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Original Scientific Paper

EARLY ONSET OF MULTIPLE SCLEROSIS – CLINICAL FEATURES

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SUMMARY – The onset of multiple sclerosis (MS) in childhood is a diagnostic challenge. The aim of our study was to analyze the parameters of MS with an early onset in relation to the symptoms and course of the disease in adult patients. This study included patients treated with signs and symptoms of initial central nrvous system demyelinating disease, which were divided into a group of 52 patiensts who developed the disease before the age of 18 (children) and another group aged 20-55 years (adults). Children rarely had polysymptomatic onset (p=0.020). The most common initial symptoms in children were optic neuritis (35.3%) and ataxia (35.3%). In the group of adult patients, sensory disturbances (41.6%) were the most common initial symptoms, followed by pyramidal symptoms (37.6%). Monitoring the time of second relapse revealed it to have occurred in 40 (78.4%) pediatric patients and 79 (78.2%) adult patients after a median of 12 months and 9 months, respectively. In conclusion, the initial manifestations of MS in children do not differ much from MS in adults according to the disease characteristics.

Key words: *Multiple sclerosis, pediatric; Multiple sclerosis, adulthood; Clinical presentation of disease*

Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS), characterized by motor deficits, cognitive deficits, and reduced quality of life. About 3% to 10% of MS patients develop the disease during childhood or adolescence[1]. The term early onset of MS (EOMS) in this study is used to mean that the first clinical presentation of a demyelinating episode occurred before 18 years of life. First clinical presentation of EOMS can be visual, sensory, motor, brainstam/cerebellar, spinal deficits, and frequency of these symptoms varies widely. Patients with EOMS tend to have more relapses and increased disease activity on magnetic resonance imaging (MRI) in the first few years after disease onset[2]. Disability also tends to progress more slowly in children. Since the disease begins at an earlier age, it is common for people with pediatric MS to have severe disease-related disabilities by the age of 30.

In order to clarify the frequency and clinical characteristics of EOMS, we report here clinical

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findings at presentation and outcome of the deasase in our group of EOMS patients compared to those with MS onset in adult age (AOMS).

Patients and Methods

The cross-sectioanal study included 152 patients admitted and treated at the Department of Neurology, Clinical Center of Vojvodina in Novi Sad over a period of twelve years, from January 2003 to January 2015, with signs and symptoms of initial demyelinating CNS disease. In each patient, the following clinical findings were recorded: age at onset, sex, family history, caracteristics of initial symptoms (visual, pyramidal, sensory, brainstam/cerebellar, spinal), time until the second attack and clinical characteristics of second attack. All patients underwent a diagnostic protocol that included history, neurological examination, MRI of the endocranium, cytochemical examination of cerebrospinal fluid, and isoelectric focusing of cerebrospinal fluid, and visual evoked potentials (VEP). Diagnosis of clinically definitive MS or clinically probable MS was established according to McDonald criteria[2]. All patients in both groups were found to have relapsing-remitting MS (RRMS). Study patients were divided into two groups, as follows: a group of patients with disease onset before age of 18 and another group of patients diagnosed with clinically isolated syndrome or MS at the age >18 years. The data collected were compered between the groups of EOMS patients and randomly chosen 101 AOMS patients.

The research was conducted in accordance with the Helsinki Declaration on ethical principles in research involving human subjects. The research was approved by the Ethics Committee of the Clinical Center of Vojvodina, Novi Sad.

Data were analyzed using SPSS statistical program. Pearson's χ^2-test was used to test differences between the groups, and Cramer's V was used to test the strength of the connection. Non-parametric data were processed by the Mann-Whitney U test. The level of ststistically significant difference was set at $p<0.05$.

Results

The study included 152 patients with the first clinical demyelinating event. Study patients were divided into two groups of 51 patients with EOMS (children) and 101 patients with common onset of MS (adults, AOMS). In the group of EOMS patients, the youngest patient was aged 5 years and the oldest 18 years. In this group, the average age at the onset of the disease was 16 years (mean ± standard deviation [SD], 14.75±2.857 years). In the group of AOMS patients, the oldest patient was aged 55 years and the youngest 20 years. In this group, the average age at the onset of the disease was 30 years (32.20±8.728 years). The female to male ratio was 1.3:1 in the group of EOMS patients and 2.2:1 in the group of AOMS patients.

In the group of children, 44 (86.3%) had a negative family history of MS and other immune diseases, while 4 (7.8%) had a positive family history of MS, and 3 (5.9%) positive for autoimmune disease other than MS. In adults, 95 (94.1%) had a negative family history of MS and other immune diseases, 6 (5.9%) patients had a positive history of MS, and 3 (2%) patients had a history of another immune disease.

When we summarize all the initial symptoms of the first demyelination event in children and adults (Table 1), we notice that the most common initial symptoms in children were optic neuritis and ataxia/brainstem symptoms (35.3% both). In the group of adult patients, sensory disturbances (41.6%) were the most common initial symptoms, followed by pyramidal symptoms (37.6%).

An owerview of the initial symptoms is shown in Table 1. A review of individual symptoms in both groups indicated that pyramidal symptomatology as an initial symptom was statistically significantly different between the groups of children and adults. Disorder of the pyramidal system was more common as an initial symptom in the adult group (37.6% *vs.* 15.7%; p=0.010). Sensory symptoms were statistically significantly more common in adults than in children (41.6% *vs.* 17.6%; p=0.006). A comparison of the presence of optic neuritis as the initial symptom of a demyelination event in children and adults did not reveal a statistically significant difference in the prevalence between the two groups (p=0.366 and p>0.05). In the group of examined children, no sphincter disorder was recorded as the initial symptom, whereas in the group of adult patients, two patients had sphincter disorder as the initial symptom of the disease (p=0.797).

When we examined the presence of spinal symptoms as an initial demyelinating event, we obtained results indicating that in the group of children, 4 (7.8%) had spinal symptoms as an initial demyelinating event, whereas in the adult group none of the patients had spinal symptoms of transverse

myelitis (p=0.21). Adults and children differed in the prevalence of spinal symptoms. In the two groups of patients, both children and adults, none of the patients had headache as the initial symptom of a demyelinating event. Polysymptomatic onset was reported by 17.6% of children and 37.6% of adults (p=0.02). Polysymptomatic onset was statistically significantly more prevalent in patients in whom the onset of the disease occurred later.

Table 1. Symptoms of disease onset in adults and children

Symptoms		Children	Adults	p
Motor symptoms	n	8	38	0.01
		15.7%	37.6%	
Sensory symptoms	n	9	42	0.006
		17.6%	41.6%	
Optic neuritis	n	18	27	0.366
		35.3%	26.7%	
Brainstem/ cerebellum	n	18	32	0.791
		35.3%	31.7%	
Sphincter disorder	n	0	2	0.551
		0.0%	2.0%	
Myelitis	n	4	0	0.02
		7.8%	0.0%	

Frequency of exacerbation in relation to clinical features of the disease

During the follow-up, which was at least 2 years, 21% (n=11) of EOMS patients and 20.8% (n=21) of AOMS patients did not experience second relapse. According to statistical assessment of all the above symptoms, the shortest time to second relapse in patients with sphincter disorders would be expected in about 3 months, and the longest time to second relapse in children with sensory disorders in 18 months. In general, the time to second worsening is longer in all pediatric categories except for the category with ataxia/ brainstem symptoms as initial clinical presentation.

There were 8 of 40 children with polysymptomatic onset of the disease and 32 of 40 children with monosymptomatic onset in relation to the occurrence of second exacerbation. There was no statistically significant difference between these two groups (p=0.587). In patients with polysymptomatic exacerbations, second relapse is expected in 11 months on average. According to the same criteria, in adult patients, 32 of 79 had polysymptomatic onset and 48 of 79 patients monosymptomatic onset, without statistical significance in the occurrence of second relapse (p=0.456). Second relapse in adult patients with polysymptomatic onset is expected in about 8 months (Fig. 1).

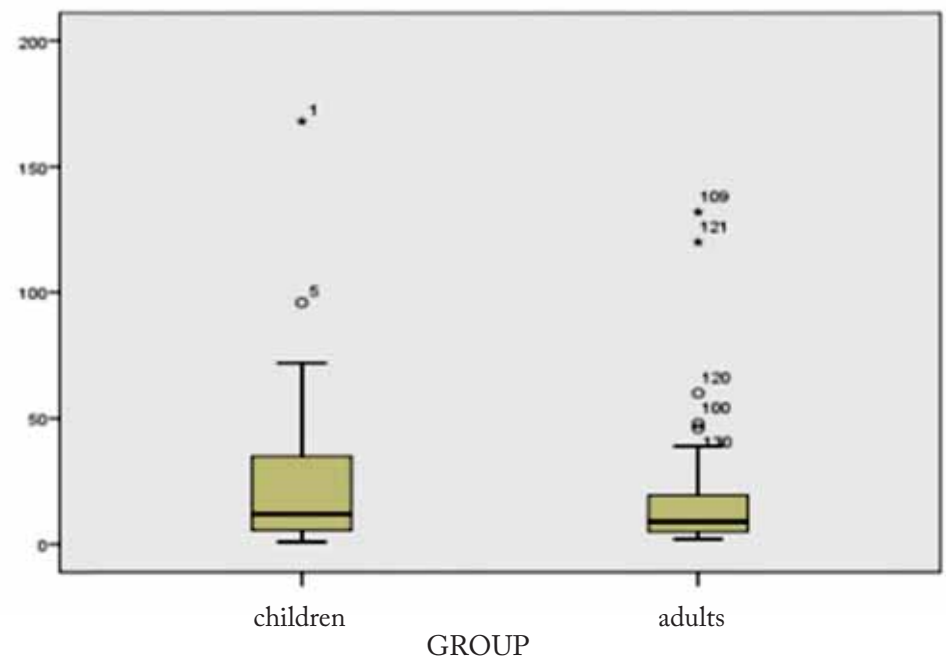

Fig. 1. Timing of second relapse occurrence compared to the initial one.

Discussion

The onset of MS before 18 years of age ranges from 2.2%-5.0% of all MS patients, and the onset of disease before 10 years of age is recorded in 0.2%-0.6% of patients[3-5]. The youngest so far documented patient with MS is a 24-month-old child[6]. In our study, the youngest patient, with the first demyelination event, was 5 years old.

The average age at the onset of the disease was 16 years (14.75±2.85) in our group of children and 30 years (32.2±8.72) in the group of adults. In the group of patients with early onset, the average age of patients was slightly higher than in other studies, e.g., in the Canadian study by Banwell *et al.*, the mean age of patients was 10.5 years[7], in the French study by Mikaeloff *et al.* the average age of patients included in the study was 12 years[7], in the Dutch study by Neuteboom *et al.*, the average age of patients was 8.5 years[8]. Data from the Australian Registry show a similar age as in our group[1].

In adult patients, the onset of the disease usually occurs at the average age of 30 years.

The predominance of females was confirmed in studies conducted so far in both pediatric and adult populations with MS, showing a ratio of up to 3.2:1[9]. Our study showed a male to female ratio in children with the first demyelination event of 1.3: 1.0. The literature shows a variable female to male ratio, from 1.4:1 to 1.3:1.0, Ghezzi *et al.* found the female/male ratio in patients with EOMS to be 1:0.5 over a 12-year period, which may suggest an effect of hormones on the onset of MS. As children get older, the female/male ratio increases at the expense of girls[10].

In pediatric patients with MS, a positive family history was found in 6%-8% of children and adolescents[11]. Studies with a long follow-up period find the prevalence of MS within the family to be about 20%[12]. Our data indicate that a positive history of MS and other immune diseases is significantly more common in children than in the group of adult patients. In patients with early onset in our community, a positive family history of MS was recorded in 7.8% and of other immune diseases in 5.9% of subjects. In the group of adult patients, 5.9% of them had a positive family history of MS but interestingly, there was no positive family history of other immune diseases.

Insight into the existing literature shows that the results of the conducted research indicate that in childhood, 96% of children were diagnosed with RRMS, and only 3.7% were diagnosed with a primarily progressive form of the disease[13]. All our patients from the early onset group were diagnosed with RRMS. Polysymptomatic onset of the disease is observed in 50%-70% of children, while 15%-30% of children have monofocal onset of the disease, including motor impairment in 30%, sensory impairment in 15%-30%, ataxia in 5%-15%, and brainstem symptoms in 25% of patients[14-19]. In our study, significantly more children had a monofocal onset of the disease (82.4%), which could probably be explained by the average age of our group of 16 years and their similarity with the adult population.

The most common initial symptoms in children were optic neuritis and ataxia (35.3% both), i.e., stable symptoms. In the group of adult patients, sensory disturbances (41.6%) were the most common initial symptoms, followed by pyramidal symptoms (37.6%). In our study, disorder of the pyramidal and sensory systems was more common as an initial symptom in the adult group.

In the pooled data that contain all studies on EOMS[2], most studies show that the most common clinical manifestation of MS in children is motor weakness[14,17-19]. Cerebellar symptoms follow in frequency[14,19]. Equally present are sensory disturbances that were most common in the studies by Duquette *et al.*[3] and Boiko *et al.*[5]. If some authors believe that pediatric MS is most often presented for the first time with sensory problems, more than half of the research[20] found the signs of pyramidal pathway disorders to be much more common (from 6% to 90%)[3,5,16], but in our pediatric group they differed, with optic neuritis and ataxia predominating as the initial symptom. The occurrence of unilateral or bilateral optic neuritis reported in various studies range from 0 to 50% of patients[4]; most published studies agree that at least 10% of patients have optic neuritis as the initial symptom of the disease[20]. In our study, the most common initial symptom in the group of patients with EOMS was unilateral optic neuritis, which occurred in 35.3% of patients. The KIDMUS study indicated that optic neuritis was the initial symptom in 22% of the children examined[20]. Spinal symptoms or myelitis occur as an isolated inflammatory event, as part of a multifocal demyelinating disease of the CNS such as acute disseminated encephalomyelitis, MS, or neuromyelitis optica (NMO), and it may also be

associated with systemic rheumatic disease. According to the literature, myelitis as an initial symptom of MS in the pediatric population occurs in less than 10% of children[21]. In the KIDMUS study, myelitis was observed in 14% of children examined. Gulay *et al.* dealt with idiopathic transverse myelitis in children. These authors followed-up 27 children for an average interval of 5 years. Two of these children were later diagnosed as NMO, and none of other children was suspected of having MS. In our group of patients, only four (8%) pediatric patients presented symptoms in the form of myelitis, which is in line with the results of other studies[22].

In our study, 17.6% of children and 37.6% of adults had a polysymptomatic onset of the disease. In the EOMS, the first clinical manifestation is less polysymptomatic than in its later onset. We found no significant difference in the occurrence of polysymptomatic onset and relapse rate. Neutebomm *et al.*[22] in their study on 117 pediatric patients showed that 43% had a monosymptomatic and 21% polysymptomatic onset. Children with polysymptomatic (multifocal) onset of the disease are more likely to develop MS than those with monosymptomatic onset[23-25]. According to the results of the KIDMUS study, monofocal onset is more common in adolescents[15].

Studies that followed-up children for 2-5 years from the first demyelination episode found a higher frequency of relapse (0.9-1.1) compared to adults in the same period (0.5-1)[26]. Our results differ from the above, as the early-onset group had a lower relapse rate (1.0) compared to adult patients (0.9). In 2002, Ghezzi *et al.* published the results of a prospective multicenter study in which 54 children participated and were followed-up for 2 years; the relapse rate in that study was 1.3[10].

Boiko *et al.* published the results of a retrospective study on 116 patients with EOMS, followed-up for 16.3 years, where the relapse rate was 0.54[5]. Gorman *et al.* published the results of a prospective study in which 21 children participated and were followed-up for 3.7 years; the relapse rate in this study was 1.1[27].

Establishing an early reliable diagnosis of EOMS, patients with clinical symptoms have a high risk of developing MS. Considering clinical presentation and initial course of the disease would help recognize the disease and introduction of therapy as early as possible, thus delaying and slowing down disease progresion and rate of disability. The existing studies on EOMS are based on small groups of patients, so additional research is highly warranted.

The limiatations of this work were a small number of patients with EOMS and a small number of patients with initial symptoms of MS before 10 years of age. Our group of patients with EOMS were of adolescent age on average.

Conclusion

It is very important to predict further course of the disease. Knowing further course is most helpful in making therapeutic decisions, optimal choice of therapy and speed of its application. Polysymptomatic onset is more common in adults, optic neuritis is the most common symptom in children, and sensory and motor disorder in adults. In a patient with EOMS, the period until the second worsening is longer.

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Sažetak

RANI NASTUP MULTIPLE SKLEROZE – KLINIČKA OBILJEŽJA

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Početak multiple skleroze u djetinjstvu predstavlja dijagnostički izazov. Cilj našeg istraživanja bio je analizirati kliničke manifestacije bolesnika oboljelih od multiple skleroze s ranim početkom u odnosu na simptome i tijek bolesti kod odraslih bolesnika. Ovom studijom obuhvaćeni su bolesnici liječeni na Klinici za neurologiju Kliničkog centra Vojvodine s početnim znacima i simptomima demijelinizirajuće bolesti središnjega živčanog sustava, koji su podijeljeni u skupinu od 52 bolesnika koji su oboljeli prije 18. godine i skupinu u dobi od 20-55 godina. Djeca rijetko imaju polisimptomatski početak (p=0,020). Najčešći početni simptomi kod djece su optički neuritis (35,3%) i ataksija (35,3%). U skupini odraslih bolesnika najčešći su početni simptomi bili senzorni poremećaji (41,6%), a zatim piramidni simptomi (37,6%). U našoj skupini ispitanika s ranim početkom bolesti tijekom praćenja od najmanje dvije godine pogoršanje je imalo 40 (78,4%) bolesnika. U skupini djece medijan za pojavu drugog recidiva bio je 12 mjeseci. U skupini odraslih bolesnika 79 (78,2%) ih je imalo drugi recidiv, a prosječno vrijeme do drugog recidiva bilo je 9 mjeseci. Početne manifestacije multiple skleroze kod djece se po karakteristikama bolesti ne razlikuju puno od onih kod odraslih bolesnika.

Ključne riječi: *Multipla skleroza, djeca; Multipla skleroza, odrasli; Klinička prezentacija bolesti*