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Epidemiological and clinical characteristics of multiple sclerosis in paediatric population in Slovenia: A descriptive nation-wide study

Neli Bizjak[a], Damjan Osredkar[a,*], Mirjana Perković Benedik[a], Saša Šega Jazbec[b]

[a] Departments of Child, Adolescent and Developmental Neurology, University Children's Hospital, University Medical Centre Ljubljana, Slovenia
[b] Department of Neurology, University Medical Centre Ljubljana, Slovenia

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ABSTRACT

Background: Although multiple sclerosis usually affects young adults, paediatric-onset multiple sclerosis (pMS) is increasingly recognized in the past ten years. The aim of the present study was to evaluate the incidence of pMS in Slovenia and to characterize the clinical, laboratory and neuroradiological characteristics of pMS at the disease onset.

Methods: We performed a national retrospective descriptive study including all patients diagnosed with pMS between January 1992 and June 2017. We reviewed data of all patients younger than 18 years at the first demyelinating event.

Results: The estimated incidence of pMS was 0.66/100,000 children per year. We included 61 patients (77% were female) with a median age at diagnosis of 16.3 years. In 4 patients, onset of pMS was before the age of 12 years old (childhood-onset pMS). Relapsing-remitting multiple sclerosis was most prevalent, with only 2 patients presenting a primary progressive pMS. Polysymptomatic pMS was found at onset in 59% of patients and monosymptomatic in 41%. In the cerebrospinal fluid study, 88% of patients had positive oligoclonal bands. Brain magnetic resonance imaging studies showed a predominant supratentorial involvement (100% of patients).

Conclusion: The clinical pattern of pMS in our cohort of patients was characterized by polysymptomatic presentation and predominantly sensory symptoms at onset, developing a relapsing-remitting pMS pattern. It is important to gather more information about the incidence of pMS and its initial presentation and clinical course to improve early recognition and appropriate initiation of immunomodulatory treatment.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) characterized by demyelinating lesions of the CNS which cause focal neurological symptoms and signs disseminated in time and space. MS usually affects young adults between 20 and 40 years of age (Ghezzi et al., 2010). However, 2–10% of all MS patients have their first clinical event in childhood (Duquette et al., 1987; Boiko et al., 2002; Ghezzi et al., 1997; Simone et al., 2002; Banwell et al., 2007; Renoux et al., 2007; Chitnis et al., 2009), therefore paediatric health care providers must be aware of the clinical features and management of this disease. Despite increased awareness and research in the field of paediatric MS (pMS) in the past 10 years, the diagnosis of pMS remains a challenge due to overlapping signs and symptoms with other diseases (McDonald et al., 2001). Paediatric MS patients reach a comparable degree of disability 10 years earlier than patients with adult-onset of the disease (Simone et al., 2002). Therefore, early diagnosis and recognition of particular clinical characteristics associated with pMS is of importance for long-term management and patient well-being.

The aim of this study was to evaluate the incidence of pMS in Slovenia and to describe clinical, cerebrospinal (CSF) and magnetic resonance imaging (MRI) findings at the onset of pMS.

2. Material and methods

This study was approved by the National Medical Ethics Committee of the Republic of Slovenia. In this retrospective nation-wide study, we collected data from all patients with an established diagnosis of pMS, whose first symptoms related to a demyelinating lesion appeared before 18 years of age and who were treated at the Department of Child, Adolescent and Developmental Neurology at the University Children's Hospital Ljubljana between January 1, 1992 and June 30, 2017. According to a national agreement between hospitals in Slovenia, all pMS patients are referred to our department for treatment, which makes it the only tertiary centre treating pMS patients in Slovenia. We

* Corresponding author.

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therefore believe that this study includes the entire pMS population in Slovenia from the last 25.5 years. To make sure no children were missed in the study, we have contacted the only other tertiary medical centre in Slovenia treating children with neurological disorders (University Medical Centre Maribor) and they confirmed that no pMS patients were treated in their centre. Also, we have contacted all neurological departments in Slovenia treating adult MS patients – according to their own registries, they have confirmed they have not treated any patients, in whom the first symptoms of MS would present before 18 years of age. Therefore, we believe this is a true nation-wide study of pMS patients in Slovenia.

All cases fulfilled McDonald's diagnostic criteria (Polman et al., 2005, 2011), and the recommendations of the expert consensus for diagnosing pMS (Krupp et al., 2007, 2013).

Case records were reviewed for gender, age at first symptoms of pMS, time to diagnosis, symptoms at onset, disease course at presentation (relapsing-remitting or progressive), family history of MS, associated secondary disease, cerebrospinal fluid (CSF) findings, magnetic resonance imaging (MRI) findings at the first demyelinating event and data about prescribed treatments.

We have subdivided the patients into two age groups, the childhood-onset group (12 years or younger) and the adolescent-onset group (older than 12 years).

2.1. Statistics

To estimate the incidence of pMS in Slovenia, demographical data of the Statistical Office of the Republic of Slovenia were used. We have calculated the incidence by dividing the number of pMS patients having their first symptoms in a particular year with the average population at risk for that year, multiplied by 100.000 to be able to give the incidence as number of patients per 100.000 children per year. The yearly incidence for the year 2017 was estimated on the basis of the half-year data. We have than averaged the yearly incidences over the 25.5-year period.

Statistical analyses were performed using SPSS software version 24 (SPSS Inc., Chicago, IL, USA). Student's *t*-test was used for continuous data. Where data were not normally distributed, the Mann-Whitney *U* test was used for 2-group comparisons to get exact 2-tailed *p* values. However, due to the characteristics of the study, many results are presented only in a descriptive manner. A p value of < 0.05 was considered as statistically significant.

3. Results

We included 61 patients in our study, 47 (77%) were females and 14 (23%) were males, F: M ratio was 3.4:1.

The estimated incidence of pMS in Slovenia was 0.66/100,000 children per year. Detailed information on yearly incidences is given in the Supplementary Table S1.

The median age at the time of disease onset was 15.4 years (range 8.0 – 17.8 years) and the median age at diagnosis of MS was 16.3 years (range 10.0 – 20.0 years). Median time between the first demyelinating event to the time of diagnosis was 8 months (range 0 – 72 months).

Thirty-six patients (59%) had a poly-symptomatic manifestation (Table 1), most frequently with pyramidal symptoms (29), followed by sensory (Pohl et al., 2004) and cerebellar symptoms (Sindern et al., 1992). Patients had symptoms related to a median of 3 CNS regions (range 2–5). Two of them presented with encephalopathy and were initially diagnosed as having acute disseminated encephalomyelitis (ADEM). ADEM-like presentation was found in 1 patient in the childhood-onset group and in 1 patient in the adolescent-onset group.

Within the group of the 25 (41%) mono-symptomatic patients, the presenting symptoms were most often optic neuritis (12 patients), followed by sensory symptoms (8 patients), brain-stem symptoms (3 patients) and motor symptoms (2 patients). Regarding the primary symptom, there were no significant differences when comparing gender or the two age subgroups.

Table 1
The presenting symptoms at the onset of pMS in our cohort of 61 patients; number (percentage).

Monosymptomatic pMS	25 (41%)
Optic neuritis	12 (20%)
Sensory symptoms	8 (13%)
Motor symptoms	2 (3%)
Brain stem symptoms	3 (5%)
Polysymptomatic pMS	36 (59%)
Optic neuritis	7 (11%)
Sensory symptoms	27 (44%)
Motor symptoms	29 (48%)
Cerebellar symptoms	20 (33%)
Brain stem symptoms	16 (26%)
Spinal cord symptoms	1 (2%)
Encephalopathy	2 (3%)

All patients had brain MRI and 54/61 had spine MRI. The MRI findings revealed that all of the patients (100%) had supratentorial lesions, 55% infratentorial lesions and 56% spinal cord lesions. Of all patients, 33% had lesions in all three regions.

CSF analysis was performed in 59/61 patients (2 families rejected the investigation). Cerebral spinal fluid analysis showed that 58% of pMS patients had mononuclear pleocytosis, 61% had an elevated IgG index and 88% had IgG oligoclonal bands (OCB) in the CSF.

Of all patients, 59 (97%) had relapsing-remitting disease course (RRMS), while only 2 (3%) patients had a primary progressive disease course (PPMS). The 2 patients with a PPMS were girls (aged 13 and 15 years), both showing poly-symptomatic manifestation with pyramidal and sensory symptoms and intrathecal oligoclonal bands (OCB). All of the childhood-onset pMS patients had positive OCB.

An associated secondary disease was reported in 13 patients (21,3%), with the most frequent being an allergy (5 patients). A concomitant autoimmune disease was found in 4 children, 2 had autoimmune thyroiditis, 1 had insulin-dependent diabetes, and 1 uveitis. Out of 61 children, 11 (18%) had at least one first-degree family members with MS: 4 patients had a mother with MS, 2 patients had a father with MS, 4 patients had a sibling with MS, 3 patients had an aunt with MS, and 1 patient had a grandmother with MS. In one family both sisters were affected and in another two sisters, father and aunt were affected.

Treatment of the first acute MS episode consisted in 43 (70%) patients of high dose steroid therapy. Forty-six patients (75%) had received immunomodulatory therapy at some point during their disease. Thirty-seven of these patients (81%) were treated with interferon-beta, seven (15%) with glatiramer acetate and two (4%) with dimethyl fumarate. Nine patients were switched to other disease modifying therapy: 3 to natalizumab, 2 to fingolimod (1 was before treated with natalizumab), 4 to dimethyl fumarate and 1 to alemtuzumab. The median age at which immunomodulatory therapy was started was 17.1 years (range 13.4 – 21.7) and the median interval from onset of disease to the start of immunomodulatory therapy was 15 months (range 2 – 147). There were 16 patients (35%) who were not treated with immunomodulatory therapy because they and their families refused such treatment.

According to the age of the first demyelinating event we divided our patients into two groups (childhood-onset group, < 12 years, and adolescent-onset group, ≥ 12 years). Four patients (7%; 3 female, 1 male) had the disease onset before the age of 12 years and in 57 patients (93%; 44 females, 13 males) onset was between 12 and 18 years of age. The median age at the diagnosis of pMS in the childhood-onset group was 9.9 years (range 8.0 – 11.9), and all of these patients had a RRMS. One of these patients had a positive familiar history of MS. The median age at the diagnosis of pMS in the adolescent-onset group was 15.8 years (range 12.6 – 17.8), and 55 (96%) patients had RRMS.

Median time lapse between disease onset and age at diagnosis was 1.2 years in the total cohort, 2.4 years in the childhood-onset group and 1.1 years in the adolescent-onset group.

In the childhood-onset group, all 4 (100%) patients underwent treatment with immunomodulatory therapy at some point. One of them underwent treatment with immunoglobulin as initial therapy. In the adolescent-onset group, 40 (70%) of the patients underwent treatment with immunomodulatory therapy at some point. Seventeen patients underwent treatment with immunoglobulin as their initial therapy.

4. Discussion

We report on a nation-wide cohort of Slovenian pMS patients. We estimated the incidence of pMS in Slovenia, as ours is the only tertiary centre in Slovenia for treating patients with pMS younger than 18 years. The estimated incidence of pMS in Slovenia was 0.66/100,000 children per year. This number is very close to those previously reported incidence of pMS in other countries (Langer-Gould et al., 2011; Reinhardt et al., 2014).

Of all patients with pMS, 7% of the total cohort presented with childhood-onset pMS (under the age of 12 years) which is in agreement with previously reported studies, estimating that up to 17% of pMS patients had childhood-onset MS (Banwell et al., 2007; Correia and Augusto, 2016). In our cohort, all childhood-onset pMS patients had positive OCB in CSF, although some studies suggest patients with childhood-onset pMS are less likely to have positive OCB, as younger children with MS have a distinct CSF inflammatory profile at disease onset (Chabas et al., 2010). We only found two patients (3%) with PPMS, with disease onset in adolescence. These findings are in agreement with most pMS studies, which have reported low frequencies for primary progressive courses ranging from 0% to 7% (Boiko et al., 2002; Simone et al., 2002; Pohl et al., 2007; Banwell, 2004; Sindern et al., 1992). In our cohort, 18% of patients had a positive family history of MS. Other studies on pMS have reported a relatively lower prevalence of a positive family history for MS, ranging from 2 to 13,9%. (Simone et al., 2002; Renoux et al., 2007; Reinhardt et al., 2014; Correia and Augusto, 2016; Pohl et al., 2007).

In our cohort, 59% of patients had a polysymptomatic disease at onset, with pyramidal, sensory and cerebellar symptoms being the most prevalent. In patients with monosymptomatic (41%) disease at onset, cerebellar and pyramidal symptoms were rarely observed but appeared to be more common in younger children, whilst sensory symptoms prevailed in the adolescent-onset group. The polysymptomatic MS at the disease onset is more common in children than in adults (Mikaeloff et al., 2004), and our results are in concordance with this as well.

ADEM, characterized by multifocal deficits and encephalopathy, is the most frequent acute demyelinating syndrome in children (Mikaeloff et al., 2004; Banwell et al., 2011). Typically, ADEM is a monophasic disorder, but may also represent the first attack of pMS (Verhey et al., 2011). An ADEM-like presentation as first MS attack has been reported in the literature in 2–19% of pMS cases (Mikaeloff et al., 2004; Banwell et al., 2011; Verhey et al., 2011; Verhelst et al., 2017). In our pMS cohort presented here, two out of 61 patients (3%) presented with ADEM-like episode which is consistent with the notion that paediatric ADEM in children older than 11 years is a rare onset symptom of MS.

We have found CSF pleocytosis in 58%, elevated IgG index in 61% and positive OCB in 88% of pMS patients in our cohort. Other studies reported pleocytosis in 30–66% patients, elevated IgG index in 40–87% and positive OCB in 74–92% (Correia and Augusto, 2016; Verhelst et al., 2017; Atzori et al., 2009; Ghezzi et al., 2002; Pohl et al., 2004). CSF analysis is helpful in distinguishing MS from ADEM since only 4–10% of ADEM patients have OCB and 13–15% have an elevated IgG index at the first demyelinating event (Atzori et al., 2009; Tenembaum et al., 2002). Routine CSF examination and OCB analysis are with MRI an important tool in distinguishing the first attack of MS from ADEM and other diseases.

Regarding MRI findings at first demyelinating event, all (100%) of our patients had supratentorial lesions, 55% infratentorial lesions and 56% spinal cord lesions; 33% of patients had lesions in all three regions, demonstrating dissemination in space occurring already at the first clinical presentation. These findings are underlining the importance of both, brain and spinal cord MRI for early diagnosis of pMS.

Treating pMS patients is not an easy task. The aim of the treatment is to reduce the frequency of relapses and to prevent disability arising from disease progression. In our cohort study 75% of patients had received immunomodulatory therapy at some point during their disease. The mean age at which immunomodulatory therapy was started was 17.1 years and the mean interval from onset of disease to the start of immunomodulatory therapy was 2.1 years.

Our study has several weaknesses. It is a retrospective study, while more relevant data can be obtained in prospective studies. Also, we do not have precise neuropsychological and disability follow-up data to assess the full-scale disability of these patients. This would also allow us to examine the effect of different treatment strategies on the outcome, as well as whether earlier treatment is related to a better outcome.

5. Conclusion

Since pMS patients reach a comparable degree of disability 12 years younger than do patients with adult-onset disease, early diagnosis and early start of treatment is very important. Therefore, awareness of pMS characteristics might improve early diagnosis of MS in paediatric population.

Conflict of interest

The authors declare that they have no conflict of interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.msard.2017.09.017.

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