ORIGINAL ARTICLE

Clinical and Epidemiological Findings of Pediatric Onset Multiple Sclerosis in East-Azerbaijan, Iran; A Population-based Study

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Abstract

Objectives

Multiple sclerosis (MS) is among the most prevalent chronic immune-mediated inflammatory diseases. If MS onset is under 18, it is defined as pediatric-onset MS (POMS). This study aimed to determine the clinical and epidemiological aspects of POMS.

Materials & Methods

This population-based study was conducted in East-Azerbaijan (EA) province and concerned POMS patients. The data concerning almost all of the POMS patients of the province was gathered from the only MS registry center in the university hospital of the Tabriz University of Medical Sciences by the end of 2017. The diagnosis of patients was based on McDonald's criteria.

Results

Out of 2976 total cases of MS, eighty-five (2.85%) were POMS. The overall regional prevalence of POMS was 11.67 per 100,000 (95% CI:9.43-11.43). Sixty-seven cases were female (prevalence: 18.94 per 100,000 [95% CI:14.91-24.07], and eighteen were male (prevalence: 4.80 per 100,000 [95% CI:3.03-7.62]. The crude regional incidence in 2017 was 1.37/100,000 (95% CI:0.74-2.55). The mean age of onset was 15.81±1.33 years, with a minimum age of 12. 71.76% of the patients were diagnosed in the 16- or 17-years old age group. 7.05% had a positive family history, and 87.5% of the patients diagnosed the disease promptly. The most common first clinical presentations were blurred vision (43.75%), sensory (28.12%), cerebellar (15.62%), and brainstem (9.37%) symptoms.

Conclusion

POMS is not a rare condition, and it mainly affects females. POMS prevalence increases significantly after age 15 years old, and the first manifestation of the disease is usually blurred vision.

Keywords: Children; Epidemiology; Incidence; Multiple sclerosis; Pediatric; Pediatric-onset multiple sclerosis; Prevalence.

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Introduction

Multiple sclerosis (MS) is among the most prevalent chronic immune-mediated inflammatory diseases, usually seen in young adults aged 20 to 40 (1, 2). Based on the latest consensus statement, MS onset under 18 years old is defined as pediatric-onset MS (POMS) (3). MS presents in four common phenotypes, including relapsing-remitting (RRMS), primary progressive (PPMS), secondary progressive (SPMS), and progressive relapsing (PRMS) (4). Although no separate phenotype has been defined for POMS, many aspects of its clinical presentation, prognosis, outcome, and treatment differ from those of adult-onset MS (1, 5, 6). Thus, gathering as much information as possible about POMS's demographic and clinical aspects is important. Studies found that almost all POMS cases have an RRMS phenotype (7).

The incidence of POMS varies from 0.05 to 2.85 per 100,000 children in different populations, and the overall prevalence ranges from 0.69 to 26.92 per 100,000, with a 2.8 to 1 female-to-male ratio (8). In addition, positive family history is seen in 6 to 20 percent of children with MS (9, 10). Nowadays, revised McDonald's criteria allow timely diagnosis based on clinical features, magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) analysis (11). A wide variety of symptoms, including optic neuritis, sensory problems, and motor symptoms, can present in POMS (12). A recent systematic review study reported the negative impacts of POMS on school performance, physical functioning, and mental health in children and adolescents (13). A 1.53 per 100,000 population of the incidence rate of POMS in 2019 was also reported in a study in Iran, which found an increase in the incidence rate from 2000 to 2019 (14).

An accurate understanding of the pathogenesis of the disease and early diagnosis and treatment of POMS is important. Therefore, more information on epidemiology, clinical presentation, and the prognosis of the disease should be provided. The epidemiologic data on POMS in the Middle East and Iran is limited. This study aimed to determine the prevalence and incidence of POMS in northwest Iran. Demographic and clinical characteristics, family history, and the gap between the first presentation and the definite diagnosis were evaluated.

Materials & Methods

Area of investigation

The study occurred in East-Azerbaijan (EA) province, northwest of Iran. In the latest census in 2016, the population of EA was 3955187, including

2013078 men and 1942109 women. The capital of EA is Tabriz, with an estimated population of 1558693. The target population under 18 years old for this study was 728,420.

Case ascertainment

This study was performed by referring to the patients' files in the only MS registry center in the Tabriz University of Medical Sciences (TUOMS) hospital. MS registry center of EA, as the only one in this province, includes almost all MS cases. Suspected patients with MS refer to this system for further evaluation and confirmation of the diagnosis. Registration of patients is necessary for future medical follow-up and public insurance laws. This registry program was started in 2008, but patients diagnosed before were also inserted into this system (15). Patients were contacted by phone if there was a need for more information, which was not reported in the registry. This study includes almost all POMS patients in the province who registered from the beginning of the registration by the end of 2017, in whom MS started before age 18.

Eligibility criteria

Diagnosis of MS was according to the 2005 version of McDonald's criteria (16) for patients until 2011, and then the 2010-revised version was used (17). An experienced neurologist diagnosed all patients. Brain and spinal MRI (1.5 Tesla) was performed for all patients. The following tests were requested to rule out other diseases, if necessary; anti-phospholipids and anti-cardiolipin immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies, anti-nuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA), anti-neutrophil cytoplasmic antibodies (ANCA), angiotensin-converting enzyme inhibitors (ACEIs), serum B12 level, and other laboratory tests as needed. In case of necessity, oligoclonal bands (OCB), Aquaporin-4 antibody, and anti-MOG antibody were also assessed.

Inclusion criteria were all patients who were diagnosed as definite MS in all subtypes (relapsing-remitting, secondary progressive, and primary progressive), clinically isolated syndrome (CIS), and exclusion criteria were isolated optic neuritis, radiologically isolated syndrome (RIS), Neuromyelitis Optica spectrum disorder (NMOSD), anti-MOG antibody syndrome, and isolated transverse myelitis. In case of suspected other autoimmune diseases or vasculitis, an experienced rheumatologist was consulted to rule out the other diagnosis.

In this study, the authors selected patients with disease onset before 18 years old, known as POMS. The authors considered the age of the disease onset, gender, first clinical presentations, family history, and the gap between the first presentation and definite diagnosis in months. Clinical presentations were classified as blurred vision, brainstem, cerebellar, sensory symptoms, and seizure. In addition, the prevalence of POMS and age- and gender-specific prevalence were collected based on the total population of EA province. The 2017 age- and gender-specific incidence rates were defined based on the number of births in the mentioned year. All incidence and prevalence rates were calculated per 100,000 population.

Ethical considerations

The study was approved by the Ethics Committee of TUOMS (Approval No. IR.TBZMED.REC.1398.455), according to the declaration of Helsinki.

Statistical Analyzes

Analyses were conducted by IBM SPSS Statistics 26.0 (SPSS Inc., Chicago, IL, USA) with a 0.05

level of significance and 95% confidence interval (CI). Values are given as mean ± standard deviation cut to two decimal places. Descriptive statistics were reported in percent, independent sample T-test and chi-square were used to compare means between male and female POMS cases. 95% CIs were calculated on the assumption of a Poisson distribution.

Results

Prevalence and incidence

The total number of MS patients in EA by the end of 2017 was 2976, of which eighty-five cases (2.85%) were POMS. The age and sex prevalence of the disease are mentioned in Table 1. Out of 728,420 population under 18 years old in EA, the overall regional prevalence was 11.67 per 100,000 (95% CI: 9.43-11.43). Sixty-seven cases were female, with a prevalence of 18.94 per 100,000 (95% CI: 14.91-24.07), and eighteen were male, with a prevalence of 4.80 per 100,000 (95% CI: 3.03-7.62). As shown in this table, the prevalence was higher in females, with a 3.94:1 ratio of female to male, which means 79.82% of cases were female. Six cases (7.05%) had a positive family history of MS. There were ten new cases in 2017, so the crude regional incidence was 1.37/100,000 (95% CI: 0.74-2.55).

Age of the disease onset

The mean age of the disease onset (the mean age from the first presentation) was 15.81 ± 1.332 years old, with a minimum age of 12 years old, and naturally, the maximum age was 17 years old. The mean ages of the disease onset were 15.77 ± 1.16 in male patients and 15.82 ± 1.38 in female patients (p= 0.90). As can be seen in Figure 1, from the age of 12 to 17, the number of patients increased, so 71.76% of the patients had onset of the disease at 16 or 17 years old. The peak of the prevalence was 17 years old (109.93/100,000) in females and 16 years old (30.22/100,000) in males.

First clinical presentation

The first clinical presentations are shown in Figure 2. The reported early symptoms were blurred vision (43.75%), sensory (28.12%), cerebellar (15.62%), and brainstem (9.37%) symptoms, and seizure (3.12%), respectively. The most common first symptom among males was brainstem and sensory symptoms, which constituted 36.75% of male cases, but the first presentation in females was blurred vision, which constituted 54.16%. In one case, the first clinical symptom of MS was a seizure. There was a statistically significant difference between male and female cases regarding the first clinical presentation ($p<0.01$).

The gap between the first presentation and the definite diagnosis

There was a mean of 3.00 ± 9.63 months of the gap between the first presentation and definite diagnosis. In most cases (87.5%), the disease was diagnosed timely; in 6.3% of the cases, the disease was diagnosed after one year; in 3.15% of cases, the disease was diagnosed after 24 months, and in 3.15% of cases the disease was diagnosed after 48 months. The most common first clinical presentations of patients with delayed diagnosis were blurred vision and brainstem symptoms.

Table 1: Age and sex-specific prevalence of multiple sclerosis in East-Azerbaijan, Iran, in 2017.

	Males				Females				Both Sexes			
Age	**No. of cases**	**Population**	**per 100,000**	**95% CI**	**No. of cases**	**Population**	**per 100,000**	**95% CI**	**No. of cases**	**Population**	**per 100,000**	**95% CI**
≤11	0	213049	0	0	0	201186	0	0	0	414235	0	0
12	0	27290	0	0	2	25826	7.74	1.94-30.96	2	53116	3.76	0.94-15.6
13	1	27022	3.70	0.52-26.27	5	25867	19.32	8.05-46.44	6	52889	11.34	5.1-25.25
14	2	26990	7.41	1.85-29.63	4	25908	15.43	5.80-41.13	6	52898	11.34	5.1-25.25
15	2	27359	7.31	1.83-29.23	8	25482	31.39	15.7-62.77	10	52841	18.92	10.18-35.17
16	8	26472	30.22	15.11-60.42	21	24763	84.80	55.3-130.04	29	51235	56.60	39.34-81.44
17	5	26646	18.76	7.81-45.08	27	24560	109.93	75.41-160.27	32	51206	62.49	44.2-88.36
Total	18	374828	4.80	3.03-7.62	67	353592	18.94	14.91-24.07	85	728420	11.67	9.43-14.43

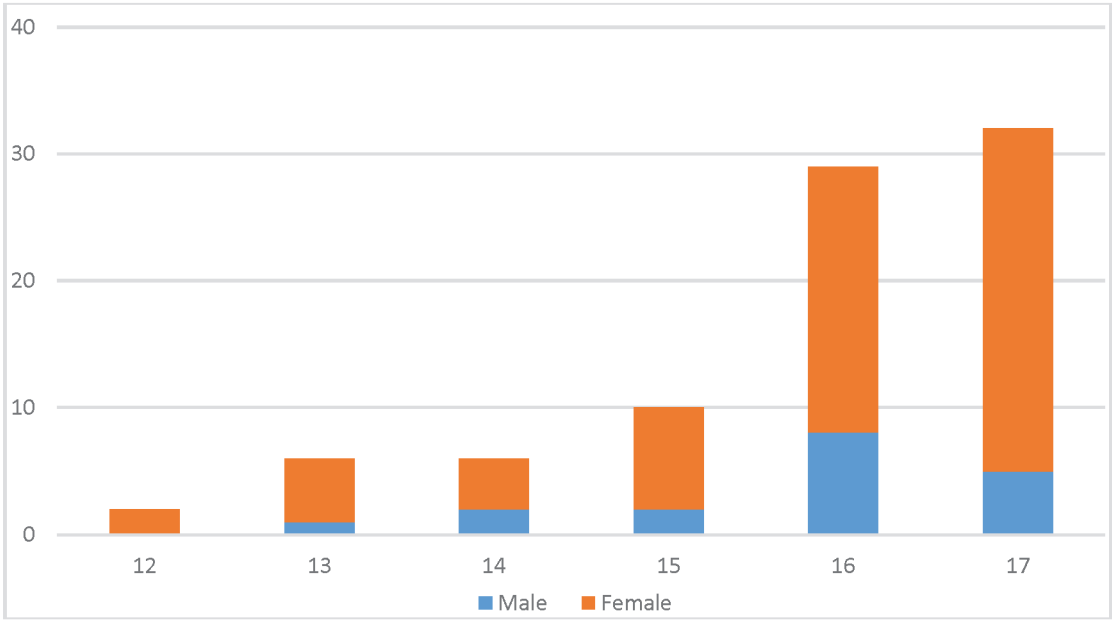

Figure 1. *Number of patients and male to female ratio in each age.*

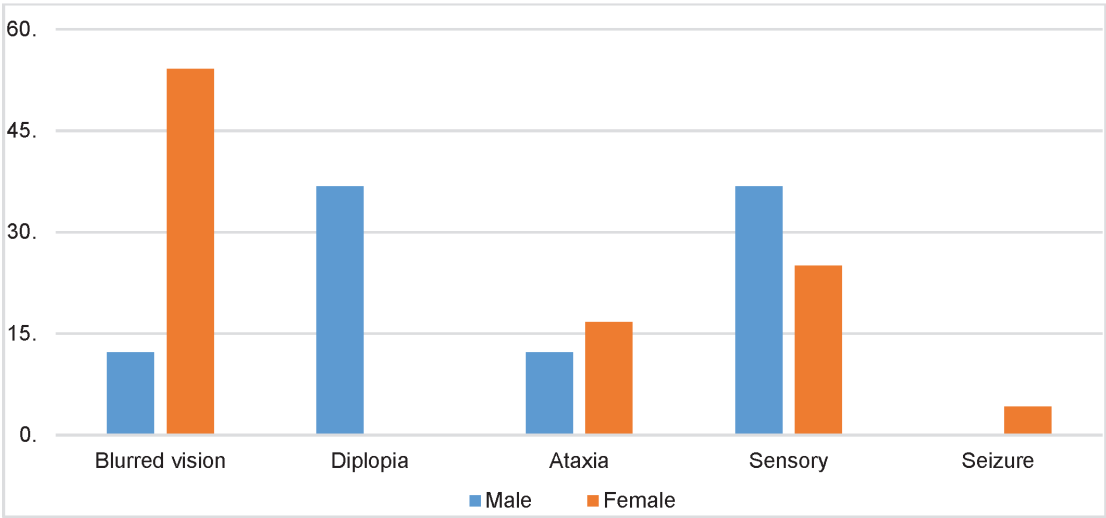

Figure 2. *first sign of MS in pediatric onset males and females (p-value <0.01).*

Discussion

This study described the prevalence of POMS in EA, Iran, which was 11.67 per 100,000. Prevalence increased with age, increasing from 2 per 100 000 (age 12 years) to 32 per 100 000 (age 17 years). The incidence rate was 1.37/100,000. 2.85% of total patients with MS in the province were POMS. The prevalence of POMS among females was higher. The female-to-male ratio was 3.94:1. The mean age of the disease onset was 15.81± 1.332 years old, without a significant difference between males and females (p=0.90). In most cases, the disease diagnosis was in ages above 15, with the peak prevalence at 17 years old at 62.49/100,000. Positive family history was seen in 7.05% of patients. The most common symptom in female cases was blurred vision, while in males were brainstem and sensory symptoms. The mean

gap between the first presentation and the definite diagnosis was 3.00 ± 9.63 months.

According to a recent systematic review, there are only 12 studies in which POMS incidence rates have been investigated. The incidence rate varies from 0.05/100,000 in Tunisia to 2.85/100,000 in Sardinia, Italy (18). This variability could arise from methodological differences. Diversity in the patients' age selection can affect the results, too. Some studies have considered the age below 16 (19, 20), and in some of them, the age ≤19 was considered as POMS (21). The incidence rate in this study is similar to Abu Dhabi, United Arab Emirates, which is located in the Middle East, such as Iran. In this study, the research team selected 19 years old as the cut-off for POMS (21). The incidence of POMS has not been determined in the other provinces of Iran. The incidence rate in a very high-risk area is reported as 2.3 per 100,000 in the population of <18 years old (22). Furthermore, a recent cross-sectional study based on the Iranian MS registry found 4544 cases of POMS between 2000-2019, with incidence rates of 0.26 per 100,000 in 2000 and 1.53 in 2019 (14). The current study's regional incidence rate was 1.37/100,000 in 2017, which did not differ significantly from the mentioned study.

Seven reported prevalence rates, of which only two studies provided age-dependent rates. The overall prevalence rate varied from 0.69 per 100,000 in Japan (20) to 26.92 per 100,000 in Sardinia, Italy (23). A recent study of Sardinian children (<18y of age) found a 35.6 per 100,000 prevalence of POMS, which makes it a very high-risk area (22). This study's prevalence rate was 11.67 per 100,000, which increased with age, like the United States (US) study (24). One population-based study on the prevalence of POMS in Iran reported 16.20 per 100,000 population in Tehran in 2017 (25). One significant reason for the difference in prevalence rates between Tehran and EA may be the use of different cut-off points. The cut-off point in this study was <18, but in the mentioned study, it was <19. Additionally, the referral of the patients to Tehran, the country's capital, leads to a greater number of patients and can affect the study's findings. Unlike some studies (26-28), this study found no cases of MS before the age of 12.

According to studies conducted in the last 15 years, the onset of symptoms before age 16 or 18 is called POMS or early-onset MS (8). Although different reports used different cut-off points, most studies considered 18 years old as a POMS cut-off (26), which has caused problems in the accuracy and integrity of the prevalence in different studies.

The mean age of the disease onset in the present study was 15.81 ± 1.332 years old, which was similar to Tehran (15.09 ± 2.27) (25), but it was higher than the other provinces of Iran, such as Fars (11 ± 4.71) (29) and Isfahan (14.7 + 1.8) (28). The mean age in Iranian POMS cases between 2000-2019 was reported as 14.3±4.6 years old (14). It is also similar to Italy, the US, and Kuwait (23, 30, 31) but is higher than Japan (8.3 ± 0.48), France (13.7 ± 2.4), and Canada (12.0 ± 3.8) (32-34).

The current study revealed that 79.82% of POMS cases were females, which was approximately at a similar level with recent studies in Isfahan (75.7%) and Tehran (77.80%) settings (27, 35). In addition, it is similar to Iranian national statistics, which was 78.1% in a recent study (14). The female-to-male ratio was 3.94:1 in this study was higher than the reported ratio in Japan (1.8:1), France (2.78:1), Canada (1.9:1), and Turkey (1.7:1) (32-34, 36). In a recent retrospective cohort study in the Polish children population (age ≤ 18 years), a

significantly higher prevalence of POMS in girls was also reported (37).

Although MS is not an inherited disease, studies found that genetics is a risk factor for MS (38-41). A 6-20% rate of positive family history in POMS has been reported by different studies (9, 10). A recent systematic review found a higher familial MS rate in POMS cases (42). A 15.1% rate was reported in a recent study in Tehran (35), approximately two folds greater than the present study (7.05%). A 7.9% rate of positive family history was also reported in the Polish children population (37). Studies have shown that ethnic aspects of POMS are different from adult-onset MS (43).

Blurred vision was the most frequently seen first clinical presentation among patients in this study. Although the most common first symptom in females was blurred vision, they were brainstem and sensory symptoms in males. A seizure was only seen in female patients (4.1%). Unlike the other studies (26, 27), motor symptoms were not seen as the first presentation in the present study. In a study in Isfahan, blurred vision (36.1%) and ataxia (14.6%) were the most common symptoms of POMS (28). In the other studies in Italy, Taiwan, and Turkey settings, optic neuritis, and sensory symptoms were the most common presentation at the disease onset (23, 44, 45).

The mean gap between this study's first presentation and the definite diagnosis was 3.00 ± 9.63 months, with a maximum of four years. The biggest gap in this study was ten years ago, possibly due to the limited number of MRI machines in EA then, lower knowledge about POMS, and old diagnostic criteria. Sixty-one days of interval between the onset of symptoms and diagnosis of POMS in ≥12 children were reported in a study in the US (26).

The sample size in most previous reports was limited, so the number of patients was less than 150 in most of them. Therefore, the available information about POMS is not consistent and complete (33, 46, 47), so further studies could help clinicians to close the present gap between the first presentation and definite diagnosis for more effective treatment plans and diminution the consequences of the disease, as much as possible. Besides the limited number of participants in this study, the lack of reliable data about the MRI findings, MS subtypes, and the severity of disability due to MS were the other limitations suggested to be addressed in future studies.

In conclusion

with a prevalence of 11.67 per 100,000, POMS is not rare in EA province. It mainly affects females, and its prevalence increases significantly after the age of 15 years old. The study showed that the first manifestation of the disease in males differed from females. Increasing knowledge of the MS diagnosis, easy access to MRI, available revised diagnostic criteria, and increasing awareness of the disease in the general population can lead to early diagnosis followed by increasing the disease incidence.

Acknowledgment

The study was approved by the Ethics Committee of TUOMS (Approval No. IR.TBZMED.REC.1398.455), according to the declaration of Helsinki

Author's contribution

EN: Software, Validation, Investigation, Writing - Original Draft. AN: Formal analysis, Investigation, Ressources, Data Curation. MT: Conceptualization, Methodology, Validation, Writing - Review &

Editing, Supervision, Project administration.

Conflict of interest

The authors have declared no competing or potential conflicts of interest

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