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Multiple Sclerosis in Tehran: Rising Prevalence alongside Stabilizing Incidence – True Increase or Enhanced Diagnosis?

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Abstract

Background: Multiple sclerosis (MS) is a chronic and potentially progressive demyelinating disease of the central nervous system. The incidence and prevalence rate of the disease has been increasing globally, especially in females.

Methods: In this cross-sectional population-based study based on Iranian MS Society data (1989-2016), we aimed to present most recent age-standardized incidence and prevalence rate of MS, female to male ratio, mean onset age, and prevalence of positive family history of MS alongside with their time trend via Joinpoint regression analysis in 27 years. Additionally, a linear regression model was used for evaluating the association of onset age with sex and family history in patients.

Results: In 18,061 registered cases: female to male ratio was generally 3.06:1, showing a general decreasing trend. The mean onset age of the disease was 28.50 ± 8.61 with a general increasing trend. 12.52% of the cases had at least a positive any-degree family history of MS, exhibiting a weak increasing trend. The age-standardized incidence and prevalence rate was 1.8 (95% CI: 1.3, 7.2) and 116 (95% CI: 96, 139) per 100 000 populations, respectively, both presenting a significant increasing trend, however, incidence rate ended in plateaued and finally decreasing trend. Finally, onset age was predicted to be lower in females and subjects with positive family history of MS.

Conclusion: Tehran is among MS high-risk areas with increasing trends in prevalence and increasing followed by plateaued incidence rates indicating necessity of extra investigations of the underlying reasons and health system preparedness for further health care requirements of MS patients.

Keywords: Age of onset, Epidemiology, Incidence, Multiple sclerosis, Prevalence, Sex ratio

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system which may lead to progressive disabling condition. MS is distributed heterogeneously in populations, attributable to variations in genetic backgrounds, environmental exposures to risk factors, and interaction of these components.[1] A global increase in the incidence and prevalence of MS has been observed since 1965, generally and specifically in females.[1] The globally median estimated prevalence and incidence of MS was 112.0 and 5.2 per 100 000 populations in 2014, respectively.[2] Iran is among the countries with high prevalence rate of MS (51.52/100 000, 2015) in the Middle East, ranging from 14.7/100 000 to 101.4/100 000 in different provinces.[3] The prevalence of MS was 88/100 000 in Tehran, the capital of Iran, in 2013,[4] highlighting this populated province as a high risk area of MS.

In this study, we investigated the most recent and comprehensive available data for estimating the measure and the average annual percent change of the prevalence and incidence rates of MS, female to male ratio, mean age of the disease onset, and positive family history of MS in Tehran, Iran, 1989–2016.

Patients and Methods

Study Design

This was a population-based, observational cross-sectional study conducted in Tehran, with the estimated population of 13 267 627 in 2016,[5] investigating the most recent point estimates and the trends of MS incidence and prevalence rates, female to male ratio, positive familial history of MS prevalence, and the mean age of the disease onset (onset age) from 1989 to 2016.

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Data Collection

The data consisted of the characteristics of cases with a definite diagnosis of MS in the Iranian MS Society (IMSS) in Tehran, who voluntarily became its member. Although the registration is not mandatory, it seems the majority of MS patients are referred to this center due to its facilities and the support. Their characteristics including sex, onset age, and family history of MS were collected for all patients and their first (mother, father, sister/brother or offspring), second (grandmother, grandfather, maternal aunt/uncle or paternal aunt/uncle) and third (maternal cousin, paternal cousin or others) degree relatives. The IMSS members' disease was approved by neurologist based on the McDonald criteria.[6] Deceased people are excluded from the yearly updated data bank.

Data Analysis

The last update of data was March 20, 2017, with 18 061 registered cases. The study period from March 21, 2016 to March 20, 2017 was reported as year 2016, and for other years accordingly. Annual incidence rates were calculated for a period with a one-year length from March 21, 1956 to March 20, 2017. The incidence rate was defined as the cases with their self-reported disease onset in a specific year per 100 000 inhabitants of the province in that year. Prevalence rate was defined as the cases with their disease beginning in a specific year plus all other cases with their disease beginning in the previous years who are present in the data and are considered alive and resident in Tehran, per 100 000 inhabitants of the province in that year. The population data source was the Statistical Centre of Iran.[5] Incidence and prevalence rates were adjusted by the direct method standardization, using year age grouping of the 2000–2025 WHO population, as a standard, to remove the bias of the different age structures of the population.[7] The 95% confidence intervals (CI) were calculated by Wilson method.

In patients with a positive report for family history, who refused to choose their relative's degree, any-degree positive family history was considered positive. Pediatric MS was defined as less than 18-year-old self-reported onset age. Odds ratio and chi-square test analyses were used for indicating associations for categorical variables. Means were compared using the *t* test. To indicate the predictors of the onset age, sex and positive family history (1st or 2nd or 3rd degree, concurrently and separately) was used in linear regression modeling. Joinpoint regression analysis was used for studying time trends from 1989 to 2016. Joinpoint is statistical software, supported by the Surveillance Research Program (SRP) in NCI's Division of Cancer Control and Population Sciences (DCCPS), that analyses trends using joinpoint models which are consisted of several different lines connected at the joinpoints and uses Monte Carlo Permutation method for the tests of significance.[8] The Poisson variance was chosen as heteroscedastic errors and logarithmic transformation was performed on the dependent variable. Finally, grid search method was used (with minimum and maximum numbers of joinpoints as 0 and 5, respectively). Years identified as joinpoints with average annual percent change (AAPC) of the periods are reported. Two tailed *P*-values less than 0.05 were considered significant.

Results

The baseline characteristics of the patients are presented in Table 1. More than 70% of cases were female with overall and in 2016 female to male ratio of 3.06:1 and 3.23:1 respectively, showing a general decreasing trend (AAPC = -0.4% (95% CI: -1.0, 0.1)). The ratio was 2.80:1 and 3.10:1 in patients with and without positive family history of MS. The mean age of the disease onset was 28.50 ± 8.61years. A multiple linear regression analysis was conducted to evaluate predicting the onset age by sex and family history and it was lower in females by 0.87 (95% CI: 0.57, 1.17) year and in patients with any degree of positive family history by 0.54 (95% CI: 0.15, 0.92) year. Details are shown in Table 2. The mean onset age started with 26.39 in 1989 and ended with 30.80 in 2016 with a general AAPC of 0.50% (95% CI: 0.30, 0.70). 12.52% of cases had any positive family history (first degree: 5.36%, second degree: 1.87%, and third degree and others: 5.80%) and the odds of having any-degree positive family history was higher in males compared females (OR: 0.90; 95% CI: 0.81, 0.99), and in patients with pediatric MS in comparison with non-pediatric MS (OR: 1.23; 95% CI: 1.05, 1.45). In general run, the proportion of positive family history in the population exhibited a weak non-significant increasing trend (APC: 0.3%; 95% CI: -0.3, 0.8).

The crude and age-standardized incidence rate of MS was 2.04/100 000 (95% CI: 0.54, 7.29) and 1.8/100 000 (95% CI: 1.3, 7.2), respectively, in 2016 with its peak in

Table 1. Baseline Characteristics of the Population

Variable	General (n =18052) (95% CI)	Positive FH (n = 2260) (95% CI)	Negative FH (n =15792) (95% CI)	*P* Value[a]
Female to male ratio	3.06:1 (2.96, 3.16)	2.80:1 (2.55, 3.08)	3.10:1 (2.99, 3.21)	0.049
Mean age of onset (y) ± SD	28.50 ± 8.61	28.03 ± 8.69	28.56 ± 8.59	0.007
Pediatric MS (%)	6.89 (6.52, 7.26)	8.18 (7.05, 9.31)	6.71 (6.32, 7.10)	0.009

FH, Family history of MS;
[a] The *P* value of tests investigating the difference of baseline characteristics with patients with and without positive FH.

Table 2. Predicting Onset Age of the Disease by Sex and Positive Family History in the Population

Model	Variable	Difference of Age-Onset Means in Years (95% CI)	*P* Value
1	Sex: female vs. male	-0.87 (-1.17, -0.57)	<0.001
	FH: positive in any degree vs. negative in all degrees	-0.54 (-0.92, -0.15)	0.006
2	Sex: female vs. male	-0.86 (-1.16, -0.57)	<0.001
	FH: 1st degree vs. negative	-0.07 (-0.64, 0.49)	0.800
	FH: 2nd degree vs. negative	-2.54 (-3.49, -1.60)	<0.001
	FH: 3rd/other degree vs. negative	-0.00 (-0.55, 0.53)	0.980

95% confidence intervals are presented in parentheses; FH, Positive family history of MS.

2011 (9.42/100 000 (95% CI: 4.74, 17.11). The crude incidence rate showed an increasing trend over the years 1989–2016 (AAPC: 2.40%; 95% CI: 0.50, 4.50), but almost plateaued from 2003, and the only period with decreasing trend in incidence rate was 2013 to 2016 (APC: -32.50%; 95% CI: -42.30, -21.00), as presented in Figure 1.

These trends were almost the same for females and males with a lower slope in males. The age-standardized and crude prevalence rates were 136/100 000 (95% CI: 114, 160) and 116/100 000 (95% CI: 96, 139), respectively, in 2016 with the highest crude prevalence rate (129.05/100 000; 95% CI: 108, 153) in 2015. Figure 2 presents that the crude prevalence rate of MS has been increasing since 1989 (AAPC: 11.4%; 95% CI: 10.4, 12.5) with more rapid increasing in females. Table 3 presents the detailed analysis of time trend for female to male ratio, onset age, positive family history of MS, crude incidence rate, and crude prevalence rate, years 1989–2016.

Discussion

This study, not only revealed the highest prevalence rate of MS ever reported in the Iranian population residing inside or outside of the country, but also demonstrated the highest prevalence reported in Middle East countries including Kuwait, Jordan, Tunisia, and Saudi Arabia.[4,9,10] It was determined that MS crude prevalence rate has been increasing over the years 1989–2016 and the crude incidence rate presented increasing trend, followed by plateau, and ended in decreasing trend in Tehran, Iran. Considering that Iran is reported to be among countries with low to medium risk for MS (20.01–60 MS/100 000).[10,11] It is noticeable that the investigated prevalence of MS in Tehran (116/100 000) is higher than the estimated median global prevalence of MS (112.0/100 000), however, the age-standardized incidence rate (1.8/100 000) in 2016 was lower than the median estimated global incidence of MS (5.2/100 000).[2] The investigated incidence rate in Jordan compared to Iran, is lower but that are higher in Kuwait and United Arab Emirates.[3] The incidence and prevalence trends in Tehran were almost similar to previous reports; the only difference was the decreasing incidence rate of MS after 2014.[4,10] In global reports, there were an increasing pattern of MS prevalence, between 2008 and 2013 and incidence was reported to have an increasing trend since 1980, especially in lower latitudes.[1,11] Increasing MS incidence has also been reported for Norway, Italy and Japan.[1] However, a report of Saskatoon, Canada indicated a stable incidence rate of MS.[12] Therefore, due to different inclusion criteria and methodologies and also different MS background in these populations, results should be

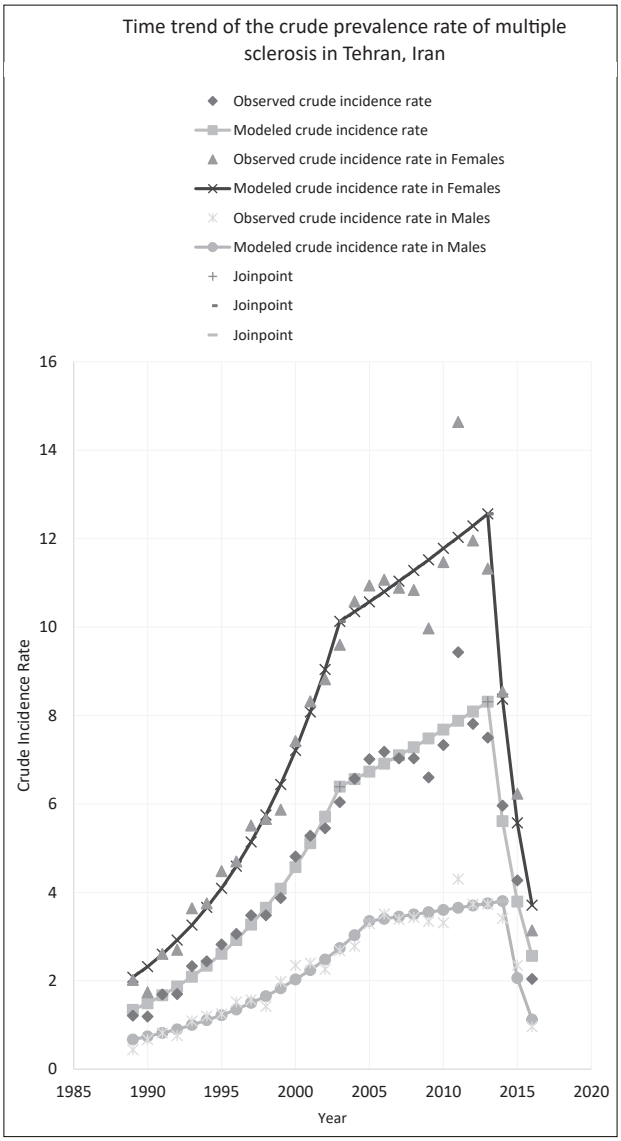

Figure 1. Comparing Observed and Modeled Crude Incidence Rates of MS (1989-2016).

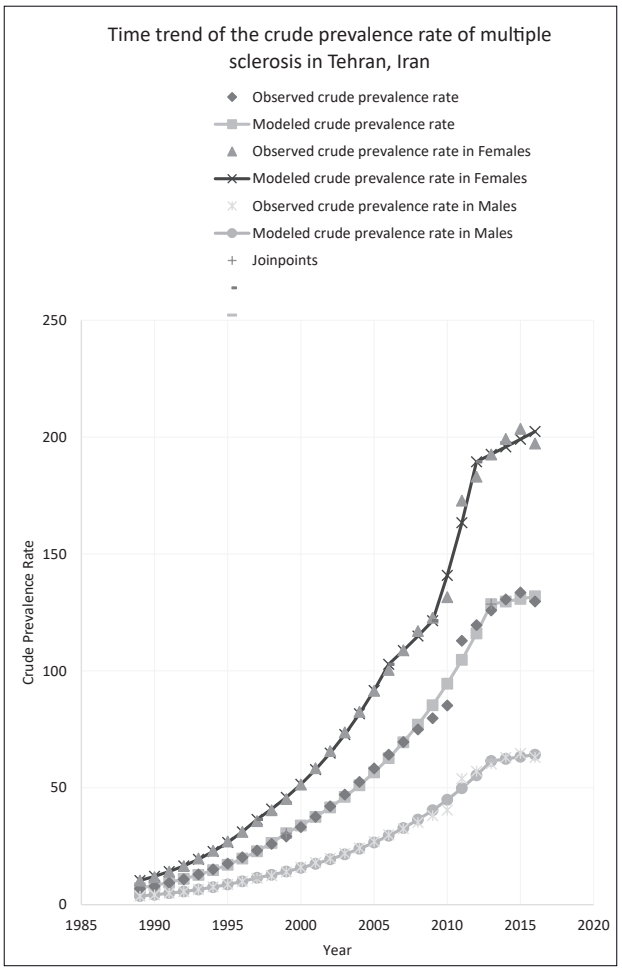

Figure 2. Comparing Observed and Modeled Crude Prevalence Rates of MS (1989–2016).

compared cautiously. Increasing trend of MS in Tehran might be partly due to improved diagnostic methods, higher rates of diagnosis and reporting, more convenient access to neurologists, imaging facilities and other related health services, public awareness rising, active patient finding, clinical registries establishment, increasing life expectancy in patients, epidemiologic publications, promotion of physician awareness, and most importantly, increased MS incidence.[9,11] Considering a report of Elhami et al that only a negligible change occurred in final results when considering the delay time between the disease onset and the diagnosis time,[9] the increasing trend may be mainly attributable to the actual increase in the number of cases than improvement in the early detection of cases. Besides, a less likely explanation for a portion of the increase could be hygiene promotion after 1981 Iranian revolution, consistent with the hygiene hypothesis that suggest increase chance of autoimmune disorders like MS with less exposure to foreign antigens.[9] Moreover, Western life style modifications as the environmental triggers on a susceptible genetic background in Iranian population are proposed as another explanation.[9,13] The decreasing pattern of MS incidence, since 2004 may be due to the time lag between disease onset and diagnosis and registering to IMSS and it is less likely to be caused by real decrease.[4] Importantly, higher prevalence rate and lower incidence rate comparing to the median global estimates of MS suggests relatively longer survivals of MS patients in Iran, which might be interest of healthcare providers in regions with an opposite pattern.

Whit focusing on males and females separately, our incidence rates of both sexes were lower than a recent global weighted mean incidence rate of MS.[14] The female to male ratio (3.06:1) was almost similar, but it was a little less than previous studies in Tehran,[4,9] and it was higher than the median estimated ratio in Europe, Eastern Mediterranean, America, and Southeast Asia, , almost similar to Africa and lower than Western Pacific.[15] Furthermore, the general trend was opposing the increased ratio in Thuringia, Germany (associated with late onset of the disease), France, Norway, Australia, Canada, and Denmark.[1] This decreasing trend may be partly due to a disproportional increase in the incidence of MS in males. More rapid changing in males comparing to females, could be resulted by men facing relatively more outdoor pollution, obesity, and smoking.[16,17] Also, in recent years, relatively more availability of disease treatment and increased awareness could have resulted in more medical advice seeking, and in result, more diagnosis of MS in males. In addition, more and earlier health care seeking behavior, resulted augmentation of diagnosis in male patients, could proceed to a more incidence rate increase in males comparing to females.[10] And finally, the mean onset age of our population (30.79) was lower than the Eastern Mediterranean region (26.9), which has the lowest age of the disease onset.[15] These findings are important, because men are the main part of the labor force of Iran (more than 70%) and most of the world's countries,[18] so increasing male to female ratio, could affect the work productive capacity. Additionally, the earlier onset age, which is equal to loss of more productive years of patients, calls for immediate policies targeting preventive, treating, and rehabilitative cares for younger adults.

This study reported incidence rate of MS, which was more sensitive to demographic changes and was not affected by survival of the disease.[1] Additionally, the population-based design and adequate years of observation for reporting the trends, strengthen the results. However, our study had several limitations. This study was unable to detect diseased and emigrated patients or the unregistered MS population in the IMSS, which may lead to an underestimation of the real incidence. However, the emigration and mortality rate of the disease are low, in our study area.[5] Therefore, these factors may have not significant effects on the reported yearly results or observed trends. Moreover, because relatives probably inform each other of their membership, we would probable see more relatives in a

Table 3. Trend Analysis of Statistics in the Population, Years 1989–2016

Variable		Segments Separated by Joinpoints	APC (95% CI)	AAPC (95% CI)
Female to male ratio		1989–2016	-0.4 (-1.0, 0.1)	-0.4 (-1.0, 0.1)
Mean age of the disease onset in years	Overall	1989–2006	0.3 (0.1, 0.5)	0.5 (0.3, 0.7)
		2006–2016	0.9 (0.5, 1.3)	
	Males	1989–2016	0.4 (0.3, 0.6)	0.4 (0.3, 0.6)
	Females	1989–2016	0.5 (0.4, 0.6)	0.5 (0.4, 0.6)
Positive familial history of MS	Overall	1898–2016	0.3 (-0.3, 0.8)	0.3 (-0.3, 0.8)
	Males	1989–2000	-6.1 (-10.3, -1.8)	-0.8 (-3.0, 1.6)
		2000–2016	3.1 (0.4, 6.0)	
	Females	1898–2016	0.6 (0.1, 1.1)	0.6 (0.1, 1.1)
Crude incidence rate	Overall	1989–2003	11.8 (10.0, 13.7)	2.4 (0.5, 4.5)
		2003–2013	2.7 (0.7, 4.7)	
		2013–2016	-32.5 (-42.3, -21.0)	
	Males	1989–2005	10.6 (9.0, 12.3)	1.9 (-0.9, 4.9)
		2005–2014	1.4 (-1.1, 4.0)	
		2014–2016	-45.7 (-62.8, -20.8)	
	Females	1989–2003	12.0 (10.1-13.9)	2.2 (0.1, 4.3)
		2003–2013	2.2 (0.2, 4.2)	
		2013–2016	-33.4 (-43.6, -21.3)	
Crude prevalence rate	Overall	1989–1999	15.7 (13.2, 18.3)	11.4 (10.4, 12.5)
		1999–2013	10.8 (11.6, 31.8)	
		2013–2016	0.9 (-3.5, 5.4)	
	Males	1989–1997	15.4 (11.9, 19.0)	11.2 (10.1, 12.3)
		1997–2013	11.1 (10.4, 11.7)	
		2013–2016	1.5 (-2.9, 6.0)	
	Females	1989–1997	17.1 (15.8, 18.4)	11.6 (10.9, 12.4)
		1997–2006	12.2 (11.5, 12.9)	
		2006–2009	5.7 (1.5, 10.1)	
		2009–2012	16.0 (12.0, 20.1)	
		2012–2016	1.7 (0.7, 2.7)	

Abbreviations: APC, annual percent change; AAPC, average annual percent change.
Note: Repeated years are joinpoints.

volition-based registry comparing to a mandatory registry. Finally, our data does not clarify the reasons behind the observed trends, which are required for further planning. Taken together, considering that Tehran is among high-risk areas for MS with an age-standardized prevalence of 116/100 000, the increasing trends of incidence and prevalence rates of MS, indicate extra investigations of underlying reasons, epidemiological characteristics of patients and health care requirements for managing MS, including prevention strategies, up-to-date therapeutic plans, and rehabilitative programs. The relatively higher observed prevalence rate and lower incidence rate comparing to global estimates, suggest the presence of effective health care programs of MS patients in Iran and could be a guidance for other developing countries. The observed rapid increase of MS incidence brings the notion of a probable environmental and, less probably, genetic change. Despite that, a part of the increase may be due to easier access to neurologists, improvement of their skills and familiarities with the disease, diagnostic equipment access and increased awareness and health seeking behaviors. Decreasing trend of female to male ratio is a key insight for planning healthcare strategies and policies, especially for research, prevention and disease management in men, who are main workforces of countries,[18] moreover, it raises questions about new changes in health seeking behaviors, lifestyles or genetics in males. This finding could be a new substrate for research, considering inconsistency with worldwide trends of increasing female to male ratio, besides, further studies are required to investigate the incidence and prevalence rate of MS consisting absent cases in this study, and the reasons behind the trends.

Authors' Contribution

FM and SE developed the idea and designed the study. FM performed the data analysis and data interpretation with the support and monitor of MM. FM drafted the manuscript with the support of SE, MM, BM, and MS. All authors reviewed the manuscript, provided feedback, and FM applied comments and finalized the manuscript.

Conflict of Interest Disclosures

All the authors declare no competing interest.

Ethical Statement

The study was approved by the institutional review boards (IRB) at ethics committee of Tehran University of medical sciences (ref.no. IRTUMS.VCR.REC.1396.2314), and all of the patients have given their informed consent.

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