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RESEARCH

Long-term disability in multiple sclerosis: a longitudinal study over 20 years

Multipl sklerozda uzun dönem yeti yitimi: 20 yıllık uzunlamasına bir çalışma

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Abstract

Purpose: This study investigated the long-term clinical and demographic characteristics of multiple sclerosis (MS) patients to predict disease prognosis.
Materials and Methods: Two hundred and seventy-five MS patients diagnosed using the Poser or McDonald criteria were retrospectively analyzed. They were categorized based on their Expanded Disability Status Scale (EDSS) scores: below 4 (group 1) and 4 or above (group 2).
Results: The average patient age was 55.45 ± 9.63 years, with a disease duration of 26.76 ± 6.08 years. The initial EDSS scores increased from 2.56 ± 2.36 to 4.23 ± 1.8 after 20 years. Of the patients, 69.1% had EDSS scores of 4 or higher after 20 years. Notably, patients with supratentorial and spinal cord involvement at onset had higher EDSS scores. Logistic regression analysis revealed that a higher initial EDSS score, no full recovery after the first attack, and a longer duration between attacks were associated with a higher risk of an EDSS score of 4 or above.
Conclusion: Thisr study shows that an increase in the initial EDSS score is predictive of long-term disability in patients with MS. Having information on long-term, real-life data in MS is highly valuable in terms of understanding the course of the disease, its monitoring, and treatment selection.
Keywords: Multiple sclerosis, disability, prognosis

Öz

Amaç: Bu çalışma, hastalık prognozunu tahmin etmek için Multipl Skleroz (MS) hastalarının uzun vadeli klinik ve demografik özelliklerini araştırmaktadır.
Gereç ve Yöntem: Poser veya McDonald kriterleri kullanılarak teşhis konulan 275 MS hastası retrospektif olarak incelendi. Genişletilmiş Engellilik Durumu Ölçeği (EDSS) puanlarına göre 4'ün altı (grup 1) ile 4 ve 4'ün üzerinde (grup 2) olarak sınıflandırıldı.
Bulgular: Hastaların ortalama yaşı 55.459.63, hastalık süresi 26.766.08 yıldı. İlk EDSS puanları 20 yıl sonra 2.56 ± 2.36'dan 4.23 ± 1.8'e yükselmiştir. %69,1'inin 20 yıl sonra EDSS puanı 4 veya daha yüksekti. Özellikle, supratentoryal ve omurilik tutulumu başlangıçlı hastalar daha yüksek EDSS skorları gösterdi. Lojistik regresyon analizi, daha yüksek bir ilk EDSS puanının, ilk ataktan sonra tam iyileşme olmamasının ve ataklar arasında daha uzun bir sürenin, 4 veya daha yüksek bir EDSS puanı riski ile ilişkili olduğunu ortaya koydu.
Sonuç: Çalışmamız, başlangıçtaki EDSS'deki artışın MS'te uzun süreli sakatlığın öngörücüsü olduğunu desteklemektedir. MS'te uzun dönemli gerçek yaşam verileri hakkında bilgi sahibi olmak, hastalığın seyrini anlamak, takibi ve tedavi seçimi açısından oldukça değerlidir.

Anahtar kelimeler: Multipl skleroz, yeti yitimi, prognoz

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune neurological disease characterized by demyelination and axonal degeneration in the central nervous system (CNS). Although it is more common in young adults, it can also occur in children and the elderly[1,2].In individuals with MS, motor symptoms, brainstem and cerebellar involvement, and genitourinary problems are poor prognostic clinical onset findings, whereas sensory symptoms and optic neuritis are good prognostic clinical features[3-6].These symptoms, observed during both the attack and progression phases, can significantly impact the

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disease's trajectory, particularly if they present as mono- or polysymptomatic during the disease's onset[6]. Both physical and cognitive impairment can be seen in MS patients at every stage of the disease and vary from person to person[7]. MS, with its potential to affect individuals of all ages, can affect the quality of life of both patients and their relatives in various ways[8,9].

When following up on individuals with MS, the most frequently used and most valid scale to monitor the severity of the disease and attack severity is the Expanded Disability Status Scale (EDSS), which was developed and revised by Kurtzke and forms the main endpoint of many clinical and real-life studies[10,11]. The most significant advantage of using EDSS, which has remained unchanged for many years, is that it enables the provision of very valuable data about the disease course in the long-term follow-up of patients. There are two definitions used to monitor the accumulation and characteristics of physical disability in MS patients. The first definition and the basis of disability in relapsing remitting multiple sclerosis is relapse-associated worsening (RAW), and the other is progression-independent worsening (PIRA), which forms the basis of the progression[12,13]. Both RAW and PIRA use the EDSS as the main parameter in defining disability accumulation in confirmed disability progression (CDP).

The first step in tracking the progression of a disease is proper monitoring. Data from standard and MS-specific clinical parameters can lay the foundation for new clinical parameters to be developed in the future. In monitoring the course of the disease, the first parameter is disease activation and progression, the second concerns disease symptoms, and the last pertains to comorbid features. Evaluating and monitoring each parameter individually provides the potential for understanding the natural course of the disease and expanding the scope of intervention. This study aims to present real-life data on the disease activity, progression, and initial symptoms of MS patients who have been regularly monitored over the long term. Furthermore, even though the EDSS has certain disadvantages, this study aims to show that it will continue to be the primary endpoint in the long term. Documenting the long-term clinical and demographic characteristics of MS that can cause physical disability is of great importance in creating algorithms and decision models to predict the prognosis at the start of the disease[13,14].

MATERIALS AND METHODS

Ethics committee approval for the study was obtained from the Kocaeli University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee, dated June 16, 2023, approval number GOKAEK-2023/11.32. The study was conducted in accordance with the principles of the Declaration of Helsinki. An informed consent form was obtained from all patients included in the study.

Sample

Patients who had been regularly followed up at the Kocaeli University MS Clinic for at least 20 years and who were diagnosed with MS according to the Poser or McDonald criteria were included in the study. The patients were evaluated by an experienced MS specialist. The data were regularly recorded in the clinical database. The long-term results were obtained retrospectively from the recorded data. All patients with 20-year follow-up data were included in the study. Due to the design of the study, all patients who did not have regular follow-up data and did not agree to share their data were excluded from the study.

Procedure

Data on age, gender, initial clinical symptoms, the period between the first and second attacks, recovery status post-attack, EDSS, and functional system (FS) involvement from the first and last visits were retrospectively gathered from the recorded database.

The demographic and clinical baseline characteristics of the patients were obtained from the recorded data. Patients whose physical condition was evaluated with EDSS at least once a year were included in the study. Evaluations were performed according to the baseline EDSS-Functional System Scores (FSS) and last-visit EDSS scores.

EDSS

The EDSS is widely used to assess the level of disability and course of the disease in MS patients. This scale, based on neurological examination findings, uses a scoring system ranging from 0 to 10, where 0 represents no signs of disability and 10 represents the death of the patient.

The foundation of the EDSS is the FSS, which is used to detect neurological function deficits in MS patients. These scores relate to the following functions: Pyramidal, assessing motor functions;

Cerebellar, measuring coordination and balance; Brainstem, evaluating brain stem functions; Mental, assessing cognitive and emotional states; Sensory, measuring sensory functions; Bowel and Bladder, assessing control of urination and defecation; Visual, evaluating visual capacity; and Cerebral, measuring other brain functions. Each functional system score is typically rated on a scale of either 0–5 or 0–6, and these scores are then combined using a specific formula to produce the overall EDSS score. The study population was divided into two groups: those with an EDSS score of below 4 (group 1) and those with an EDSS score of 4 or above (group 2). These two groups were compared on the basis of their clinical characteristics at the end of the 20-year period.

Statistical anlaysis

All analyses were performed using SPSS 28.0 software. The normality of the data distribution was verified using the Shapiro-Wilk test and by examining histograms and graphs. Because the data followed a normal distribution, the values were represented as the mean ± standard deviation (SD). In addition, the chi-square test was employed to compare the ratios of categorical variables (gender, EDSS group (defined above), and spinal cord involvement), and when necessary, the p-value obtained from the Fisher test was used. Spearman analysis was performed to identify relationships between the variables (demographic features, EDSS scores), and binary logistic regression analysis was used to investigate the parameters effective in predicting an EDSS score of 4.

RESULTS

The study included 275 MS patients (F/M; 193/82), with an average age of 55.45 ± 9.63. The average disease duration of the study group was 26.76 ± 6.08 years. The average EDSS score at the first admission was 2.56 ± 2.36, while at the end of 20 years, the average EDSS score was assessed as 4.23 ± 1.8. When examining the initial clinical features of the study group, 26% presented with optic neuritis, 32.4% with brainstem/cerebellum symptoms, 43.6% with supratentorial symptoms, and 28% with spinal attacks. Upon the final neurological evaluations based on neurological examinations, and when analyzing the EDSS and functional systems (FS) scores, the pyramidal system was found to be the most commonly affected (42.9%), with the cerebellar system the least affected (Figure 1).

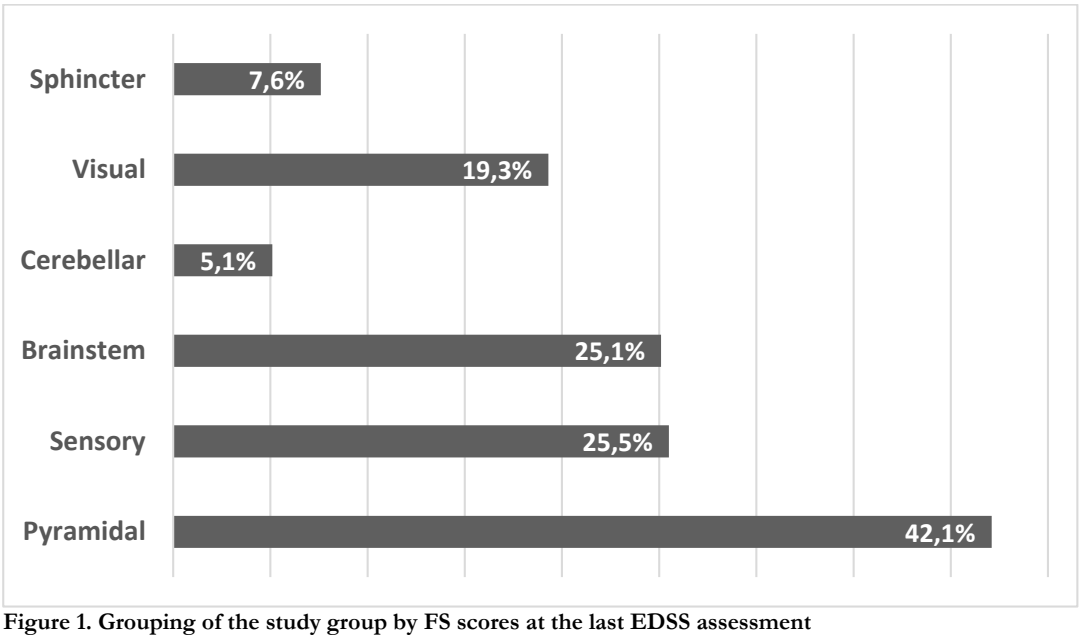

Figure 1. Grouping of the study group by FS scores at the last EDSS assessment

FS: functional system, EDSS: Expanded Disability Status Scale

Upon the final EDSS evaluation, the scores were grouped into those below 4 (group 1) and those with EDSS scores of 4 and above (group 2). At the end of the 20 years, 69.1% of the study group had an average EDSS score of 4. When comparing both groups in terms of gender, similar proportions of females were observed in both groups, with no statistically significant differences observed (respectively, 68.3%, 69.4%; p = 0.887).

Upon evaluation of groups 1 and 2 based on clinical onset features, among patients with a supratentorial onset, the proportion of patients with EDSS scores of 4 and above at the end of 20 years was 75.5%, whereas this rate was 62.6% in the group with EDSS scores below 4, representing a statistically significant difference (p = 0.009). Among those patients with optic neuritis as the first clinical event, the proportion in group 2 was 48.6%, and 76.4% in group 1, with a statistically significant difference between the two (p < 0.001). Additionally, in the patient group with spinal cord involvement onset, the proportion in group 2 was 87%, whereas it was 62.1% in group 1 (p < 0.001). There was no significant difference with the other clinical onset features. Moreover, in the group displaying polysymptomatic onset features, the proportion in group 2 was 88.1%, whereas this rate was 60.7% in those without polysymptomatic onset (p < 0.001).

When recovery rates were examined following pulse steroid therapy after the first clinical event, the proportion in group 2 was 91.7% in the group without improvement, 87.6% in those exhibiting partial improvement, and 55.1% in the group experiencing full recovery after the attack. In the group with full recovery, the EDSS score was significantly less likely to be 4 at the end of 20 years compared with both groups (p < 0.001).

At the end of 20 years, the group 1 and group 2 proportions were examined in terms of the FSS scores in the last EDSS evaluation, and within the groups receiving scores from the pyramidal and sphincter FSS, the proportions in group 2 were significantly higher (respectively, 78.8% vs. 61.8%; p = 0.004; 90.5% vs. 72.5%; p = 0.019) (Table 1).

Table 1. Percentage of group 1 and group 2 according to functional system scores

FS	Group 1	Group 2	p value
Pyramidal	61.8%	78.8%	*0.004*
Cerebellar	69%	71.4%	0.846
Brainstem	70.4%	65.4%	0.421
Sensory	65.7%	70.2%	0.577
Sphincter	67.3%	90.5%	*0.027*
Visual	72.5%	54.7%	*0.019*

FS: functional system

Table 2. Factors predicting a final EDSS score of 4 and above

Factors	p value	Odds Ratio	95% C.I.for EXP(B)*	
			Lower	Upper
Age	0.091	1.033	0.995	1.073
The first EDSS	***0.038***	1.184	1.009	1.390
Time between 1st and 2nd attack	***0.001***	0.992	0.988	0.997
Supratentorial onset	0.636	1.222	0.533	2.799
Optic neuritis onset	0.084	0.423	0.160	1.123
Spinal onset	0.124	2.074	0.819	5.248
Improvement of relapse	***0.001***	1.563	0.156	15.609
Presence of pyramidal FSS	0.328	1.500	0.666	3.381
Presence of visual FSS	0.190	2.056	0.700	6.040
Polysymptomatic onset	0.058	2.418	0.971	6.019

FSS: functional system score

*95% C.I.for EXP(B): 95% C.I. stands for the 95 percent confidence interval. EXP(B) represents the exponential of the B coefficient (often from logistic regression output).

The relationship between the onset EDSS scores, EDSS scores from the final evaluation, and clinical features was assessed using Spearman's correlation. A significant weak positive correlation was observed

between the final EDSS score and age (rho = 0.147; p = 0.015), whereas no significant correlation was observed between disease duration and the final EDSS score (p = 0.248). A significant positive correlation was observed between the initial onset EDSS score and age, the final EDSS score, and disease duration (respectively, rho = 0.131, p = 0.03; rho = 0.282, p < 0.001; rho = 0.199, p = 0.001).

When the effect of clinical and demographic features on the final EDSS score of 4 or above was evaluated with logistic regression analysis, it was observed that a 1-point increase in the initial EDSS score increased the risk of the final EDSS score being 4 by 1.184 times. Additionally, a longer duration between two attacks reduced this risk by 0.992 times, while the absence of a full recovery from the initial attack increased the risk of the final EDSS score being 4 by 1.56 times (Table 2).

DISCUSSION

MS is characterized by various clinical onset features, such as optic neuritis, brain stem involvement, spinal cord involvement, supratentorial onset, and even polysymptomatic onset[6,15]. This study demonstrated that approximately 70% of the MS group followed for at least 20 years had an EDSS score of 4 or above, which is a milestone for physical disability. Furthermore, the higher proportion of those with poor prognostic characteristics in terms of clinical onset features among the group with an EDSS score of 4 or above during the 20-year follow-up supports the view that clinical onset features are one of the parameters that must be considered in patient monitoring and treatment selection.

Optic neuritis is a common symptom at the onset of MS and usually presents with symptoms such as vision loss, eye pain, and difficulty in eye movements. It represents the first attack of MS in 8–33% of cases, is part of a multifocal first attack in 24–41% of cases, and develops in 27–66% of all MS cases[16]. Many studies suggest that optic neuritis is a good prognostic feature in MS patients, predicting a disease with less progression[6,17]. However, considering the pathogenesis of MS and the fact that its prognostic factors include different parameters, it is crucial to evaluate each patient individually and personalize the process, despite optic neuritis being considered a good prognostic feature. In our study, it was observed that at the end of 20 years, the group whose first clinical event was optic neuritis had a lower EDSS score of 4, a significant limit for physical disability and progression, than those who did not start with optic neuritis.

In the presence of spinal cord involvement at the first clinical event, the existence of a positive family history, a high EDSS score, the presence of oligoclonal bands in CSF, and abnormal findings in brain MRI are risk factors for conversion to MS[18]. In the current literature, spinal cord involvement is associated with poor prognostic features in MS. In a prospective study, spinal cord involvement was reported to be associated with physical disability and progression in individuals with MS[19]. A meta-analysis also showed that spinal cord involvement negatively affected the course of the disease and was associated with the development of progressive MS[20]. In our study, although the presence of spinal cord onset did not predict an EDSS score of 4 or above at the end of 20 years, the proportion of patients with spinal cord involvement at onset who had an EDSS score of 4 or above at the end of 20 years was higher. Therefore, spinal cord involvement in the onset of clinical features should be considered one of the poor prognostic features in MS and kept in mind in the interpretation of changes observed in patients.

The severity of relapse and residual findings are other clinical parameters to consider in follow-up, treatment intervention, and long-term treatment decisions. Moreover, studies by Naldi, Baghizadeh et al. have shown that relapses involving polysymptomatic presentation tend to be more severe, and both parameters are considered poor prognostic factors[21-25]. In our study, recovery from an attack predicted an EDSS score of 4, and in those with a polysymptomatic onset, the proportion of those with an EDSS score of 4 was also higher. In addition, in this study, it was shown that a short interval between the first two attacks predicted an EDSS score of 4. Other studies have shown that a short interval between two attacks is a risk factor for long-term disability and that an interval of 2 years is predictive of the prognosis[26,27].

Although some publications regarding the impact of gender on the prognosis of MS suggest that the male gender is among the poor prognostic factors, other publications state that the impact of gender on prognosis is not significant[28,29]. In a study that included 1,074 men and 2,025 women, it was observed that there was no difference between the genders when looking at the progressive MS phenotype[30]. In our study, there was no significant

difference in terms of gender between the group with EDSS below 4 and the group with EDSS 4 and above. In a study evaluating data from over 27,000 MS patients with a follow-up period of up to 15 years, Lublin et al. stated that persistent focal inflammatory activity in the early stages of the disease is a harbinger of long-term EDSS deterioration[31,32]. Our study supports this finding by showing that an increase in the initial EDSS score is predictive of long-term disability. In a study evaluating 186 MS patients with progression as the primary endpoint, it was shown that the rates of sphincter and pyramidal relapses, as well as early increases in EDSS scores, were significant prognostic determinants. In our study, it is not surprising that at the end of the long follow-up, there were more patients with an EDSS of over 4 among those who scored with sphincter and pyramidal FSS. Recovery from relapse is also an important parameter during MS. In one study, it was found that patients who recovered well from relapse entered the progressive and advanced stages later than those who did not recover well from relapse[33]. In our study, the likelihood of having an EDSS score of 4 or higher 20 years later was found to be significantly lower in the group that fully recovered from the relapse than in the other groups.

The strength of our study is that the patients were followed for a long time, and a comprehensive evaluation, which included FSS at the onset and at the final evaluation, was conducted. A limitation of our study is the inability to examine the impact of disease-modifying drugs on disability. Other important limitations of this study are the absence of MRI data and the absence of physical parameters other than EDSS. In addition, the fact that cognitive parameters closely related to disability could not be evaluated is another limiting factor. To the best of our knowledge, in the absence of definitive criteria and predictive biomarkers for forecasting the prognosis of MS, more studies are needed to anticipate its prognosis and to suggest appropriate follow-up and treatment approaches. It is very important to evaluate all aspects of long-term data in a chronic disease such as MS.

In conclusion, given the findings and limitations presented, it becomes imperative for subsequent research on MS to embrace a more holistic methodology. Incorporating MRI data will potentially shed light on the intricate structural changes within the CNS, deepening our understanding of its correlation with disease trajectory. Furthermore, diving deeper into cognitive parameters beyond the scope of just the EDSS can offer a more comprehensive perspective on a patient's functional status and quality of life. As our comprehension of MS evolves, it's paramount that we integrate multifaceted metrics, including cutting-edge imaging, cognitive assessments, and the role of disease-modifying drugs.

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