Multiple Sclerosis and Related Disorders 36 (2019) 101377

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Pediatric multiple sclerosis and its familial recurrence: A population based study (1999–2017)

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ARTICLE INFO

Keywords:
Multiple sclerosis
Pediatric
Familial history
Risk factor
Prevalence

ABSTRACT

Background: The Pediatric onset multiple sclerosis (POMS) prevalence is increasing worldwide accounting for around 3 to 10% of MS cases. The risk of POMS is supposed to reflect a complex interaction between environmental and genetic risk factors that may occur during the childhood, adolescent, or post-pubertal years.

Objective: The present study aimed at estimating the prevalence of POMS and assessing the epidemiology of familial recurrence of POMS in Tehran.

Method: A retrospective population based cross-sectional study was designed from 1999 to 2017. The baseline characteristic information was collected from MS patient's ≤18 years old (y/o). Pearson's chi-square test and logistic regression were used to analyze the relationship among variables and estimate the odds ratio (OR) via SPSS software, version 23.

Results: A total of 1937 POMS patients (77.80% female and 22.20% male patients) participated in the study. The point prevalence of POMS was 16.20 per 100,000 populations in 2017. Mean age at disease onset was 15.96 ± 2.28 y/o. The female to male ratio was 2.02:1 in pre-pubertal cases (3–12 y/o), but it increased to 3.69:1 in 13–18 y/o age groups (*P* value = 0.001, OR = 1.82; 95% CI = 1.27–2.26). There were 288 (14.9%) cases with positive familial history of MS. The strongest association between MS risk and positive familial history was observed in second degree relatives who presented MS (*P* value = 0.046, OR = 1.74; 95%CI = 1.01–3.01). A significant association was observed among maternal second degree relatives with POMS (*P* value = 0.018, OR = 2.27; 95%CI = 1.15–4.47).

Conclusion: In comparison to other large studies, the prevalence of POMS was high in the data collected from Tehran. POMS risk is higher among females and the sex ratio increases after puberty. We found a significant association between POMS risk and familial history in maternal second degree relatives. Further studies of POMS epidemiology might yield greater understanding of the natural history of this disease.

1. Introduction

Pediatric onset multiple sclerosis (POMS) is usually defined as the first clinical symptom of MS before the age of 18 and accounts for about 10% of all MS cases (Alroughani and Boyko 2018; Banwell et al., 2007a).

MS in children is presented differently, mostly as a relapsing–remitting (RR) course, and rarely as primary or secondary progressive forms. The disease pattern is more likely to be 'inflammatory' than 'degenerative' with slower progression and good recovery from relapses (Banwell et al., 2007b; Renoux et al., 2007).

Epidemiological data about incidence and prevalence of POMS is limited globally (Eskandarieh et al., 2016). According to MS International Federation, the worldwide prevalence of POMS was 0.63 per 100,000 population in 2013 (Browne et al., 2014). Data on POMS prevalence is also limited in Iran. In Tehran, the prevalence of adult MS was 101.39 per 100,000 in 2014. The incidence of POMS was 4.79 among girls and 1.36 among boys per 100,000 population (Eskandarieh et al., 2017). The point prevalence of MS increased to 148.06 per 100,000 in 2017 in Tehran of whom 10.2% presented POMS (Eskandarieh et al., 2018b). In a study on 8000 patients in Tehran in 2008, 6.1% were reported to have disease onset under the age of 16 (Sahraian et al., 2010).

Individuals with one or more MS affected relatives (approximately 2–5% in first degree relatives) are thought to be more at risk of MS compared to the general population (Eskandarieh et al., 2018a).

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https://doi.org/10.1016/j.msard.2019.101377
Received 16 January 2019; Received in revised form 20 July 2019; Accepted 26 August 2019

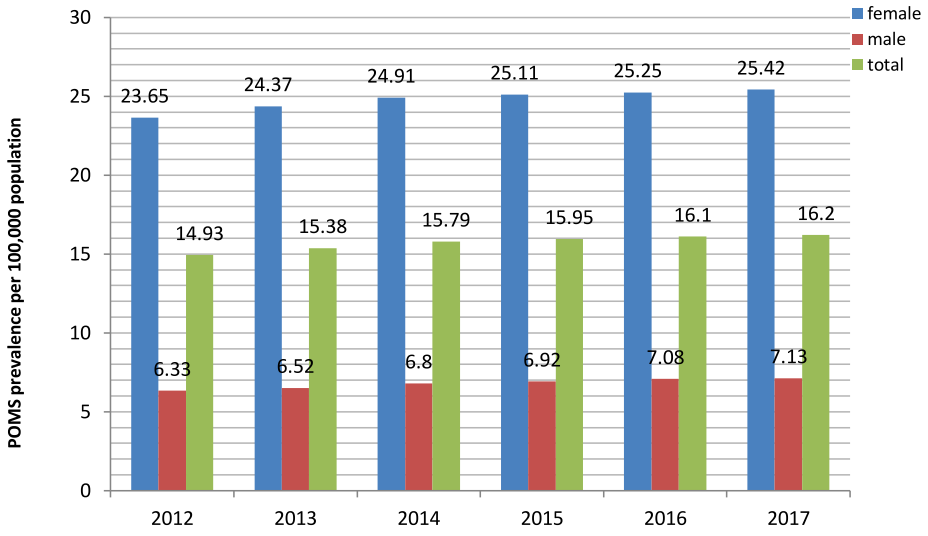

Fig. 1. Annual Prevalence of POMS in Tehran (2012–2017).

Moreover, the identical twins of MS patients are claimed to be more at risk of MS, although this tendency is probably an over-estimate (Hawkes and Macgregor 2009; Islam et al., 2006).

In Tehran, a positive familial history of MS was found in 12.6% of female and 13.6% of male patients. The strongest association among first-degree relatives was observed in siblings (P value $\leq$ 0.001) (Eskandarieh et al., 2018a).

A positive family history of demyelinating diseases was estimated to be 10% in pediatric MS patients living in Shiraz (Inaloo et al., 2014). Furthermore, in Isfahan, about 9% of POMS individuals had a positive family history of MS in first or second degree relatives (5% in first and 3% in second degree relatives) (Etemadifar et al., 2007).

The aim of the present study was to examine the epidemiology and familial recurrence rate of POMS in Tehran.

2. Methods

2.1. Data collection

A population based cross-sectional study was undertaken on the Iranian MS Society (IMSS) registry system of Tehran from 1st April 1999 to 31st December 2017. The Iranian Multiple Sclerosis Society (IMSS) (Eskandarieh et al., 2018a; Eskandarieh et al., 2018b) is a subset of the MS International federation (MSIF) that was established in Tehran, Iran, in 1999 with the aim of educational, research, and social support. All clinically definite MS patients diagnosed by neurologists are referred to IMSS. As the diagnostic criteria has been revised several times during our study, the diagnosis of patients referring before 2001 was made based on Poser criteria (Zipoli et al., 2003), and patients who were referred after 2001 were diagnosed according to the current version of McDonald criteria at the time of diagnosis (Csepany 2018).

The MS patients approved by neurologists who fulfilled McDonald criteria are registered in the IMSS. Neurologists persuade all patients to refer to the IMSS for registration and get tracking code for receiving support.

The questionnaire designed in MS research center of Tehran University of medical sciences covered most of the important epidemiological variables associated to risk for recurrence of MS including pediatric onset cases, age at disease onset, sex, familial history of MS, and degree of relatives (Eskandarieh et al., 2018a).

The goals of the MS registry were explained by interviewer in IMSS and all patients provided written informed consent and filled up a detailed questionnaire. The existence of familial history of MS was reported by separate members. Patients should renew their membership every 5 years by receiving their membership card in IMSS and only the patients whose diagnoses were confirmed in the follow up referrals, remained in the study. To determine the familial history of MS, we categorized relatives of patients into 3 subgroups including first, second, and third degree relatives (Eskandarieh et al., 2018a). The information was collected among POMS patients $\leq$18 y/o.

Even though the majority of the MS patients were registered in the IMSS, some of patients might not have been registered through the years of disease onset, thus the number might be underestimated.

2.2. Study area

The study was conducted and designed to estimate the prevalence of POMS in Tehran in 2017. Tehran is the capital of Iran located in the northern part of Iran extending from latitude 50°21′–53°09′ and longitude 34° 51′–36°08′ with an estimated population of 13,441,124 in 2017. According to the last census of the Iranian statistical center, there were 3,022,000 individuals $\leq$18 in 2017 living in Tehran.

2.3. Statistical analyses

The chi-square test was used to analyze the relationship among variables. Logistic regression analysis was performed to estimate the odds ratio (OR) for individual variables to predict factors leading to familial POMS. P values less than 0.05 were considered as statistically significant. SPSS version 23 was used for statistical analyses.

3. Results

3.1. MS prevalence

Totally, 1937 POMS patients participated in this study. The point prevalence of POMS was 16.20 per 100,000 in 2017.The age standardized POMS prevalence was 25.42 and 7.13 per 100,000 general population for females and males, respectively (Fig. 1).

3.2. Sex ratio trend

In total, 1507 (77.80%) participants were females and 430)22.20%) were males. The average female to male ratio was 3.5:1 in 2017. This index was 2.02:1 in cases with pre-pubertal onset at 3–12 years old, but it increased dramatically during and after puberty (Fig. 2). The logistic regression analysis revealed that age was significantly associated with sex ratio when different age groups were compared (i.e., female to male

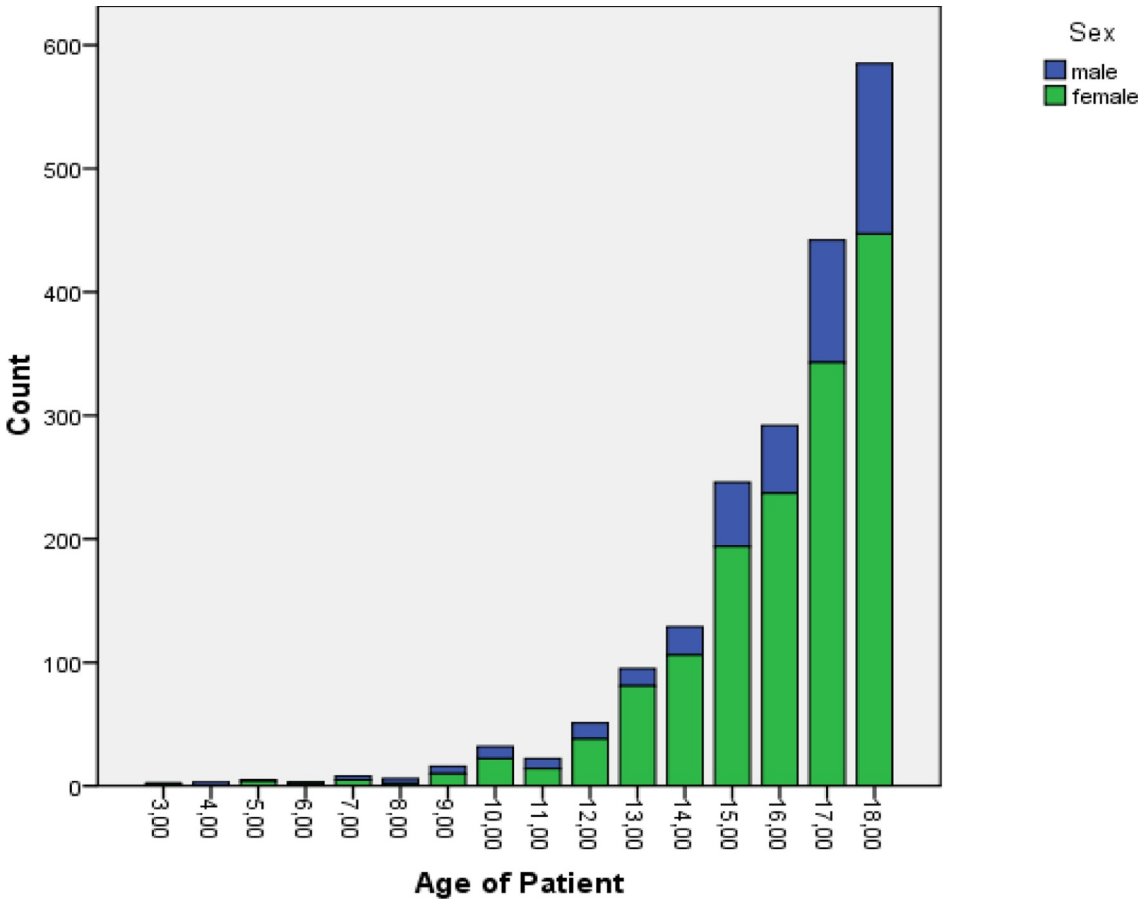

Fig. 2. Age groups and sex ratio trends of POMS patients.

Table 1
Baseline characteristics and comparison of crude risk of patients.

Variables	Female *N* = 1507 (%)	Male *N* = 430 (%)	Total *N* = 1937 (%)	OR (95%CI)	*P* value
Age group (year)					
3–10	47 (3.1)	28 (6.5)	75 (3.8)	Reference	–
11–13	133 (8.8)	35 (8.1)	168 (8.7)	**2.26 (1.24–4.11)**	0.007
14–18	1327 (88.1)	367 (85.4)	1694 (87.5)	**2.15 (1.33–3.48)**	0.002
Familial history of MS					
Yes	217 (14.6)	71 (16.9)	288 (14.9)	Reference	–
No	1273 (85.4)	350 (83.1)	1623 (85.1)	1.19 (0.88–1.59)	0.24
Degree of relatives					
First degree	83 (5.5)	27 (6.3)	110 (5.7)	1.14 (0.73–1.79)	0.54
Second degree	41 (2.7)	20 (4.7)	61 (3.1)	**1.74 (1.01–3.01)**	**0.046**
Third degree	59 (3.9)	14 (3.3)	73 (3.8)	0.82 (0.45–1.49)	0.52
Maternal relatives	74 (4.9)	27 (6.3)	101 (5.2)	1.29 (0.82–2.04)	0.26
Paternal relatives	62 (4.1)	18 (4.2)	80 (4.1)	1.01 (0.59–1.74)	0.94
Maternal second degree	22 (1.5)	14 (3.3)	36 (1.9)	**2.27 (1.15–4.47)**	**0.018**
Paternal second degree	22 (1.5)	6 (1.4)	28 (1.4)	0.95 (0.38–2.37)	0.92

OR = odds ratio, 95% CI = 95% confidence interval by logistic regression analysis.
Maternal Relatives: mother, maternal grandmother/grandfather, maternal aunts/uncles, maternal cousins.
Paternal Relatives: father, paternal grandmother/grandfather, paternal aunts/uncles, paternal cousins.
Bold numbers correspond to significant values.

ratio increased to 3.69:1 in 13–18 years old age group, *P* value = 0.001, OR = 1.82; 95% CI = 1.27–2.26) (Table 1).

3.3. Age at disease onset

The mean age at disease onset was 15.96 ± 2.28 years old. The mean ages at disease onset for female and male patients were 16.00 ± 2.19 and 15.82 ± 2.69 years old, respectively.

This value was 15.87 ± 2.28 in patients with positive family history of MS and 15.98 ± 2.33 in patients without family history of MS. The logistic regression analysis showed that the age factor was significantly associated with MS recurrence in different sexes ($P \leq 0.007$). The association was seen in pediatric age group who were 11–13 years old (OR = 2.26; 95% CI = 1.24–4.11) and 14–18 years old (OR = 2.15; 95% CI = 1.33–3.48) (Table 1).

The distribution of cases by age groups per year is demonstrated in Fig. 3.

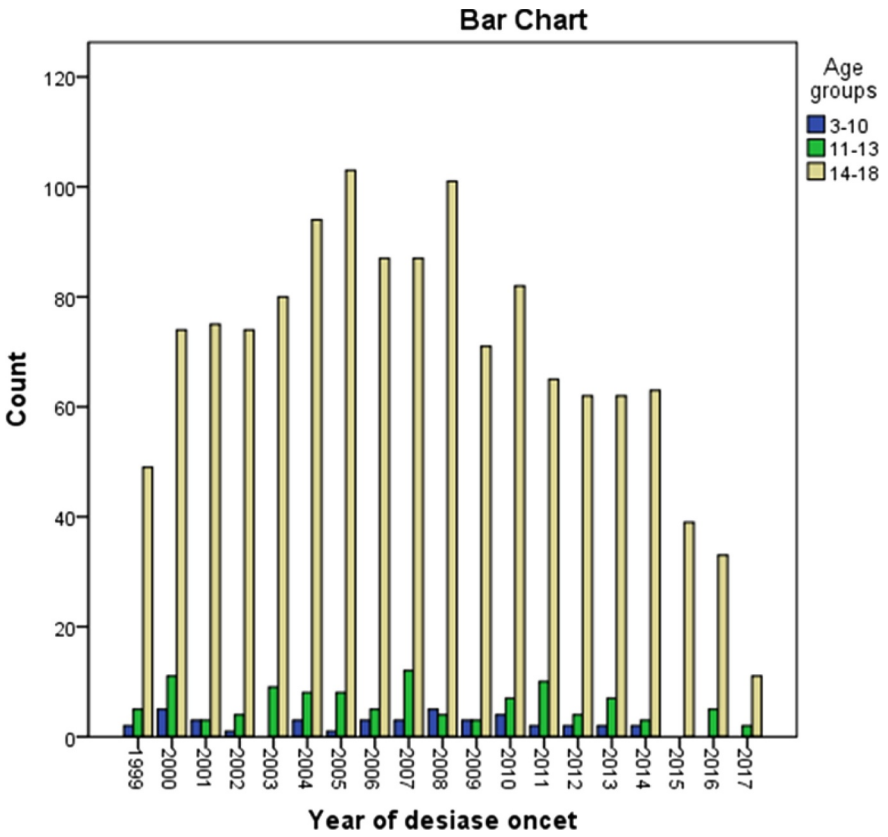

Fig. 3. Distributions of cases by different age groups per year.

3.4. Familial history of MS

There were 288 (14.9%) cases of POMS patients with a positive family history of MS; 217 (14.6%) females and 71 (16.9%) males. Despite the fewer number of men, the familial recurrence of MS appeared to be higher among men, although it was not statically significant (*P* value = 0.24). Compared to the reference group (3–12 years old), the *P* value was 0.94 (OR = 1.01; 95% CI = 0.63–1.63) for the 13–18 age group. MS familial recurrence was 5.7% in first degree, 3.1% in second degree, and 3.8% in third degree relatives (Table 1). The strongest association was seen in second degree relatives (*P* value = 0.046, OR = 1.74; 95%CI = 1.01–3.01) and in this category the significant association was found in maternal second degree relatives (*P* value = 0.018, OR = 2.27; 95% CI = 1.15—4.47) (Table 1). Classifying relatives according to their maternal and paternal relatives revealed that the maternal familial history of MS was 5.2% (*P* value = 0.26, OR = 1.29; 95% CI = 0.82–2.04) and the paternal familial history of MS was 4.1% (*P* value = 0.94, OR = 1.01; 95% CI = 0.59–1.74) (Table 1). Among second degree relatives, the most significant association was seen in maternal aunts/uncles (*P* value = 0.007, OR = 2.63; 95% CI = 1.31–5.30) (Table 2).

Table 2
Familial recurrence of multiple sclerosis according to the degree of relatives.

Relative	Female N (%)	Male N (%)	Total N (%)	*P* value
First degree				
Mother	33 (2.2)	10 (2.3)	43 (2.2)	0.86
Father	8 (0.5)	3 (0.7)	11 (0.6)	0.68
Siblings	44 (2.9)	14 (3.3)	58 (3)	0.71
Offspring	2 (0.1)	0 (0)	2 (0.1)	0.99
Second degree				
Maternal grandmother/ grandfather	4 (0.3)	1 (0.2)	5 (0.3)	0.90
Paternal grandmother/ grandfather	5 (0.3)	1 (0.2)	6 (0.3)	0.74
Maternal aunts/uncles	19 (1.3)	14 (3.3)	33 (1.7)	**0.007**
Paternal aunts/uncles	17 (1.1)	5 (1.2)	22 (1.1)	0.95
Third degree				
Maternal cousins	23 (1.5)	5 (1.2)	28 (1.4)	0.57
Paternal cousins	37 (2.5)	9 (2.1)	46 (2.4)	0.66
Other relatives	41 (2.7)	12 (2.8)	53 (2.7)	0.93

4. Discussion

The majority of POMS patients were females, with a considerable predominance in the post-pubertal age group. Positive familial history was higher among males and the mean age at disease onset was similar in patients with and without positive familial history of MS. Logistic regression analysis revealed no significant association between age groups and familial history of MS. MS familial recurrence was higher in second degree relatives compared to first and third degree relatives and the strongest association was seen in maternal second degree relatives. In this group, the strongest correlation was seen in maternal aunts/uncles. Our data revealed an increasing trend in POMS prevalence in Tehran, thus confirming previous findings (Elhami et al., 2011; Eskandarieh et al., 2016).

Our sample size was higher than that of previous studies in Iran (Eskandarieh et al., 2018a; Inaloo et al., 2014; Moosazadeh et al., 2017).

The prevalence of POMS in Tehran is higher than that found in Japan (0.69/100,000) (Yamaguchi et al., 2016) and Kuwait (6.0/100,000) (Alroughani et al., 2015); however, it is lower than POMS prevalence in Italy (26.92/100,000) (Dell'Avvento et al., 2016).

Based on our findings, a significant increasing trend in POMS prevalence was observed during 2012–2017, annually. One important reason for the difference in prevalence rates reported for POMS could

be the use of a different cut-off point for POMS in various pediatric cohorts, ranging from 15 to 18 years old.

Most of pediatric definitions set the cut-off at 18 years (Krupp et al., 2007) but our cut of was 19 years like the studies conducted in Italy (Dell'Avvento et al., 2016) and Shiraz (Inaloo et al., 2014) which may push our mean age up.

The mean age at disease onset was 15.09 ± 2.27 years in our study which is higher than that reported in previous studies conducted in Tehran (14.28 ± 1.87) (Sahraian et al., 2010) and other provinces of Iran such as Fars (11 ± 4.71) (Inaloo et al., 2014) and Isfahan (14.1 ± 2) (Etemadifar et al., 2007). It is also significantly higher than the value reported in the studies conducted in France (13.7 ± 2.4) (Renoux et al., 2007), Japan (8.3 ± 0.48) (Yamaguchi et al., 2016), Canada (12.0 ± 3.8) (Banwell et al., 2011), and Belgium (14.3) (Banwell et al., 2011). However, it is similar to the data reported for Kuwait (15.4 ± 2.1) (Alroughani et al., 2015), Italy (15.4 ± 2.2) (Dell'Avvento et al., 2016), and USA (15.7 ± 2.9) (Yamamoto et al., 2018).

We found the female to male ratio of 3.5:1 in our survey that was similar to the previous findings in other provinces of Iran such as Tehran (3.6:1) (Sahraian et al., 2010) and Fars (3:1) (Inaloo et al., 2014). This ratio was significantly higher than the value reported for other countries such as France (2.78:1) (Renoux et al., 2007), Japan (1.8:1) (Yamaguchi et al., 2016), Kuwait (2.8:1) (Alroughani et al., 2015), Italy (0.36:1) (Dell'Avvento et al., 2016), Canada (1.9:1) (Banwell et al., 2011), Belgium (2.06:1) (Deryck et al., 2006), Turkey (1.7:1) (Yilmaz et al., 2017), and Germany (2.07:1) (Reinhardt et al., 2014).

Our data demonstrated an increasing trend in female to male ratio after puberty as shown in previous studies (Chitnis 2013). Increasing presentation of POMS after puberty especially among females may be related to the endocrine changes occurring during puberty and its effect on disease development and disease course. It seems that environmental factors have more influence on MS risk in females (Chitnis 2013).

Exposure to MS risk factors in the post-pubertal females, proposing that interaction with endogenous biological factors occurs during adolescent years, would synergize to cause the development of MS (Chitnis 2013).

In our study, the number of very young children diagnosed with MS has been decreased since 2015 which might be due to specific attention in differential diagnosis of MS in very young children, specially diagnosis of autoimmune myelin oligodendrocyte glycoprotein (MOG) and neuromyelitis optica spectrum disorder (NMOSD) (Yamamoto et al., 2018).

Recently, a positive familial history of MS has been observed to have an important role in disease recurrence (Eskandarieh et al., 2018a). The frequency of familial POMS was estimated to be 14.9% in our study which was in keeping with previous findings in France (13.5%) (Renoux et al., 2007), Canada (16%) (Banwell et al., 2011), Germany (13.9%) (Reinhardt et al., 2014), and Turkey (13.2%) (Ozakbas et al., 2003). It is also lower than the reported data for Belgium (18.4%) (Deryck et al., 2006), USA (32%) (Yamamoto et al., 2018), and Canada (18%) (Ebers et al., 2004). Therefore, it is comparable with other provinces in Iran such as Fars (10%) (Inaloo et al., 2014) and Isfahan (9%) (Etemadifar et al., 2007).

From all POMS patients, the positive family history of MS in first degree relatives was 5.7%, confirming previous findings reported from Tehran (5.3%) (Eskandarieh et al., 2018b) and Isfahan (5%) (Etemadifar et al., 2007). Moreover, positive family history of MS in second and third degree relatives was similar to data reported for Isfahan (Etemadifar et al., 2007) and lower than that reported for Canada (Banwell et al., 2011).

Our findings suggest that positive familial history of MS in maternal relatives has more effect on the recurrence of the disease. It seems that affected maternal aunts/uncles are more likely to transmit MS compared to other affected relatives. This observation confirms previous evidence of a "maternal parent-of-origin" effect in MS susceptibility (Ebers et al., 2004; Herrera et al., 2008). Based on parent-of-origin theory, mitochondrial transmission, interaction between genes, and unidentified specific female determinants (such as hormones or sex-dependent gene expression, intrauterine, and prenatal factors) may have roles in transmission of MS from affected mothers to their offspring. On the other hand, the results from Sweden showed an equal relative risk among maternal and paternal relatives (Westerlind et al., 2014). They also pointed out that the highest risk of MS recurrence in second degree relatives related to maternal aunts (1.50%) (Westerlind et al., 2014).

Recent studies in Tehran showed a high familial recurrence of MS in siblings (Eskandarieh et al., 2018a). The population examined in this study was under the age of 18 and their siblings were expected to be in the same range of age, so they did not reach the mean age of MS onset reported in the study conducted in Tehran (25–29 years old) (Eskandarieh et al., 2017). Thus, evaluation of MS familial recurrence risk among siblings in POMS is challenging.

Despite higher female to male ratio, the percentage of familial MS was higher among men. Therefore, men would be expected to transmit MS to their family more often than women, an occurrence known as the Carter effect (Kantarci et al., 2006).

Nevertheless, the recent study in Sweden revealed a higher transmission rate from father to offspring compared with mother to offspring, and confirmed the presence of Carter effect in MS recurrence (Kantarci et al., 2006).

5. Limitations

There were some limitations in our study in spite of covering a large sample size.

The first limitation relates to voluntary registration of patients in IMSS which may affect the prevalence rate. The second limitation seems to be the delay between the first episode of the disease and registration process of newly diagnosed POMS cases.

The third possible limitation is that the diagnoses were made by an adult neurologist.

The fourth limitation is that small children should be registered by their parents.

6. Conclusions

The prevalence of POMS in Tehran is high and may be related to increasing knowledge and interest in MS diagnosis by physicians, more MRI scanners, revisions of diagnostic criteria, awareness about this disease among general population, and changes in people's life style. Increasing presentation of POMS after puberty especially among females revealed the considerable effect of environmental factors on MS risk in females and suggested that sex hormones may play a role in the immune system and cause sex diversity in basal immune responses.

It was also found that among various modest familial risks, affected maternal relatives have more effect on the recurrence of the disease. Furthermore, exposure to environmental risk factors provides a higher chance for POMS occurrence.

Understanding pediatric MS would yield important insights into the natural history of MS and identify key genetic and environmental factors during the earliest stages of disease pathogenesis.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None.

References

Alroughani, R., Akhtar, S., Ahmed, S.F., Behbehani, R., Al-Abkal, J., Al-Hashel, J, 2015. Incidence and prevalence of pediatric onset multiple sclerosis in Kuwait: 1994–2013. J. Neurol. Sci. 353 (1–2), 107–110.

Alroughani, R., Boyko, A, 2018. Pediatric multiple sclerosis: a review. BMC Neurol. 18 (1), 27.

Banwell, B., Bar-Or, A., Arnold, D.L., Sadovnick, D., Narayanan, S., McGowan, M., O'Mahony, J., Magalhaes, S., Hanwell, H., Vieth, R., et al., 2011. Clinical, environmental, and genetic determinants of multiple sclerosis in children with acute demyelination: a prospective national cohort study. Lancet Neurol. 10 (5), 436–445.

Banwell, B., Ghezzi, A., Bar-Or, A., Mikaeloff, Y., Tardieu, M, 2007a. Multiple sclerosis in children: clinical diagnosis, therapeutic strategies, and future directions. Lancet Neurol. 6 (10), 887–902.

Banwell, B., Krupp, L., Kennedy, J., Tellier, R., Tenembaum, S., Ness, J., Belman, A., Boiko, A., Bykova, O., Waubant, E., et al., 2007b. Clinical features and viral serologies in children with multiple sclerosis: a multinational observational study. Lancet Neurol. 6 (9), 773–781.

Browne, P., Chandraratna, D., Angood, C., Tremlett, H., Baker, C., Taylor, B.V., Thompson, A.J, 2014. Atlas of multiple sclerosis 2013: a growing global problem with widespread inequity. Neurology 83 (11), 1022–1024.

Chitnis, T., 2013. Role of puberty in multiple sclerosis risk and course. Clin. Immunol. 149 (2), 192–200.

Csepany, T., 2018. Diagnosis of multiple sclerosis: a review of the 2017 revisions of the McDonald criteria. Ideggyogy. Sz. 71 (9–10), 321–329.

Dell'Avvento, S., Sotgiu, M.A., Manca, S., Sotgiu, G., Sotgiu, S, 2016. Epidemiology of multiple sclerosis in the pediatric population of Sardinia, Italy. Eur. J. Pediatr. 175 (1), 19–29.

Deryck, O., Ketelaer, P., Dubois, B, 2006. Clinical characteristics and long term prognosis in early onset multiple sclerosis. J. Neurol. 253 (6), 720–723.

Ebers, G.C., Sadovnick, A.D., Dyment, D.A., Yee, I.M., Willer, C.J., Risch, N, 2004. Parent-of-origin effect in multiple sclerosis: observations in half-siblings. Lancet 363 (9423), 1773–1774.

Elhami, S.R., Mohammad, K., Sahraian, M.A., Eftekhar, H, 2011. A 20-year incidence trend (1989–2008) and point prevalence (March 20, 2009) of multiple sclerosis in Tehran, Iran: a population-based study. Neuroepidemiology 36 (3), 141–147.

Eskandarieh, S., Allahabadi, N.S., Sadeghi, M., Sahraian, M.A, 2018a. Increasing prevalence of familial recurrence of multiple sclerosis in Iran: a population based study of Tehran registry 1999–2015. BMC Neurol. 18 (1), 15.

Eskandarieh, S., Heydarpour, P., Elhami, S.R., Sahraian, M.A, 2017. Prevalence and incidence of multiple sclerosis in Tehran, Iran. Iran J. Public Health 46 (5), 699–704.

Eskandarieh, S., Heydarpour, P., Minagar, A., Pourmand, S., Sahraian, M.A, 2016. Multiple sclerosis epidemiology in East Asia, South East Asia and South Asia: a systematic review. Neuroepidemiology 46 (3), 209–221.

Eskandarieh, S., Molazadeh, N., Moghadasi, A.N., Azimi, A.R., Sahraian, M.A, 2018b. The prevalence, incidence and familial recurrence of multiple sclerosis in Tehran, Iran. Mult. Scler. Relat. Disord. 25, 143.

Etemadifar, M., Nasr-Esfahani, A.H., Khodabandehlou, R., Maghzi, A.H, 2007. Childhood-onset multiple sclerosis: report of 82 patients from Isfahan, Iran. Arch. Iran Med. 10 (2), 152–156.

Hawkes, C.H., Macgregor, A.J, 2009. Twin studies and the heritability of MS: a conclusion. Mult. Scler. 15 (6), 661–667.

Herrera, B.M., Ramagopalan, S.V., Lincoln, M.R., Orton, S.M., Chao, M.J., Sadovnick, A.D., Ebers, G.C, 2008. Parent-of-origin effects in MS: observations from avuncular pairs. Neurology 71 (11), 799–803.

Inaloo, S., Haghbin, S., Moradi, M., Dashti, H., Safari, N, 2014. Acquired CNS demyelinating syndrome in children referred to ShirazPediatric Neurology Ward. Iran J. Child. Neurol. 8 (2), 18–23.

Islam, T., Gauderman, W.J., Cozen, W., Hamilton, A.S., Burnett, M.E., Mack, T.M, 2006. Differential twin concordance for multiple sclerosis by latitude of birthplace. Ann. Neurol. 60 (1), 56–64.

Kantarci, O.H., Barcellos, L.F., Atkinson, E.J., Ramsay, P.P., Lincoln, R., Achenbach, S.J., De Andrade, M., Hauser, S.L., Weinshenker, B.G, 2006. Men transmit MS more often to their children vs women: the Carter effect. Neurology 67 (2), 305–310.

Krupp, L.B., Banwell, B., Tenembaum, S., International Pediatric MSSG, 2007. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. Neurology 68 (16 Suppl 2), S7–12.

Moosazadeh, M., Esmaeili, R., Mehdi Nasehi, M., Abedi, G., Afshari, M., Farshidi, F., Kheradmand, M, 2017. Prevalence of familial multiple sclerosis in Iran: a systematic review and meta-analysis. Iran J. Neurol. 16 (2), 90–95.

Ozakbas, S., Idiman, E., Baklan, B., Yulug, B, 2003. Childhood and juvenile onset multiple sclerosis: clinical and paraclinical features. Brain Dev. 25 (4), 233–236.

Reinhardt, K., Weiss, S., Rosenbauer, J., Gartner, J., von Kries, R, 2014. Multiple sclerosis in children and adolescents: incidence and clinical picture - new insights from the nationwide German surveillance (2009–2011). Eur. J. Neurol. 21 (4), 654–659.

Renoux, C., Vukusic, S., Mikaeloff, Y., Edan, G., Clanet, M., Dubois, B., Debouverie, M., Brochet, B., Lebrun-Frenay, C., Pelletier, J., et al., 2007. Natural history of multiple sclerosis with childhood onset. N. Engl. J. Med. 356 (25), 2603–2613.

Sahraian, M.A., Khorramnia, S., Ebrahim, M.M., Moinfar, Z., Lotfi, J., Pakdaman, H, 2010. Multiple sclerosis in Iran: a demographic study of 8,000 patients and changes over time. Eur. Neurol. 64 (6), 331–336.

Westerlind, H., Ramanujam, R., Uvehag, D., Kuja-Halkola, R., Boman, M., Bottai, M., Lichtenstein, P., Hillert, J, 2014. Modest familial risks for multiple sclerosis: a registry-based study of the population of Sweden. Brain 137 (Pt 3), 770–778.

Yamaguchi, Y., Torisu, H., Kira, R., Ishizaki, Y., Sakai, Y., Sanefuji, M., Ichiyama, T., Oka, A., Kishi, T., Kimura, S., et al., 2016. A nationwide survey of pediatric acquired demyelinating syndromes in Japan. Neurology 87 (19), 2006–2015.

Yamamoto, E., Ginsberg, M., Rensel, M., Moodley, M, 2018. Pediatric-onset multiple sclerosis: a single center study. J. Child. Neurol. 33 (1), 98–105.

Yilmaz, U., Anlar, B., Gucuyener, K, 2017. Characteristics of pediatric multiple sclerosis: the Turkish pediatric multiple sclerosis database. Eur. J. Paediatr. Neurol. 21 (6), 864–872.

Zipoli, V., Portaccio, E., Siracusa, G., Pracucci, G., Sorbi, S., Amato, M.P, 2003. Interobserver agreement on Poser's and the new McDonald's diagnostic criteria for multiple sclerosis. Mult. Scler. 9 (5), 481–485.