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Original Article

Early Clinical Predictors of Disability in Multiple Sclerosis

Multipl Sklerozda Erken Klinik Prognostik Belirteçler

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Summary

Objective: The aim of the study was to examine the early predictive clinical factors for long term disability and prognosis in relapsing-remitting multiple sclerosis (RRMS).

Materials and Methods: Using a retrospective design, we studied 112 RRMS patients who were followed for more than 10 years. We investigated the relationship between sex, first attack symptoms, age at the disease onset, number of relapses in the first 5 years and Kurtzke Expanded Disability Status Scale scores (EDSS) at the 5^{th} and 10^{th} years of the disease.

Results: Mean EDSS were 1.69±0.91 at disease onset, 1.84±0.98 and 2.13±1.15 at 5^{th} and 10^{th} years of the disease. First attack symptoms were optic neuritis in 15 (13.4%), brain-stem dysfunction in (13.4%), cerebral hemispheric dysfunction in 51 (45.5%), spinal cord dysfunction in 10 (8.9%), cerebellar dysfunction in 9 (8%) and multisystemic symptoms in 12 (10.7%) patients. Gender, age at disease onset and first attack symptoms were not associated with the increase in EDSS, but EDSS at 5^{th} and 10^{th} years were significantly higher in patients with more frequent relapses in the first 5 years of the disease.

Conclusion: We demonstrated that the high number of relapses in the first 5 years of the disease is a significant risk factor for disease progression. (Turkish Journal of Neurology 2015; 21:22-6)

Key Words: Multiple sclerosis, predictive factors, risk factors, prognosis, natural history

Conflicts of Interest: The authors reported no conflict of interest related to this article.

Özet

Amaç: Bu çalışmanın amacı relapsing-remitting multipl skleroz (RRMS) hastalarında erken dönemdeki demografik ve klinik prognostik belirteçlerin ortaya konulmasıdır.

Gereç ve Yöntem: On yıldan uzun süredir takip edilen 112 RRMS hastasında hastalığın başlangıç yaşı, ilk klinik bulgular ve ilk 5 yıldaki atak sayısı ile 5. ve 10. yıldaki Kurtzke Expanded Disability Status Scale (EDSS) değerleri karşılaştırılmıştır.

Bulgular: Ortalama EDSS tanıda 1,69±0,91, hastalığın 5. yılında 1,84±0,98, 10. yılında 2,13±1,15'tir. İlk atak bulguları, 15 hastada (%13,4) optik nörit, 15 hastada (%13,4) beyin sapı, 51 hastada (%45,5) serebral hemisferler, 10 hastada (%8,9) spinal kord, 9 hastada (%8) serebellar fonksiyon bozukluğunu ve 12 hastada (%10,7) birden çok sistemin tutuluşunu işaret eden bulgulardır. Cinsiyet, hastalık başlangıç yaşı ve ilk atak semptomları ile uzun dönem özürlülük arasında ilişki bulunmamıştır. İlk 5 yılda atak sayısının fazla olmasının kötü prognoz ile anlamlı birliktelik gösterdiği izlenmiştir.

Sonuç: RRMS'te tedavi planının daha erken ve doğru olarak oluşturulabilmesi için erken dönemde hastalığın ileriki seyrine ilişkin bilgi verebilecek klinik vfaktörlerin belirlenebilmesi önemlidir. Çalışmamızda RRMS'te ilk 5 yıldaki atak sayısının uzun dönemde kötü prognostik bir belirteç olduğu gösterilmiştirv. (Türk Nöroloji Dergisi 2015; 21:22-6)

Anahtar Kelimeler: Multipl sklerozis, risk faktörleri, prognoz, doğal seyir

Çıkar Çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemiştir.

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Introduction

Multiple sclerosis (MS) is a disease of the central nervous system and it is the most common cause of disability in young populations (1). The clinical progression and the prognosis of the disease vary in great amounts based on the patient (2). Especially during the planning of long-term, expensive treatments which have considerable side effects, it is important to identify the findings that shed light on the future progression of the disease.

The aim of this study is to document the early clinical prognostic markers that will shed light on the long-term course of the disease progression in MS patients.

Materials and Methods

Among the 759 MS patients being followed in İzmir Tepecik Training and Research Hospital, 645 had relapsing-remitting (RR) type. Those who were being followed for longer than 10 years in this group (n=112) were included in this study. The mean follow-up duration of the included patients were 14.5±4.4 (10-29). Seventy-seven patients were female, 35 male; the mean age was 45.58±9.35 (25-64). Until 2002, Poser classification was used for MS diagnosis, which was then replaced by McDonald classification. This study included patients who received "definite" or "possible" MS diagnosis according to Poser classification (3,4,5). The onset age, early clinical findings, the attack count in the first 5 years and the Expanded Disability Status Scale (EDSS) at the 5th and 10th years were gathered retrospectively from records and the relationship between clinical findings at the disease onset and the long-term prognosis as shown by EDSS was investigated (6). The statistical analyses were done using SPSS 22.0.0.0, Kruskal–Wallis One-Way analysis of variance (ANOVA) and Repeated-measures (ANOVA).

Results

Demographic and clinical features of the study group are presented in Table 1. The mean EDSS is 1.69±0.91 at the time of diagnosis, 1.84±0.98 at the 5th year and, 2.13±1.15 at the 10th year. There were no statistically significant differences between sex and EDSS. The mean age of diagnosis is 31.08±8.86 (16-51).

There were no relationship between the mean age of diagnosis and the EDSS scores at the 5th and 10th years. Initial and 10th year EDSS scores are maximal in the group that had the diagnosis age of 20-29. The smallest EDSS scores were seen in the youngest disease onset group and the oldest group in the 10th year. However, these differences were not statistically significant and MS onset age was associated with neither 5th nor 10th EDSS score nor the EDSS score increase in 10 years.

Table 1. Demographic and clinical features of the study group

	n=112	%	EDSS		
			Diagnosis	5th Year	10th Year
Sex					
Male	35	31.3	1.54±0.74	1.97±0.99	2.11±1.08
Female	77	68.7	1.75±0.98	1.78±0.98	2.14±1.19
MS onset age					
≤19	12	10.7	1.42±0.52	1.25±0.62	2±0.43
20-29	40	35.7	1.78±1.17	2.1±1.19	2.3±1.42
30-39	38	33.9	1.71±0.77	1.76±0.85	2.11±1.13
≥40	22	19.6	1.64±0.79	1.82±0.79	1.95±0.89
First attack symptoms					
Optic neuritis	15	13.4	2±1.51	2.13±1.6	2.73±1.44
Brainstem dysfunction	15	13.4	1.73±0.8	1.87±1	1.87±1.30
Cerebellar dysfunction	9	8	1.22±0.83	1.56±1.13	1.67±1
Spinal cord dysfunction	10	8.9	1.6±0.84	1.7±0.82	2±0.67
Cerebral hemisphere dysfunction	51	45.5	1.69±0.76	1.84±0.78	2.24±1.14
Multiple symptoms	12	10.7	1.67±0.78	1.75±0.87	1.75±0.75
Number of attacks in the first 5 years of disease					
≤2	31	27.7	1.65±0.79	1.61±0.76	1.84±0.86
3	27	24.1	1.41±0.79	1.52±0.75	1.81±0.83
≥4	54	48.2	1.85±0.99	2.13±1.11*	2.46±1.13**

EDSS: Expanded disability status scale, MS: Multiple sclerosis

EDSS, given as mean ± SD.

*p=0.009 (5th year EDSS is higher for those who had ≥4 attacks than ≤2 attacks: p=0.025; 5th year EDSS is higher for those who had ≥4 attacks than 3 attacks: p=0,005)

**p=0.013 (10th year EDSS is higher for those who had ≥4 attacks than ≤2 attacks: p=0,022; 10th year EDSS is higher for those who had ≥4 attacks than 3 attacks: p=0.024)

A poliregional onset indicating a multisystem involvement in 12 patients (10.7%) among 112 patients, and a single system involvement in the remaining 100 patients (89.3%) were seen. Among 100 patients who had monoregional onset, 15 (13.4%) had isolated optical neuritis, 15 (13.4%) had isolated brainstem dysfunction, 51 (45.5%) isolated cerebral hemispheric findings, 10 (8.9%) isolated spinal findings and 9 (8%) isolated cerebellar findings at the onset. There were no relationship between initial attack symptoms and the EDSS scores at the 5th or 10th years. Even though it was not statistically significant, it was meaningful that the patients who were having optical neuritis attacks at the time of MS diagnosis had higher EDSS values (Table 1 and Figure 2).

The groups that had 1-2 attacks, 3 attacks and 4 or more attacks in the first 5 years of the disease were different in terms of the EDSS scores at the 5th and 10th years ($p<0.05$) Those who had a larger number of attacks in the first 5 years had higher EDSS scores in the 5th ($p<0.05$) and 10th ($p<0.05$) years (Table 1 and Figure 3).

Discussion

In our study, the effect of gender, disease onset age, the first attack symptoms and frequency of attacks in the first 5 years on the long-term prognosis was evaluated. In the 1992 study by Riise et al. in Norway that included 574 patients, it was shown that gender was not a factor in MS prognosis but advanced age and pyramidal and cerebellar symptoms the at the disease onset present as markers for bad prognosis, compared to young age and sensory symptoms at the disease onset (7). A year later, Runmarker and Anderson in Sweden also reported that young age and monoregional disease onset are the indicators of good prognosis (n=308) (8). Also in the Turkish population (n=1259), male gender, late disease onset, motor symptoms and sphincter symptoms were found to be indicative of bad prognosis (9). Confavreux et al. found that female gender, young age, optical neuritis as the first attack symptom (in the absence of long tract signs), complete recovery after the first relapse, long time interval between the first two attacks and smaller number of attacks in the first 5 years all indicated a favorable prognosis in the Lyon MS cohort of 2012 patients, 1562 of which had RRMS. These variables lose their predictive values after a threshold for unrecoverable disability (EDSS=4) is reached (amnestic phenomenon) (10,11). In a study conducted in the same geographical region in Turkey as ours, it was found that advanced age of onset, myelopathy and onset with motor symptoms were associated with bad prognosis in the 122 MS patients followed for at least 5 years, but there were no relationship with male gender and bad prognosis (12). In 2008, Debouverie et al. published their findings on the natural progression of MS after following 2871 MS patients (Lorraine MS group) for at least 9.7 years. 2518 patients out of 2871 initially showed RR progression. According to this study, RRMS progressed more slowly in the young and those who had full recovery following the first relapse whereas female gender and duration between the first two attacks did not have such an effect. These markers were only meaningful until EDSS reached 4 (2).

Based on these findings, Kantarci and Weinshenker's review in 2005 listed the markers for bad prognosis in MS as the following: Male gender, disease onset after 40, disease onset with motor and

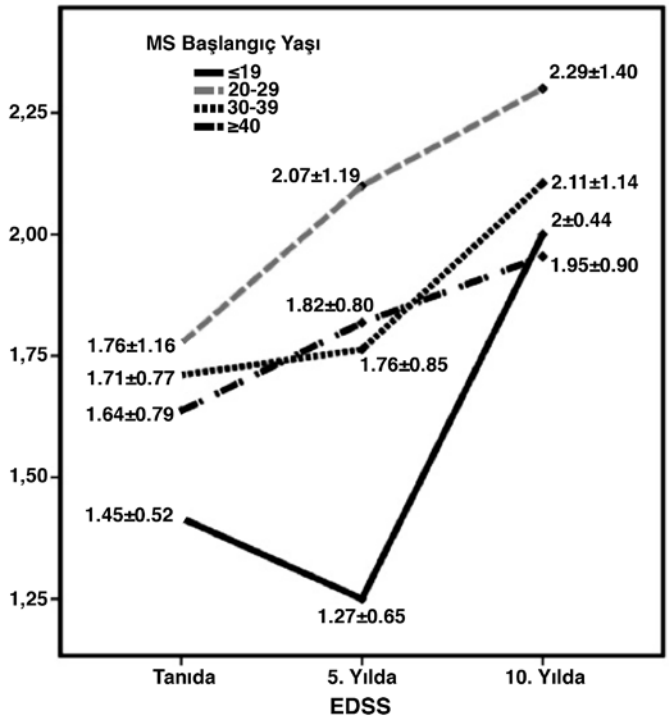

Figure 1. Expanded disability status scale (EDSS) scores at the 5th and 10th years, according to multiple sclerosis (MS) onset age

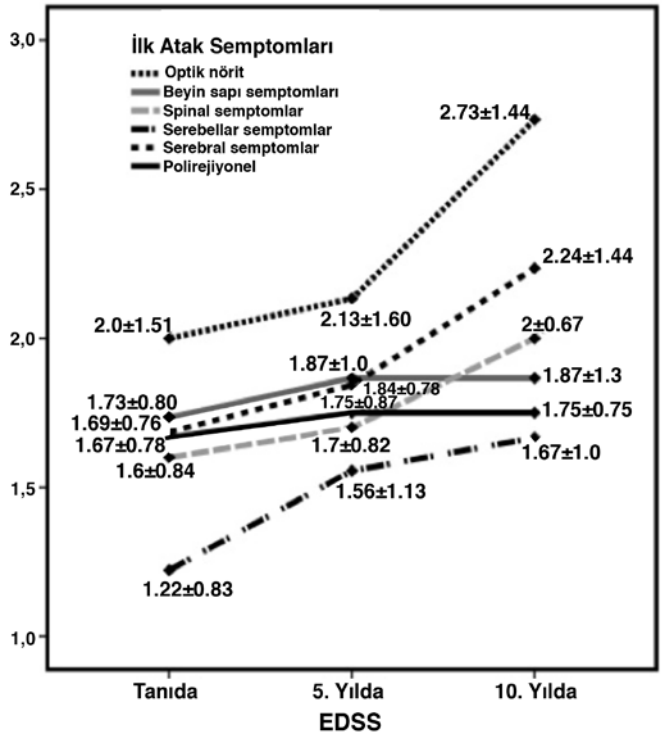

Figure 2. Expanded disability status scale (EDSS) scores at the 5th and 10th years, according to findings during the first attack

cerebellar findings, poliregional onset, frequent attacks in the first 5 years and small duration between first attacks (13). These findings were supported by the large-scale study conducted by Leray et al. in 2010. It should be kept in mind, however, that no single one of these factors by themselves have a strong predictive power on the long term prognosis (14).

In our study, the disease onset age, gender and findings at the first attack were not seem to be associated with long term disability. Much like in the previous studies, we also found that the attack count in the first 5 years is a marker for bad prognosis (10). As opposed to other studies, however, we did not find a positive influence of female gender on the prognosis. Progressive disease course is more commonly seen in males (15). The lack of an association between female gender and good prognosis in our study can be explained by the facts that our cohort only included RRMS patients and that the patients with progressive disease course, which could increase the disability in males, were excluded from the study. A lack of association between female gender and good prognosis has also been seen in Debouverie et al.'s study, which also used RRMS patients, as well as several other studies (2,12,16,17).

Even though it was described in the previous studies, our study failed to find an association between early age and good prognosis. Some other studies in the past have also obtained the same finding (16,17). In a review paper published in 2011, Renoux pointed out that reaching the threshold disability score may take longer when the disease starts at an early age but that does not necessarily point out to a good prognosis later on. Renoux suggested that when the disease starts at an early age, despite taking longer to reach the threshold disability score, young patients still reach this point earlier than late-onset patients and spend more of their lifetimes in disability (14).

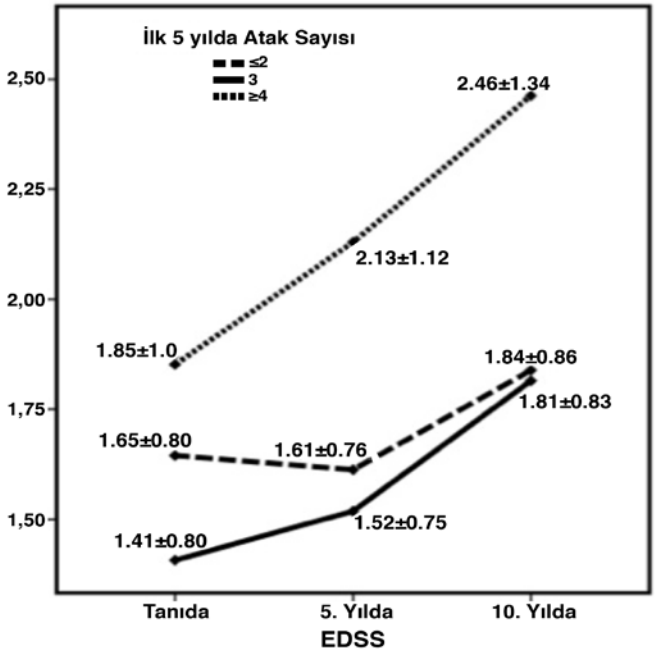

Figure 3. Expanded disability status scale (EDSS) scores at the 5th and 10th years, according to number of attacks in the first 5 years

Our study did not find an association between disease onset with optical and sensory symptoms, and good prognosis in the long term. This may be explained by our small sample size (n=112) and relatively short follow-up duration (14.5±4.4). Our study has additional limitations. Our study included patients whose disease started with RR course but it was impossible to determine at which point in the 10-year-follow-up did they switch to a progressive phase. In addition, EDSS scores at the 5th and 10th years were determined and 48.2% of the patients were found to have EDSS scores above 4, but it was impossible to determine and analyze at what time did these patients reach EDSS=4 and 6 values, which was important in terms of the effectiveness of clinical markers at the onset. Lastly, due to the variety in types and durations of use of disease modifying drugs, the effect of these drugs could not be analyzed. However, the scope of this study does not include the drugs used in MS treatment but the effect of the variables that could be identified during diagnosis on the prognosis.

Our study showed that attack frequency in the first 5 years in RRMS has a meaningful relationship with the long-term prognosis. In MS, identification of clinical findings that will give clues about the long-term prognosis is critical in determining the patients who are more suitable for aggressive treatment approaches, which could be riskier for bad prognosis. Our study contributes to this body of knowledge.

References

1. Sadovnick AD, Ebers GC. Epidemiology of multiple sclerosis: a critical overview. Can J Neurol Sci 1993;20:17-29.
2. Debouverie M, Pittion-Vouyovitch S, Louis S, Guillemin F; LORSEP Group. Natural history of multiple sclerosis in a population-based cohort. Eur J Neurol 2008;15:916-921.
3. Poser CM, Paty DW, Scheinberg L, Scheinberg L, McDonald WI, Davis FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH, Tourtellotte WW. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983;13:227-231.
4. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, McFarland HF, Paty DW, Polman CH, Reingold SC, Sandberg-Wollheim M, Sibley W, Thompson A, van den Noort S, Weinshenker BY, Wolinsky JS. Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;50:121-127.
5. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW, Sandberg-Wollheim M, Thompson AJ, Weinshenker BG, Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol 2005;58:840-846.
6. Kurtzke JF. Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983:33:1444-1452.
7. Riise T, Grønning M, Fernández O, Lauer K, Midgard R, Minderhoud JM, Nyland H, Pálffy G, Poser S, Aarli JA. Early prognostic factors for disability in multiple sclerosis, a European multicenter study. Acta Neurol Scand 1992;85:212-218.
8. Runmarker B, Andersen O. Prognostic factors in a multiple sclerosis incidence cohort with twenty-five years of follow-up. Brain 1993;116:117-134.
9. Kantarci O, Siva A, Eraksoy M, Karabudak R, Sütlaş N, Ağaoğlu J, Turan F, Ozmenoğlu M, Toğrul E, Demirkiran M. Survival and predictors of disability in Turkish MS patients. Turkish Multiple Sclerosis Study Group (TUMSSG). Neurology 1998;51:765-772.

10. Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain 2003;126:770-782.
11. Leray E, Yaouanq J, Le Page E, Coustans M, Laplaud D, Oger J, Edan G. Evidence for a two-stage disability progression in multiple sclerosis. Brain 2010;133:1900-1913.
12. Yuceyar N, Arici S, Kisabay A, Sagduyu Kocaman A. Natural history and early prognostic clinical factors in multiple sclerosis. J Neurol Sci Turk 2007;24:135-143.
13. Kantarci OH, Weinshenker BG. Natural history of multiple sclerosis. Neurol Clin 2005;23:17-38.
14. Renoux C. Natural history of multiple sclerosis: long-term prognostic factors. Neurol Clin 2011;29:293-308.
15. Kantarci O, Wingerchuk D. Epidemiology and natural history of multiple sclerosis: new insights. Curr Opin Neurol 2006;19:248-254.
16. Myhr KM, Riise T, Vedeler C, Nortvedt MW, Grønning R, Midgard R, Nyland HI. Disability and prognosis in multiple sclerosis: demographic and clinical variables important for the ability to walk and awarding of disability pension. Mult Scler 2001;7:59-65.
17. Amato MP, Ponziani G. A prospective study on the prognosis of multiple sclerosis. Neurol Sci 2000;21:831-838.