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Natural course of multiple sclerosis in the first five years of the disease in the Kujawsko-Pomorskie district

Naturalny przebieg stwardnienia rozsianego w ciągu pierwszych pięciu lat choroby w regionie kujawsko-pomorskim

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Abstract

Aim: The aim of the study was to emphasize the prognostic value of the first five years of the natural course of multiple sclerosis for the disability progression, and a comparison of the relapsing-remitting and the primary progressive disease course. **Material and methods:** Using the retrospective design, we have evaluated the first five years of multiple sclerosis in the affected residents of the Kujawsko-Pomorskie district, treated at the Department of Neurology between July 2014 and September 2015. We have assessed the relationships between the Expanded Disability Status Scale score after the first five years of the disease and the clinical course, gender, initial symptoms, age at first symptoms, first magnetic resonance imaging data, cumulative relapse number in the first two or five years of the disease. **Results:** The investigated group consisted of 129 patients: 97 with the relapsing-remitting and 32 with the primary progressive disease course. The mean patients' Expanded Disability Status Scale score after 5 years of the relapsing-remitting disease course was 2.1 ± 1.2. The mean number of relapses in the first two and five years in this subgroup was 2.2 ± 1.2 and 4.2 ± 2.5. The mean patients' Expanded Disability Status Scale score after 5 years of the primary progressive disease course was 4.1 ± 1.4. A progression to Expanded Disability Status Scale score ≥3 in the period of evaluation was predicted by the primary progressive clinical course, older age at first symptoms, and more than five relapses in the first five years from the disease onset. **Conclusions:** This study confirms that early clinical differences of the natural course of multiple sclerosis could be strong predictors for moderate disability.

Key words: relapsing-remitting multiple sclerosis, primary progressive multiple sclerosis, The Kurtzke Expanded Disability Status Scale

Streszczenie

Cel badania: Celem badania było podkreślenie znaczenia pierwszych pięciu lat naturalnego przebiegu stwardnienia rozsianego w przewidywaniu postępu niepełnosprawności chorych z uwzględnieniem różnic między postacią rzutowo-remisyjną i pierwotnie postępującą choroby. **Materiał i metody:** Przeprowadzono retrospektywną analizę naturalnego przebiegu pierwszych pięciu lat stwardnienia rozsianego wśród chorych mieszkańców regionu kujawsko-pomorskiego hospitalizowanych w Klinice Neurologii między lipcem 2014 a wrześniem 2015 roku. Przeanalizowano zależności pomiędzy stopniem niepełnosprawności ocenianym w rozszerzonej skali niepełnosprawności Kurtzkego a postacią choroby, płcią, wiekiem zachorowania, charakterem pierwszych objawów, obrazem pierwszego badania rezonansu magnetycznego oraz całkowitą liczbą rzutów w ciągu pierwszych dwóch i pięciu lat choroby. **Wyniki:** Warunki badania spełniło 129 pacjentów: 97 z rzutowo-remisyjną i 32 z pierwotnie postępującą postacią choroby. Średnia wartość rozszerzonej skali niepełnosprawności Kurtzkego po pięciu latach naturalnego przebiegu postaci rzutowo-remisyjnej wynosiła 2,1 ± 1,2, a średnia liczba rzutów w ciągu pierwszych dwóch i pięciu lat choroby – odpowiednio 2,2 ± 1,2 i 4,2 ± 2,5. Średnia wartość rozszerzonej skali niepełnosprawności Kurtzkego po pięciu latach naturalnego przebiegu postaci pierwotnie postępującej wynosiła 4,1 ± 1,4. Czynnikami ryzyka osiągnięcia niepełnosprawności w rozszerzonej skali niepełnosprawności Kurtzkego ≥3 były pierwotnie

postępujący przebieg choroby, późniejszy wiek zachorowania oraz większa całkowita liczba rzutów w ciągu pierwszych pięciu lat stwardnienia rozsianego. **Wnioski:** Wczesne różnice kliniczne naturalnego przebiegu stwardnienia rozsianego mogą być silnymi czynnikami predykcyjnymi ryzyka umiarkowanej niepełnosprawności chorych.

Słowa kluczowe: rzutowo-remisyjna postać stwardnienia rozsianego, pierwotnie postępująca postać stwardnienia rozsianego, rozszerzona skala niepełnosprawności Kurtzkego

INTRODUCTION

Multiple sclerosis (MS) is a chronic, demyelinating disease of the central nervous system with different patterns of evolution and disability accumulation. It affects mainly young adults, with a female predominance. In vast majority, the clinical course starts with a relapsing-remitting phase (RRMS), followed by a gradual progression of disability in about 80% cases (Lublin and Reingold, 1996; Weinshenker *et al.*, 1989). Approximately, 20% of patients have gradually worsening neurological deficits from the onset without clinical relapses, i.e. primary progressive MS (PPMS) (Cottrell *et al.*, 1999). Nowadays, many patients in Poland with RRMS may start the immunomodulatory treatment after the diagnosis of MS. Because of the potential side effects, a proper indication of the patient with a poor outcome is required as soon as possible (Frohman *et al.*, 2006; Pittock *et al.*, 2006). We present data from the first five years of MS natural course which can be helpful to identify the patients likely to experience the progression of disability, and need early or aggressive therapies.

MATERIAL AND METHODS

We have assessed a cohort of 129 patients with diagnosis of MS treated at the Department of Neurology between July 2014 and September 2015. All of them were residents of the Kujawsko-Pomorskie district, a region situated in mid-northern Poland, with a population of about 2.1 million people (http://bydgoszcz.stat.gov.pl). The prevalence of multiple sclerosis in Poland varies from 45 to 92 per 100,000 inhabitants, and the incidence varies from 2.4 to 4.3 per 100,000 (Potemkowski, 2009). Patients were enrolled in the study if they had at least five years of documented disease duration. None of the patients underwent immunomodulatory or immunosuppressive therapy during the period of the evaluation. The disease onset was the year of the first symptom. The diagnosis was established according to Poser's criteria (Poser *et al.*, 1983), McDonald's criteria (McDonald *et al.*, 2001) or Polman revisions to McDonald's criteria (Polman *et al.*, 2005). The course of the disease was classified as RRMS or PPMS (Weinshenker *et al.*, 1989). A relapse was defined as the occurrence of new or the worsening of previous MS-related symptoms lasting over 24 hours (Lublin and Reingold, 1996; Poser *et al.*, 1983). PPMS was defined as at least one year of deterioration with or without superimposed episodes of worsening (Scalfari *et al.*, 2010; Weinshenker *et al.*, 1989). The onset of MS before age 16 was classified as early onset MS (EOMS), and above age 50 as late onset MS (LOMS) (Martinelli *et al.*, 2004; Tardieu and Mikaeloff, 2004). The neurological manifestations at onset were divided into isolated symptoms: motor deficit, sensory symptoms, brain-stem involvement, optic neuritis, gait disturbances or a combination of these symptoms. Magnetic resonance imaging (MRI) exams were performed on two different scanners of 1.0-tesla and 1.5-tesla without using a standardized protocol. The disability was assessed on Kurtzke's Expanded Disability Status Scale (EDSS) (Kurtzke, 1961, 1983). All patients provided informed consent for having their data saved in the database.

Statistical analysis

The differences between the investigated groups were calculated by Student's *t*-test for parametric data and *U* Mann–Whitney test for nonparametric data. Chi-squared test was used to compare proportions in the groups. An association was considered statistically significant at a p-value ≤ 0.05.

RESULTS

Clinical characteristics

The investigated group consisted of 85 women (66%) and 44 men (34%), with a mean age of 48.3 ± 11 years. The mean age at the disease onset was 34.6 ± 11.5 years. The mean disease duration was 13.7 ± 7.3 years. Ninety-seven patients (75%) were distributed into RRMS, and 32 (25%) into PPMS with respect to the disease course. With regard to the age at the disease onset, 17 (13%) patients were distributed into LOMS and 4 (3%) into EOMS. The first MRI scans of the brain were available for 103 patients, including 75 with RRMS and 28 with PPMS. The first spine MRI scans were available for 60 patients, including 35 with RRMS and 25 with PPMS (Tab. 1).

Initial presentation

The onset of the disease was monosymptomatic in 118 (91%) patients and polysymptomatic in 11 (9%) patients. Among the patients with a monosymptomatic onset, 39 (30%) had sensory symptoms, 34 (26%) motor deficit, 22 (17%) optic neuritis, 16 (12%) brain-stem dysfunction and 7 (5%) gait disturbances (Tab. 1).

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Demographic and clinical characteristics	Relapsing-remitting multiple sclerosis *n* = 97	Primary progressive multiple sclerosis *n* = 32	*p*-value
Gender – no. (%): Males Females	 30 (30.9) 67 (69.1)	 14 (43.8) 18 (56.3)	 0.18*
Current age	45.8 ± 10.4	55.9 ± 9.3	<0.0001*
Age at the disease onset	31 ± 9.9	45.3 ± 9.1	<0.0001*
Initial symptoms – no. (%): Isolated sensory symptoms Isolated motor deficit Isolated optic neuritis Isolated brain-stem dysfunction Isolated gait disturbances Polysymptomatic onset	 37 (38) 17 (18) 21 (22) 11 (11) 4 (4) 7 (7)	 2 (6) 17 (53) 1 (3) 5 (16) 3 (9) 4 (13)	 0.0007** <0.0001** 0.016** 0.52** 0.25** 0.35**
Time from the first symptom to the diagnosis	5.2 ± 5.1	4.9 ± 3.9	0.76*
EDSS score after five years of the disease	2.1 ± 1.2	4.1 ± 1.4	<0.0001***
Assignment of EDSS ≥3: Males Females	27 (28) 10 17	29 (90) 13 16	<0.0001** 0.0001** <0.0001**
The median time from the disease onset to MRI (years)	2.0 (Q1 = 0.1, Q3 = 6.0)	2.5 (Q1 = 1.3, Q3 = 5.0)	0.23***
The first MRI scans of the brain: Supratentorial lesions Gadolinium enhancement of supratentorial lesions Infratentorial lesions Gadolinium enhancement of infratentorial lesions	 73 (97) 12 (16) 47 (63) 3 (4)	 25 (89) 3 (11) 18 (64) 1 (4)	 0.042** 0.54** 0.88** 0.95**
The first MRI scans of the spinal cord: Spinal cord lesions Gadolinium enhancement of spinal cord lesions	 24 (69) 6 (17)	 21 (84) 1 (4)	 0.17** 0.12**

* Student's *t*-test.
** Chi-squared test.
*** *U* Mann–Whitney test.

Tab. 1. The demographic and clinical characteristics of relapsing-remitting and primary progressive multiple sclerosis patients

Relapsing-remitting multiple sclerosis

The group of 97 patients consisted of 67 (69%) women and 30 (31%) men with a mean age of 45.8 ± 10.4 years. The mean age at the disease onset was 31 ± 9.9 years. Among the first symptoms sensory symptoms (38%) and optic neuritis (22%) were the most common. The mean time from the first manifestation to the diagnosis was 5.2 ± 5.1 years. The median time from RRMS onset to MRI was two years (Q1 = 0, Q3 = 6). Brain MRI scans showed supratentorial demyelinating lesions in 73 (97%) patients, gadolinium enhancement – Gd(+) of these lesions was seen in 12 (16%) cases. Infratentorial lesions were observed in 47 (63%) patients, Gd(+) of these lesions was detected in 3 (4%) cases. MRI of the spinal cord detected lesions in 24 (69%) patients, with Gd(+) of these lesions present in 6 (17%) patients (Tab. 1). Thirty (31%) patients had more than two attacks in the first two years from onset. The mean relapse number in the first two years was 2.2 ± 1.2, with no significant correlation to gender ($p = 0.13$). The mean relapse number in the first five years was 4.2 ± 2.5, with no significant correlation to gender ($p = 0.34$) (Fig. 1). Forty-two (43%) patients had three or less bouts during the first five years of the disease (Fig. 2). The mean EDSS score after five years of the disease was 2.1 ± 1.2. Twenty-seven (28%) patients reached EDSS score of ≥3 (moderate disability) in the first five years of MS. A progression to EDSS score ≥3 was predicted by 34 years of age or more at first symptoms ($p = 0.04$), and more than five relapses in the first five years from the disease onset ($p = 0.003$). The relatively good prognostic factors included optic neuritis as the initial manifestation ($p = 0.005$), 30 years of age or less at the first symptoms ($p = 0.04$), and the number of relapses in the first five years of the disease ≤3. Among patients with RRMS who reached moderate disability, only 1 (4%) had had optic neuritis as the initial symptom. The mean age at the disease onset was 34 ± 9.7 years, the mean number of relapses in the first five years was 5.3 ± 2.7. There were no statistically significant differences between an increased risk of reaching EDSS ≥3 and the gender, the first MRI data, or other initial symptoms.

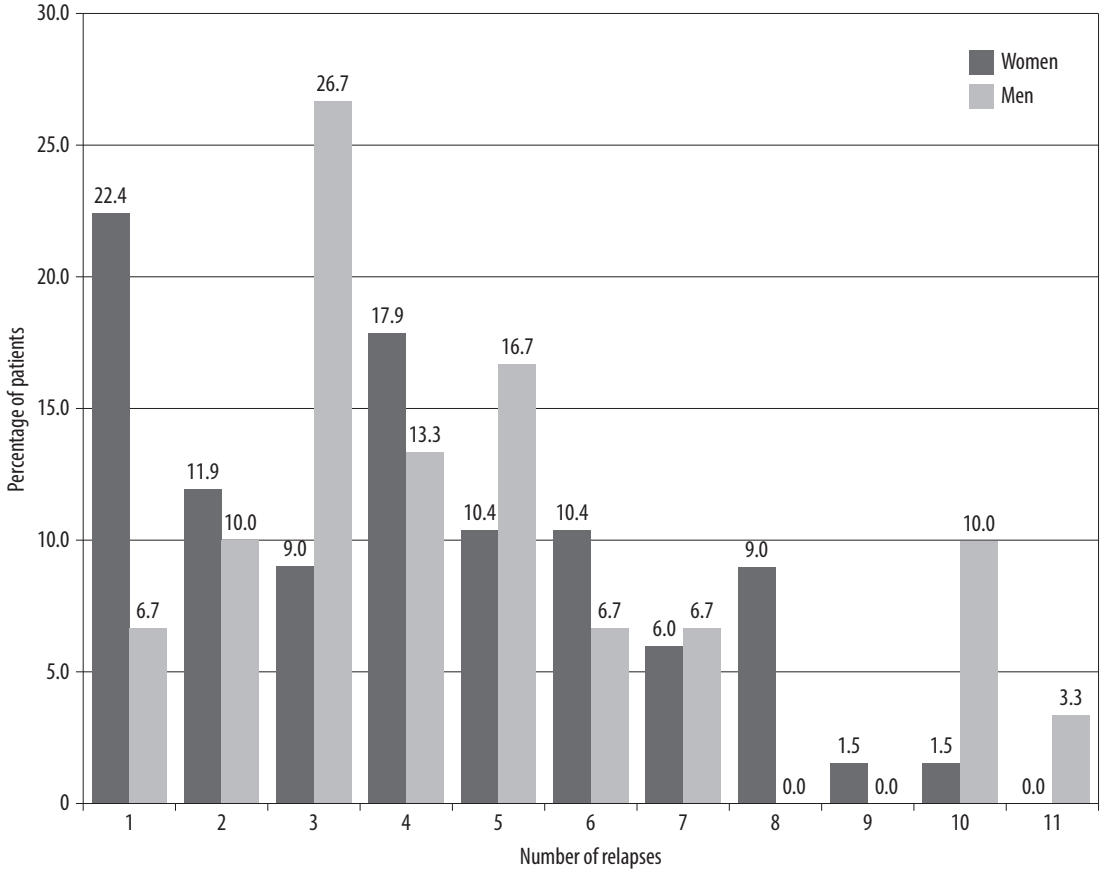

Fig. 1. The number of relapses in the first five years of relapsing-remitting multiple sclerosis according to the gender and the percentage of patients

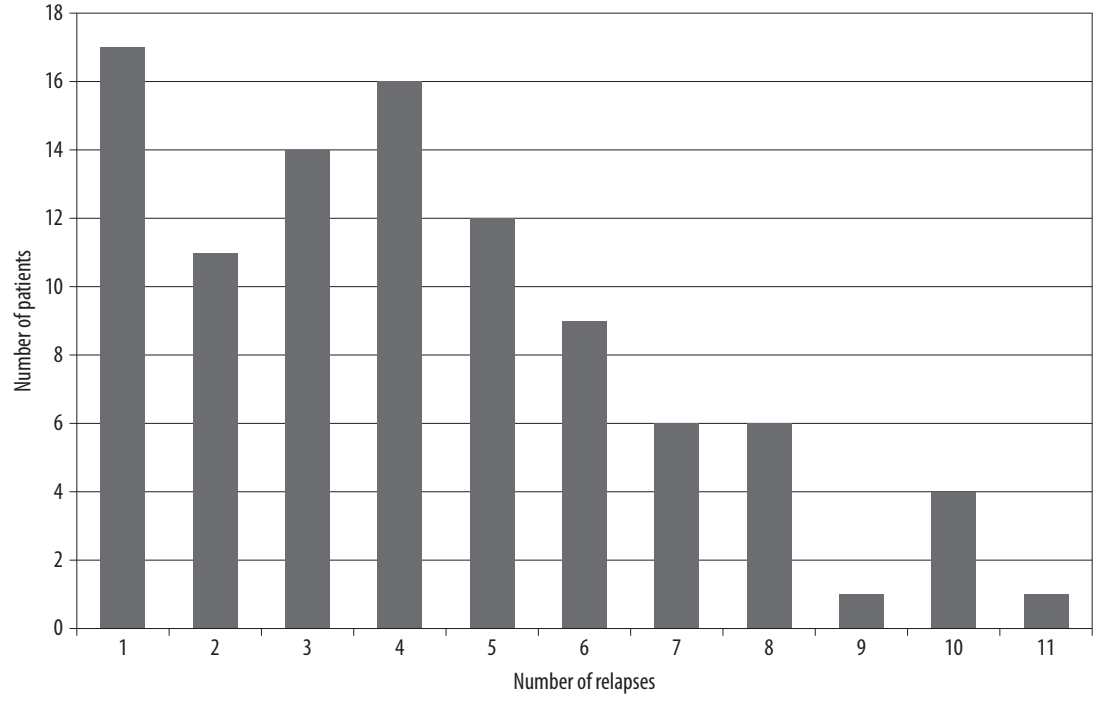

Fig. 2. The number of relapses in the first five years of relapsing-remitting multiple sclerosis according to the number of patients

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Primary progressive form of multiple sclerosis

There were 32 patients with PPMS, 18 (56%) female and 14 (44%) male. The mean age was 55.9 ± 9.3 years, and the mean age at the disease onset was 45.3 ± 9.1 years. The most frequent initial manifestation were motor symptoms (66%). The mean time from the disease onset to diagnosis was 4.9 ± 3.9 years. The median time from the onset to MRI was 2.5 years (Q1 = 1.3, Q3 = 5). Brain MRI scans showed supratentorial demyelinating lesions in 25 (89%) patients, Gd(+) of these lesions was seen in 3 (11%) cases. Infratentorial lesions were detected in 18 (64%) patients, Gd(+) of these lesions was found in 1 (4%) cases. MRI of the spinal cord detected lesions in 21 (84%) patients, with Gd(+) of these lesions present in 1 (4%) patients. The mean EDSS score after five years of the disease was 4.1 ± 1.4. Twenty-nine (90%) patients reached EDSS score ≥3 in the first five years of PPMS (Tab. 1). There were no statistically significant differences between the assignment of EDSS ≥3 and the gender, the first MRI data or the initial symptoms.

Relapsing-remitting form of multiple sclerosis versus primary progressive multiple sclerosis

These two groups differed significantly in several aspects as the first one had lower mean age ($p < 0.001$), an earlier onset of multiple sclerosis ($p < 0.001$), more frequent supratentorial lesions in the first MRI scans ($p = 0.042$). The initial manifestations were related more often to optic neuritis ($p = 0.004$), sensory symptoms ($p = 0.02$), and less frequently to motor deficit ($p < 0.0001$). There was a lower mean EDSS score ($p < 0.0001$) and a lower proportion of patients who reached EDSS ≥3 ($p < 0.0001$). In addition, 14 (82%) patients with LOMS had a primary progressive disease course ($p < 0.0001$), whereas all patients with EOMS had an initial relapsing-remitting phase of the disease.

DISCUSSION

We have demonstrated that some clinical features in the first five years of MS are important for the long-term prognosis. The demographic details of our cohort were quite similar to the previous studies. The overall male to female ratio was 0.52. The higher female predominance was seen in RRMS subgroup with the sex ratio of 0.45, versus PPMS subgroup with the sex ratio of 0.78. These findings are consistent with previous data (Atlas of MS, 2013; Cottrell *et al.*, 1999; Thompson *et al.*, 1997). The mean age at the disease onset in our group, and an earlier onset of RRMS course are comparable to the established pattern of MS and data from Szczecin province reported by Potemkowski (1999). In addition, 82% patients with LOMS had the primary progressive disease course, and all patients with EOMS had an initial relapsing-remitting form of the disease. These data are comparable to previous studies (Martinelli *et al.*, 2004; Tardieu and Mikaeloff, 2004). The mean time from the disease onset to the diagnosis was higher than in other provinces of Poland and Germany (Brola *et al.*, 2015; Łobińska and Stelmasiak, 2004; Stuke *et al.*, 2008). The possible explanation could be the heterogeneity of our cohort regarding the disease duration, usage of three different diagnostic criteria, taking into account only patients with a natural course of MS, and different attainability of MRI. This study confirmed a good prognosis in patients with younger age at the disease onset, an initial relapsing-remitting disease course, ≤3 relapses in the first five years of disease, and optic neuritis as the initial symptom. These findings are in accordance with data from previous studies (Confavreux *et al.*, 2003; Eriksson *et al.*, 2003; Runmarker and Andersen, 1993). On the other hand, ≥5 relapses in the first five years of the disease, and older age at disease onset were associated with a worse prognosis. These data are also consistent with previous findings (Confavreux *et al.*, 1980, 2003; Kantarci *et al.*, 1998). The percentage of patients with PPMS was in accordance with the data reported by Weinshenker *et al.* (1989) and Potemkowski (1999). This is probably the consequence of taking into account only the relapsing-remitting and the primary progressive disease course in our study. PPMS was associated with higher disability after the first five years of the disease. The first MRI scans showed supratentorial lesions more often in patients with RRMS than with PPMS. There were no statistically significant differences between an increased risk of reaching moderate disability and the first MRI data. The use of this parameter is problematic in most studies, because the patient didn't undergo standardised MRI imaging (Scott and Schramke, 2010). The lack of the first brain MRI scans for 26 patients and the first MRI scans of the spinal cord for 69 patients is one of the limitations of this study. Another is the relatively small number of patients. Overall, despite the above limitations, our database and findings are comparable to a larger registry in most of the clinical and demographic details.

CONCLUSIONS

This study confirms that early clinical differences of the natural course of multiple sclerosis could be strong predictors for moderate disability, and could identify patients likely to experience a progression of disability, and need early or aggressive therapies.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

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