, the data collected through this registry is the most recent data available to date and one of the largest compared to all current available data for Saudi Arabia. The national registry study group is planning to further collect prospective/longitudinal data and will update the registry in a timely manner with new information. Moreover and as aforementioned, MS is a complex disease and should be further studied in-depth by considering all the multifaceted risk factors, including environmental factors along with the genetic predisposition.

Conclusion

Results of our study showed that prevalence of familial MS among MS patients was relatively lower than anticipated and previously reported; however, parental consanguinity was comparatively prevalent. Our findings herein resonate with results of recent studies in the region, but lower than those reported by western studies, indicating that increasing prevalence of MS in Saudi Arabia could be multifactorial, and environmental factors should also be considered, in order to understand this recent rise in the prevalence of MS in Saudi Arabia.

Author contributions

Authors have made significant contributions to the study design, data acquisition, analysis, and interpretation. They have read and approved the submitted version.

Mohammed AlJumah, Reem Bunyan, Samah Ishak, Sahar Shami: Played a significant role in the planning and development of study material, sites' recruitment, data acquisition, quality assurance, data interpretation, manuscript revision.

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Ashraf El-Metwally: Played a significant role in data analysis and Interpretation, and a role in manuscript writing.

Availability of data and materials

Data and relevant material is available upon request. However, access to the data is restricted to public and require appropriate approvals from the authorized and participating parties.

Consent for publication

Individual participants in the study have provided a signed informed consent to participate in the study with the potential to publish research papers based on the aggregated and anonymous data collected by the registry.

Ethics approval and consent to participate

The study was approved by the Ministry of Health and by Ethics Committee in each of the participating hospitals in the registry. In addition, registered patients were informed about the registry and possible studies stemming from the registry and they participated after signing an informed consent.

Conflict of Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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