DOI: http://dx.doi.org/10.18502/cjn.v20i4.8348

Current Journal of Neurology

Original Paper

Curr J Neurol 2021; 20(4): 222-8

Epidemiological and clinical features of pediatric-onset multiple sclerosis: A population-based study in Isfahan, Iran, between 1997-2020

Received: 06 June 2021
Accepted: 10 Aug. 2021

Masoud Etemadifar[1], Amir Parsa Abhari[2], Ghasem Yadegarfar[3], Mehri Salari[4], Mohammadreza Ghazavi[5], Milad Rayani[2], Hosein Nouri[2], Parisa Kargaran[6], Shahrbanoo Mazaheri[7], Homa Saadat[7]

[1] Department of Neurology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[2] Alzahra Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
[3] Department of Statistics and Epidemiology, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran
[4] Department of Neurological Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5] Department of Pediatric Neurology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[6] Department of Cardiovascular Medicine, Center for Regenerative Medicine, Mayo Clinic, Rochester, Minnesota, USA
[7] Department of Diseases and Transplantation, Isfahan University of Medical Sciences, Isfahan, Iran

Keywords
Multiple Sclerosis; Pediatric; Epidemiology; Prevalence; Incidence

Abstract

Background: Pediatric-onset multiple sclerosis (POMS) is an autoimmune demyelinating disorder of the central nervous system (CNS), affecting individuals younger than 18 years of age. We sought to characterize the epidemiological and clinical features of patients with POMS in Isfahan, Iran, from April 1997 to March 2020.

Methods: The medical records of patients with POMS in the databases of Isfahan Department of Public Health and Isfahan Multiple Sclerosis Society (IMSS) were retrospectively reviewed. The 2006 and 2016 Isfahan Province population censuses were used as reference values for assessing the temporal trend of POMS.

Results: From April 1997 to March 2020, 509 individuals under18 years of age were diagnosed with POMS in Isfahan. 404 of these patients (79.4%) were girls, and 105 patients (20.6%) were boys (a female to male ratio of 3.85:1). Most of the patients (83%) were monosymptomatic at onset, with optic neuritis and brainstem-cerebellar disorders being the most frequent initial presentations. Mean ± standard deviation (SD) of age at disease diagnosis was 15.8 ± 2.5 years (ranging from 3 to 18, mode = 18).

How to cite this article: Etemadifar M, Abhari AP, Yadegarfar G, Salari M, Ghazavi M, Rayani M, et al. Epidemiological and clinical features of pediatric-onset multiple sclerosis: A population-based study in Isfahan, Iran, between 1997-2020. Curr J Neurol 2021; 20(4): 222-8.

Corresponding Author: Amir Parsa Abhari
Email: amirparsaabhari@gmail.com

From April 2019 to March 2020, the crude prevalence and the crude incidence rate of the POMS were 5.42 per 100000 and 1.86 per 100000, respectively. Poisson regression analysis revealed a 3.4% increase in the incidence rate of POMS from April 1997 to March 2020 [relative rate:1.034, 95% confidence interval (CI): 1.021-1.048].

Conclusion: The female to male ratio in our cohort was significantly higher than any other studies conducted previously. The high female to male ratio and increasing incidence of the disease suggest increasing regionalization of care.

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) characterized by demyelination and axonal degeneration.[1] Pediatric-onset MS (POMS) is a subset of MS occurring in children and young adolescents aged under 18 years presenting with distinct features from MS in adults. It accounts for almost 2%-10% of all MS cases.[2] According to numerous worldwide studies in recent years, POMS is considered a rare complication with an incidence of 0.45 to 2.85 per 100000 person-years,[3] whereas it is the most common entity among neurological disorders affecting young adults.[4] POMS is frequently associated with sensory defects, motor defects, and brainstem dysfunction.[5] Given the variable clinical presentation, medical and psychosocial complications, and irreversible disability occurring so early in life, early diagnosis and adequate POMS management are crucial. As such, a detailed investigation of demographic and clinical characteristics of patients with POMS will improve the efficiency and utility of healthcare services for this patient cohort. We present demographic and clinical features of POMS to evaluate the epidemiological trajectory of this disease.

Materials and Methods

This population-based study was carried out in Isfahan Province, situated in the central part of Iran, within the latitudes and the longitudes of 30-34^{o} North and 49-55^{o} East, respectively. The population of Isfahan was 5120850 (including 2599477 men and 2521373 women) in 2016. In 2013, Isfahan Province had the highest MS prevalence in Iran (89/100000).[6] We retrospectively identified and reviewed the medical records of patients with POMS in the database of Isfahan Department of Public Health, which had registered all patients with MS in the province since 2007, and Isfahan MS Society (IMSS) database, the primary referral center in the province before 2007.

The IMSS is located in Isfahan City (center of Isfahan Province), the third most populous metropolitan area in Iran. Including this database allowed incorporating patients registered since April 1997. All study participants were residents of Isfahan Province. Demographic and clinical data, including patient's age (at onset), gender, disease course, risk of seizure, symptoms at onset, comorbidities, treatment, and family history were obtained from their files. Expert neurologists made definitive MS diagnoses based on patients' radiological findings and clinical features following the Poser criteria[7] for patients admitted before 2001 and the latest McDonald criteria[8] for all other patients. Following the International Pediatric MS Study Group (IPMSSG) consensus definition, only patients with an MS diagnosis before their 18th birthday were included.[9] Patients with other demyelinating disorders such as neuromyelitis optica spectrum disorder (NMOSD) and acute disseminated encephalomyelitis (ADEM) were excluded from the study. Since 2015, cell-based assays were applied for MS-susceptible patients in Isfahan Province to detect antibodies against aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) in order to rule out MOG-associated disease and NMOSD, the more common differential diagnoses of POMS. The Ethical Committee of Isfahan University of Medical Sciences approved the study protocol, and the need for informed consent was waived. Although a vast majority of patients with POMS were registered in the two databases, some cases could be missed. The primary objective of this study was to elucidate the epidemiological and clinical features of POMS in Isfahan.

Mean and standard deviation (SD) of all numerical characteristics (e.g., age) were calculated and stratified by sex. A Mann-Whitney U test was conducted to assess the significance of the difference in mean age in female and male patients with POMS. A linear graph was applied to illustrate the trend between April 1997 and March 2020, for male and female patients of Isfahan Province. The pediatric population of Isfahan Province in 2006 and 2016 was used as the reference values (comprehensive national censuses were conducted all across the country in 2006 and 2016). Trends over time were compared between female and male patients using Poisson regression

analysis with a 95% confidence interval (CI). The data were analyzed at a significance criterion of 5%, using SPSS software (version 26, IBM Corporation, Armonk, NY, USA).

Results

Demographic features: From April 1997 to March 2020, 509 individuals under 18 years of age were diagnosed with POMS in Isfahan Province. 404 of these patients (79.4%) were girls, and 105 patients (20.6%) were boys (female to male ratio as 3.85:1). The mean ± SD of age at the onset of the disease was 15.8 ± 2.5 years (ranging from 3 to 18, mode = 18). The difference in the mean age at onset between boys (16.43 ± 2.20) and girls (15.68 ± 2.73) was significant (P = 0.003). Only 24 patients (0.05%) were under the age of 10 years old. Of them, 20 individuals (83%) were girls, and 4 (17%) were boys. The majority of patients were older than ten years old (95.05%), of which 384 (79.2%) were girls, and 101 (20.8%) were boys. The total population of patients with POMS by age and sex is represented in table 1. From April 2019 to March 2020, the crude prevalence and the crude incidence rate of the disease were 5.42 per 100000 and 1.86 per 100000, respectively. Poisson regression analysis revealed that the POMS incidence rate increased by 3.4% from April 1997 to March 2020 (relative rate:1.034, 95% CI: 1.021-1.048), and the incidence of the POMS in girls was more likely to be increased than boys (relative rate: 1.40, 95% CI: 1.18-1.61) (Table 2).

The total and gender-specific trends of POMS incidence are depicted in figure 1. It is worth mentioning that the annual incidence of the disease before 2001 should be taken into account with caution, considering the limited sensitivity of the Poser criteria in diagnosing POMS. No mortality occurred in our population.

Clinical features: The numbers and statistics presented below pertain to 473 patients, as the data regarding the clinical features of 36 patients, primarily diagnosed a long time ago, were not available.

Symptoms at onset: Disease onset was monosymptomatic in 390 patients (83%), whereas the remaining 83 patients (17%) had multiple disease onset symptoms. In the monosymptomatic group, optic neuritis, the most frequent initial presentation, occurred in 139 patients (29%), brainstem-cerebellar disorders in 91 patients (19%, ataxia in 23, diplopia in 55, vertigo in 7, nausea in 3, dysarthria in 2, and tremor in 1), sensory problems in 126 patients (26%, paresthesia), and motor deficit in 34 patients (7%, monoparesis, hemiparesis, and paraparesis).

Risk of seizure: Seizure episodes were recorded in 20 patients (4.2%), more frequently in those with a polysymptomatic onset (7 patients, 8.4%) as compared to those with a monosymptomatic onset of POMS (13 patients, 3.3%). Two patients had seizure episodes both before and after the MS diagnosis was made.

Family history: We divided relatives into three groups as follows: 1) first-degree relatives, including mother, father, sister/brother, and offspring, 2) second-degree relatives, including grandmother, grandfather, maternal aunt/uncle, and paternal aunt/uncle, and 3) third-degree relatives, including maternal cousins, paternal cousins, and others. 45 patients (9.5%) had a positive family history of MS, of them 35 were girls and 10 were boys. Among those forty-five, 16 (3.3%) had first-degree affected relatives, 6 (1%) had second-degree affected relatives, and 23 (4.8%) had third-degree affected relatives. 19 patients had maternal affected relatives, and 18 had paternal affected relatives. Two patients had a history of MS in both maternal and paternal relatives.

Disease course: Of all 473 patients, 436 (92.2%) were classified as relapsing-remitting MS (RRMS), 25 (5.2%) as secondary-progressive MS (SPMS), and 12 (2.6%) as primary-progressive (PPMS).

Comorbidity: Comorbidity was defined as the coexistence of 2 or more disorders that are not obvious complications of each other.[10] We divided our patients' comorbidities into five categories: psychiatric disorders, autoimmune disorders, vascular and blood disorders, cancers, and hypersensitivity reactions. 44 patients (9.3%) were suffering from another disorder besides MS.

Table 1. Total population of patients with pediatric-onset multiple sclerosis (POMS) by age and sex

Age (year)		3	4	5	7	8	9	10	11	12	13	14	15	16	17	18	Total
Sex	Girls	2	1	3	1	1	5	7	7	14	18	28	55	53	95	114	404
	Boys	0	0	0	2	1	1	0	0	1	1	7	9	16	26	41	105
Total			2	1	3	3	2	6	7	7	15	19	35	64	69	121	155

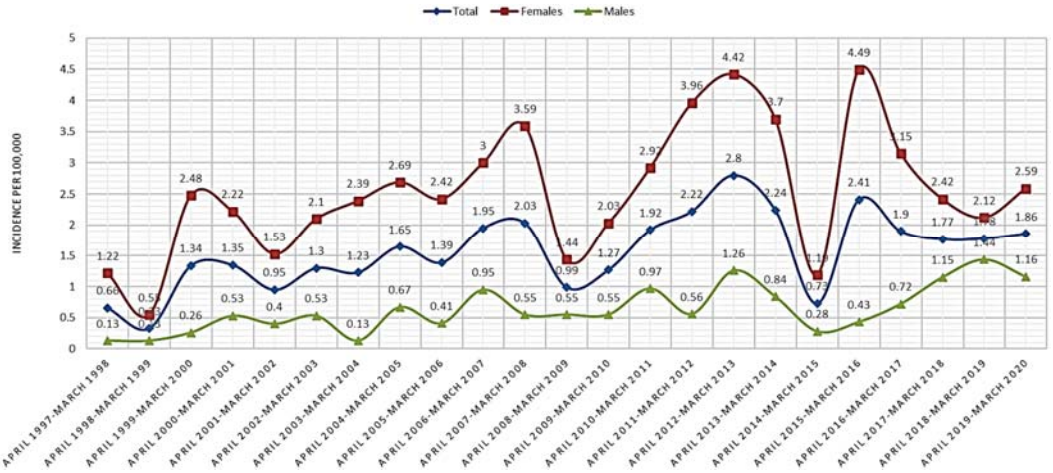

Figure 1. Yearly gender-specific incidence of pediatric-onset multiple sclerosis (POMS) in Isfahan, Iran, during April 1997 and March 2020

Table 2. Poisson regression analysis of time and gender effect on the incidence of pediatric-onset multiple sclerosis (POMS)

Variable	POMS incidence		
	Relative rate	95% CI	P
Time (year)	1.03	1.02-1.04	0.001
Gender	1.40	1.18-1.61	0.001

POMS: Pediatric-onset multiple sclerosis; CI: Confidence interval

The distribution of these disorders is shown in table 3.

Table 3. Comorbidities in patients with pediatric-onset multiple sclerosis (POMS)

Comorbidities	n (%)
Psychiatric disorders	
Anxiety	11 (2.0)
Depression	16 (3.0)
Autoimmune disorders	
Psoriasis	1 (0.2)
Diabetes mellitus (type 1)	2 (0.4)
Rheumatoid arthritis	1 (0.2)
Vascular and blood disorders	
Anemia	3 (0.6)
Hyperlipidemia	1 (0.2)
Thrombophilia	1 (0.2)
Cancers	
Fibroadenoma	1 (0.2)
Uterine cancer	1 (0.2)
Hypersensitivity reactions	
Allergic rhinitis	3 (0.6)
Asthma	3 (0.6)
Total	44 (9.3)

Treatment: To date, fingolimod is the only disease-modifying therapy (DMT) approved by the Food and Drug Administration (FDA) for patients with POMS; however, several DMTs and other drugs are widely used as off-label treatments. Out of 473 patients, 454 (96%) received DMTs, and the others (3.9%) were treated with methotrexate (1.2%) and azathioprine (2.7%). Detailed results are represented in table 4.

Table 4. Distribution of treatments consumed by patients with pediatric-onset multiple sclerosis (POMS) in Isfahan, Iran, from April 1997 to March 2020

Treatment	n (%)
Azathioprine	13 (2.7)
Dimethyl fumarate	49 (10.4)
Fingolimod	61 (12.9)
Glatiramer acetate	13 (2.8)
Interferon beta-1a	182 (38.5)
Interferon beta-1b	39 (8.2)
Methotrexate	6 (1.3)
Natalizumab	7 (1.5)
Rituximab	100 (21.2)
Teriflunomide	3 (0.6)
Total	473 (100)

Discussion

Although POMS comprises only a small portion of MS cases, between 1997 and 2020, 509 pediatric individuals were physically and psychologically afflicted. The annual incidence of POMS exhibited a 2.8-fold increase from 0.66 per 100000 in 1997 to 1.86 per 100000 in 2020. This unfortunate upward trend was also observed in similar studies in Germany,[11,12] Kuwait,[13] and Canada.[14] However, the incidence rate was relatively stable in a study conducted in Denmark.[15] Increased prevalence of obesity, a risk factor for MS, due to a sedentary lifestyle in children,[16] an increase in overall MS prevalence, higher accuracy and precision of

diagnostic criteria, enhanced POMS awareness, and increased healthcare access can explain the rising incidence of POMS. However, these factors cannot explain the significant decrease in the incidence rate in April 2014-March 2015.

The worldwide prevalence of POMS ranges from 0.69 to 26.92 per 100000 population.[17] According to four previous studies conducted in the Middle East, POMS prevalence was reportedly between 5.25 and 16.25.[18,19] The pooled global prevalence of the disease was estimated to be 8.11 (95% CI: 2.28-13.93), and the pooled prevalence in the Middle East was calculated to be 8.55 (95% CI: 0.27-16.82).[3] Although the prevalence of adult-onset MS in Isfahan was higher than in Tehran (capital of Iran), POMS was less prevalent in Isfahan than in Tehran.[6] In the Middle East, only Israel has a lower POMS prevalence than Isfahan (5.25 vs. 5.42 per 100000).

The mean age at disease onset was 15.8 ± 2.5 years in our patients, which was higher than what had been observed in other studies, including Kuwait (15.40 ± 2.10),[13] Japan (8.30 ± 0.48),[17] other Iranian provinces (15.09 ± 2.27 in Tehran[19] and 11.00 ± 4.71 in Fars[20]), Canada (12.00 ± 3.80),[21] France (13.70 ± 2.40),[22] United States of America (USA) (15.08 ± 2.95),[23] and Italy (15.40 ± 2.20).[24] Only one study conducted in the United Arab Emirates (UAE) reported a higher mean age than that in our study (15.90 ± 2.80).[25] The difference in the mean age of girls and boys was statistically significant in our study, suggesting that sex hormones may be partially involved in the induction of demyelination.[26]

The female-to-male ratio in our cohort was significantly higher than other studies conducted previously (3.85:1). Notably, there was a meaningful difference in this ratio between studies in Iran (3.5:1 in Tehran[19] and 3:1 in Fars[20]) and studies in other countries, such as Germany (2.07:1),[12] Kuwait (2.8:1),[13] Japan (1.8:1),[17] USA (2.4:1),[23] Italy (0.36:1),[24] UAE (1.8:1),[25] Turkey (1.7:1),[27] and Brazil (2.4:1).[28] We hypothesize that the female preponderance in Iran could be partly due to the Iranian dress code, leading to vitamin D deficiency from reduced sunlight exposure. In a previous study, female high school students (aged from 10 to 18) were four times more likely to have vitamin D deficiency.[29] Additionally, there are possible correlations between serum vitamin D levels and the risk of MS development and severity.[30,31] For example, Blaschek et al. observed significantly lower 25-hydroxy vitamin D levels in patients with POMS than healthy controls.[32]

Moreover, vitamin D may have an immunomodulatory effect by conferring an anti-inflammatory profile to CD8+ T cells in patients with POMS.[33] Thus, vitamin D supplementation in young Iranian girls may help to reduce the sex ratio of the POMS. It may even help prevent the development of adult-onset MS by ameliorating vitamin D deficiency in this population. Further studies are needed to clarify the potential factors contributing to the high female-to-male ratio of POMS in the Iranian population.

Psychiatric disorders were the most common comorbidities among this patient population, which occurred either as a side effect of the treatments applied or due to the disabling nature of the disease. Moreover, psychiatric disorders and MS could share a common pathomechanism, correlated with brain demyelination.[34] Notably, Boesen et al. demonstrated a doubled hazard for psychiatric disorders in patients with POMS;[35] hence, neuropsychiatric screening in patients with POMS is crucial to maximize the quality of life.

4.2% of patients in this study had seizures, while in the literature, seizure prevalence in the POMS population varies from 5% to 10%.[36,37] Of note, Ruggieri et al. reported the prevalence of seizures to be 22% in patients with POMS under six years of age.[38] The occurrence of epileptic seizures in MS is well-documented (previously, seizures were included in the spectrum of MS manifestations[39]), tending to affect pediatric patients more frequently than adult patients.[40,41]

Concerning the contribution of genetic inheritance to the pathogenesis of MS, a multifactorial disorder, we investigated the family history of each patient. The frequency of familial POMS in our study (9.5%) was less than that in France (13.5%),[9] Germany (13.9%)[12] and Canada (16.0%).[21] Familial POMS prevalence in other Iranian studies was 14.9% in Tehran[19] and 10% in Fars.[20] The lower prevalence of positive family history in patients with POMS in Isfahan, compared to other studies, may imply the crucial role of environmental interactions in the pathogenesis of MS in this region.

Studies suggest that monosymptomatic onset is a prevailing characteristic of POMS, as detected in 83% of patients of this study. It is worth noting that the frequency of polysymptomatic presentations in POMS is higher than that in adult-onset MS.[42,43] Such manifestations are quite helpful in distinguishing the disease from ADEM, which is a challenging differential diagnosis for POMS. In the

monosymptomatic group (in our patients), the most frequent initial symptom was optic nerve involvement followed by sensory problems and brainstem-cerebellar disorders, in line with the findings of Dell'Avvento et al.[24] and Chitnis et al.[44]

Conclusion

The clinical and epidemiological features of POMS in Isfahan Province in Iran from April 1997 to March 2020 were characterized. The annual incidence of the disease increased from 0.66 to 1.86 per 100000 in 23 years, and the female to male ratio was 3.85:1, which was higher than the reported ratio in other studies. In general, with respect to the increasing incidence and the significant burden of the disease to patients and healthcare system, investigating the status of POMS in this province is of high value to facilitate the decision-making and execution of public strategies aiming to further improve the long-term prognosis of MS in young adults.

Limitations: This study had several limitations. Due to the nature of the study, immigration could affect the obtained epidemiological characteristics, as diagnoses in other Iranian provinces were not included. Additionally, a vast majority of patients were diagnosed by adult neurologists. Moreover, as MOG antibody titers were not in clinical use in the earlier years of the study, the POMS incidence in the first years of the study may have been exaggerated.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

We sincerely appreciate IMSS and Isfahan Department of Public Health for permitting us to have access to the data of patients with POMS upon the ethical approval of this study.

References

1. Dobson R, Giovannoni G. Multiple sclerosis-a review. Eur J Neurol 2019; 26(1): 27-40.
2. Ruet A. Update on pediatric-onset multiple sclerosis. Rev Neurol (Paris) 2018; 174(6): 398-407.
3. Yan K, Balijepalli C, Desai K, Gullapalli L, Druyts E. Epidemiology of pediatric multiple sclerosis: A systematic literature review and meta-analysis. Mult Scler Relat Disord 2020; 44: 102260.
4. Pugliatti M, Sotgiu S, Rosati G. The worldwide prevalence of multiple sclerosis. Clin Neurol Neurosurg 2002; 104(3): 182-91.
5. Fisher KS, Cuascut FX, Rivera VM, Hutton GJ. Current advances in pediatric onset multiple sclerosis. Biomedicines 2020; 8(4).
6. Etemadifar M, Izadi S, Nikseresht A, Sharifian M, Sahraian MA, Nasr Z. Estimated prevalence and incidence of multiple sclerosis in Iran. Eur Neurol 2014; 72(5-6): 370-4.
7. Zipoli V, Portaccio E, Siracusa G, Pracucci G, Sorbi S, Amato MP. Interobserver agreement on Poser's and the new McDonald's diagnostic criteria for multiple sclerosis. Mult Scler 2003; 9(5): 481-5.
8. Csepany T. Diagnosis of multiple sclerosis: A review of the 2017 revisions of the McDonald criteria. Ideggyogy Sz 2018; 71(9-10): 321-9. [In Hu].
9. Krupp LB, Banwell B, Tenembaum S. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. Neurology 2007; 68(16 Suppl 2): S7-12.
10. Magyari M, Sorensen PS. Comorbidity in multiple sclerosis. Front Neurol 2020; 11: 851.
11. Pohl D, Hennemuth I, von Kries R, Hanefeld F. Paediatric multiple sclerosis and acute disseminated encephalomyelitis in Germany: Results of a nationwide survey. Eur J Pediatr 2007; 166(5): 405-12.
12. Reinhardt K, Weiss S, Rosenbauer J, Gartner J, von Kries R. Multiple sclerosis in children and adolescents: incidence and clinical picture - new insights from the nationwide German surveillance (2009-2011). Eur J Neurol 2014; 21(4): 654-9.
13. Alroughani R, Akhtar S, Ahmed SF, Behbehani R, Al-Abkal J, Al-Hashel J. Incidence and prevalence of pediatric onset multiple sclerosis in Kuwait: 1994-2013. J Neurol Sci 2015; 353(1-2): 107-10.
14. Marrie RA, O'Mahony J, Maxwell C, Ling V, Yeh EA, Arnold DL, et al. Incidence and prevalence of MS in children: A population-based study in Ontario, Canada. Neurology 2018; 91(17): e1579-e1590.
15. Boesen MS, Magyari M, Koch-Henriksen N, Thygesen LC, Born AP, Uldall PV, et al. Pediatric-onset multiple sclerosis and other acquired demyelinating syndromes of the central nervous system in Denmark during 1977-2015: A nationwide population-based incidence study. Mult Scler 2018; 24(8): 1077-86.
16. Gianfrancesco MA, Barcellos LF. Obesity and multiple sclerosis susceptibility: A review. J Neurol Neuromedicine 2016; 1(7): 1-5.
17. Yamaguchi Y, Torisu H, Kira R, Ishizaki Y, Sakai Y, Sanefuji M, et al. A nationwide survey of pediatric acquired demyelinating syndromes in Japan. Neurology 2016; 87(19): 2006-15.
18. Achiron A, Garty BZ, Menascu S, Magalashvili D, Dolev M, Ben-Zeev B, et al. Multiple sclerosis in Israeli children: incidence, an clinical, cerebrospinal fluid and magnetic resonance imaging findings. Isr Med Assoc J 2012; 14(4): 234-9.
19. Eskandarieh S, Sahraiain MA, Molazadeh N, Moghadasi AN. Pediatric multiple sclerosis and its familial recurrence: A population based study (1999-2017). Mult Scler Relat Disord 2019; 36: 101377.
20. Inaloo S, Haghbin S, Moradi M, Dashti H, Safari N. Acquired CNS demyelinating syndrome in children referred to Shiraz Pediatric Neurology Ward. Iran J Child Neurol 2014; 8(2): 18-23.
21. Banwell B, Bar-Or A, Arnold DL, Sadovnick D, Narayanan S, McGowan M, et al. Clinical, environmental, and genetic determinants of multiple sclerosis in children with acute demyelination: A prospective national cohort study. Lancet Neurol 2011; 10(5): 436-45.
22. Renoux C, Vukusic S, Mikaeloff Y, Edan G, Clanet M, Dubois B, et al. Natural history of multiple sclerosis with childhood onset. N Engl J Med 2007; 356(25): 2603-13.
23. Ramphul K, Mejias SG, Joynauth J. Pediatric multiple sclerosis in the United States in children ages 0-18. Mult Scler Relat Disord 2020; 38: 101874.
24. Dell'Avvento S, Sotgiu MA, Manca S, Sotgiu G, Sotgiu S. Epidemiology of multiple sclerosis in the pediatric population of Sardinia, Italy. Eur J Pediatr 2016; 175(1): 19-29.
25. Ismail FY, Gordon-Lipkin E, Huether K, Blair I, Szolics M, Alsaadi T, et al. Pediatric multiple sclerosis in the United Arab Emirates: Characteristics from a multicenter study and global comparison. J Child Neurol 2018; 33(6): 422-7.
26. Ysrraelit MC, Correale J. Impact of sex hormones on immune function and

multiple sclerosis development. Immunology 2019; 156(1): 9-22.
27. Yilmaz U, Anlar B, Gucuyener K. Characteristics of pediatric multiple sclerosis: The Turkish pediatric multiple sclerosis database. Eur J Paediatr Neurol 2017; 21(6): 864-72.
28. Cerqueira Pinto SC, Ferreira Vasconcelos CC, Aurencao JCK, Alvarenga MP, das Gracas Gomes Camargo SM, Santos Thuler LC, et al. Pediatric multiple sclerosis in Rio de Janeiro: Secondary progression and disability. Pediatr Neurol 2019; 94: 48-54.
29. Moussavi M, Heidarpour R, Aminorroaya A, Pournaghshband Z, Amini M. Prevalence of vitamin D deficiency in Isfahani high school students in 2004. Horm Res 2005; 64(3): 144-8.
30. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. Nat Rev Neurol 2017; 13(1): 25-36.
31. Miclea A, Bagnoud M, Chan A, Hoepner R. A brief review of the effects of vitamin D on multiple sclerosis. Front Immunol 2020; 11: 781.
32. Blaschek A, Langhagen T, Bechtold-Dalla Pozza S, Heinen F, Muller-Felber W. Vitamin D levels in pediatric Multiple Sclerosis patients. Neuropediatrics 2011; 42(S 01): 058.
33. Lysandropoulos AP, Jaquiery E, Jilek S, Pantaleo G, Schluep M, Du Pasquier RA. Vitamin D has a direct immunomodulatory effect on CD8+ T cells of patients with early multiple sclerosis and healthy control subjects. J Neuroimmunol 2011; 233(1-2): 240-4.
34. Rocca MA, Absinta M, Amato MP, Moiola L, Ghezzi A, Veggiotti P, et al. Posterior brain damage and cognitive impairment in pediatric multiple sclerosis. Neurology 2014; 82(15): 1314-21.
35. Boesen MS, Blinkenberg M, Thygesen LC, Eriksson F, Magyari M. School performance, psychiatric comorbidity, and healthcare utilization in pediatric multiple sclerosis: A nationwide population-based observational study. Mult Scler 2021; 27(2): 259-67.
36. Banwell B, Ghezzi A, Bar-Or A, Mikaeloff Y, Tardieu M. Multiple sclerosis in children: Clinical diagnosis, therapeutic strategies, and future directions. Lancet Neurol 2007; 6(10): 887-902.
37. Ozakbas S, Idiman E, Baklan B, Yulug B. Childhood and juvenile onset multiple sclerosis: clinical and paraclinical features. Brain Dev 2003; 25(4): 233-6.
38. Ruggieri M, Polizzi A, Pavone L, Grimaldi LM. Multiple sclerosis in children under 6 years of age. Neurology 1999; 53(3): 478-84.
39. Koch M, Uyttenboogaart M, Polman S, De KJ. Seizures in multiple sclerosis. Epilepsia 2008; 49(6): 948-53.
40. Chabas D, Green AJ, Waubant E. Pediatric multiple sclerosis. NeuroRx 2006; 3(2): 264-75.
41. Schorner A, Weissert R. Patients with epileptic seizures and multiple sclerosis in a multiple sclerosis center in southern Germany between 2003-2015. Front Neurol 2019; 10: 613.
42. Huppke B, Ellenberger D, Rosewich H, Friede T, Gartner J, Huppke P. Clinical presentation of pediatric multiple sclerosis before puberty. Eur J Neurol 2014; 21(3): 441-6.
43. Yeh EA, Chitnis T, Krupp L, Ness J, Chabas D, Kuntz N, et al. Pediatric multiple sclerosis. Nat Rev Neurol 2009; 5(11): 621-31.
44. Chitnis T, Glanz B, Jaffin S, Healy B. Demographics of pediatric-onset multiple sclerosis in an MS center population from the Northeastern United States. Mult Scler 2009; 15(5): 627-31.