NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

RESEARCH ARTICLE

Arch Neuropsychiatry 2022;59:10–13
https://doi.org/10.29399/npa.25046

Determinants of Disability in Progressive Onset Multiple Sclerosis

Melih TÜTÜNCÜ[1], Mesude TÜTÜNCÜ[2], Sabahattin SAİP[1], Aksel SİVA[1]

[1]Neurology Department, Cerrahpaşa University School of Medicine, İstanbul, Turkey
[2]Bakırköy Prof. Dr. Mazhar Osman Research and Training Hospital, University of Health Sciences, İstanbul, Turkey

ABSTRACT

Introduction: To describe the clinical and socio-demographic profiles of the patients with the progressive onset Multiple Sclerosis (MS) and to explore the determinants of disability.

Method: This is a retrospective study, which was conducted in a university hospital. Patients with a progressive clinical course at onset were included in the study. In the first analysis, the clinical and demographic properties of the cohort were defined. In the second analysis the effects of age, sex, clinical activity during course, initial clinical symptoms and cerebrospinal fluid analyses on the course were evaluated.

Results: Clinical activity during the course, older age, male gender, medulla spinalis involvement at onset and detection of paraparesis at initial neurological examination was found as a poor prognostic factor.

Conclusion: This research confirms previous findings of the studies conducted in populations of Europe and America. Further studies are needed to confirm and validate these findings and to provide greater insight into the effects of ethnic or geographical differences on the course.

Keywords: Multiple sclerosis, progressive multiple sclerosis, disability

Cite this article as: Tütüncü M, Tütüncü M, Saip S, Siva A. Determinants of Disability in Progressive Onset Multiple Sclerosis. Arch Neuropsychiatry 2022;59:10–13.

INTRODUCTION

Multiple Sclerosis (MS) is a chronic demyelinating disease of the central nervous system with an unknown cause. The clinical course of MS is highly variable and mainly described by the presence of relapses and progression. According to current disease course classification, three main phases are defined: MS high-risk phase, the relapsing-remitting phase, and the progressive phase (1). The relapsing-remitting phase and progressive phase is also grouped as active or inactive according to the presence of asymptomatic magnetic resonance imaging (MRI) activity or development of new symptomatic relapses (2).

The progressive phase is mainly characterized by the gradual accumulation of disability and thought to be the key determinant of long term disability. Available immunomodulatory drugs which are commonly used in the relapsing-remitting MS have limited effects on the progressive course of the disease, therefore progressive forms have the worst prognosis (3). The progressive phase may occur from the disease onset (primary progressive phase) or may follow a period of attacks (secondary progressive phase). 85% of patients have a relapsing-remitting phase at the onset but 60-70% of these patients switch to progressive phase while 10-15% of MS patients have a progressive phase at the onset (4). If the progressive phase is observed at the onset of the disease, the diagnostic criteria are made according to the specific criteria for the primary progressive MS (PPMS) of the 2017 revised MC Donald Criteria. These criteria include one year of disability progression (determined retrospectively or prospectively) independent of relapses plus at least two of the following; one or more T2 lesions in the characteristic regions on brain MRI, two or more spinal cord MRI lesions, or the presence of cerebro spinal fluid (CSF) oligoclonal bands (2).

Highlights

- **PPMS patients had similar female/male ratios and male gender is defined as a poor prognostic factor**
- **More than half of the initial symptoms may be attributed to the involvement of the pyramidal tract.**
- **Clinically active progressive MS patients reaches severe disability milestones like EDSS 3 and 6 faster than inactive progressive MS patients.**
- **Age was found to have an effect on the course; one decade increase in age was related with faster reaching the EDSS score of 6.**

Various studies have provided information about the initial characteristics of MS patients with a relapsing-remitting course at the onset. In contrast to this, there is less information about the patients with progressive phase at the onset because of the rarity of the disease (5). Moreover, what we know about this issue is largely based on studies conducted in populations of Europe or America. This study, therefore, was designed to determine the clinical and socio-demographic profiles of the patients with the progressive onset and also to explore the effect of clinical and radiological characteristics on the course of the disease (6).

Correspondence Address: Melih Tütüncü, Neurology Department, Cerrahpaşa University School of Medicine, İstanbul, Turkey • **E-mail:** tutuncumelih@yahoo.com
Received: 23.01.2020, **Accepted:** 01.03.2020, **Available Online Date:** 09.06.2020
©Copyright 2020 by Turkish Association of Neuropsychiatry - Available online at www.noropskiyatriarsivi.com

METHOD

Ethic Statement

The medical ethical committee of Medical School of Cerrahpasa University approved the study and written informed consent was obtained from all participants.

Patient Selection

This is a retrospective study. We retrieved and reviewed all the medical records of patients admitted to the demyelinating disesases outpatient clinic at Medical School of Cerrahpasa University between 1987 and 2010. The records of patients with progressive phase at onset were included in the study. The primary progressive MS diagnosis was made according to the 2017 revised McDonald Criteria. Patients with a history of relapse onset, who not fulfilled the McDonald's criteria for PPMS, and patients with missing data were not included.

Data Collection

At each annual visit, a detailed neurological examination was done, Expanded disability status scale (EDSS) was recorded and also the imaging data were noted in patients' files as a part of routine clinical care. Demographical characteristics (i.e. date of birth, sex, history of MS in the family members, socioeconomic status, education level), clinical characteristics (i.e. symptom at onset, date of initial symptom, possible localization according to the initial symptoms, annual EDSS, clinical course), and laboratory findings (i.e. presence of oligoclonal band, Immune globulin G (IgG) index) were obtained from the patients files.

According to their clinical course, the patients were categorized as PPMS without clinical activity and PPMS with clinical activity. In this paper, these groups will be defined as active PPMS and inactive PPMS. Therefore, when we use the term activity in this paper, we will only refer to the clinical activity.

Definition of Terms

For the active PPMS group, a clinical activity was defined as the new onset of a neurological symptom consistent with MS and lasting at least 24 hours without an infection or triggering factors. In this group, the annual EDSS were analyzed during the relapse free period or three months after the relapse. The presence of type 2 or 3 oligoclonal bands in the CSF and/or IgG index higher than 0.7 were defined as positive CSF.

Two endpoints were determined to assign the clinical course according to the EDSS scores; patients who reached EDSS score 3 at any point of the follow-up and patients with EDSS 6 at any point of the follow-up.

Statistical Analysis

All analyses was performed by using SPSS software (version 20). In this study, descriptive statistics (mean, SD, and frequency) were used for the demographic and clinical characteristics. The time from the initial symptom to EDSS 3 or EDSS 6 was estimated utilizing Kaplan Meier survival analysis. Log-rank test was used to compare survival data between groups at univariate analysis. Multiple cox regression models were created to assess the independent predictive values of clinical data, demographic characteristics, and imaging data.

RESULTS

A total of 226 patients met the inclusion criteria and were included in the study. Of the 226 patients, 123 (54.1%) were male and 103 (45.9%) were female. The mean age at the onset of symptoms was 35.17 ± 9.58 years and the mean at diagnosis was 39.01 ± 9.56 years. The mean time from onset of symptoms to diagnosis was 3.48 ± 4.03 yrs. The mean follow-up period was 10.41± 6.45 years. Although 187 (83%) patients were married at the time of disease onset, no information was available about their last marital status. At the time of the first admission, 103 (46.7%) patients were unable to work and 10.5% of those had to retire due to disability. 13 patients had a family history of MS. The demographic characteristics of the study population are seen in Table 1.

Table 1. The demographic and clinical characteristics of the study population (N: 226)

Gender (Female/Male)	103/123
Age at onset of symptoms (Yrs, mean, SD)	35.17 ± 9.58
Age at diagnosis (Yrs, mean, SD)	39.01 ± 9.56
Time to diagnosis (Yrs, mean, SD)	3.48 ± 4.03
Socioeconomic status (%)	
1- Upper	10.10
2- Middle upper	25.90
3- Middle lower	55.50
4- Lower	8.30
Education Status (%)	
Literate	2.95
Primary-Middle Primary	26.60
Middle/ High school	26.03
High School.	44.30
Family members with MS (%)	5.27
Initial Complaints (%)	
Weakness	57.32
Difficulty in walking	41.46
Imbalance	24.39
Tingling and numbness	23.17
Fatigue	8.94
Sphincter and sexual dysfunction	8.13
Initial Neurological Findings (%)	
Paraparesis	27.24
Monoparesis	25.61
Ataxia	24.39
Paresthesia	22.76
Sphincter and sexual dysfunction	7.72
Possible Localization (%)	
Medulla Spinalis involvement	55.28
Brainstem ± cerebellum involvement	32.11
Cerebral hemisphere involvement	20.33
Symptom Onset (%)	
Monosymptomatic	59.70
Polysymptomatic/multifocal	27.20
Polysymptomatic/monofocal	13
Positive CSF (%)	77

MS: Multiple Sclerosis, CSF: Cerebrospinal fluid, Yrs: years, SD: Standard deviation

According to initial complaints of the patients; weakness was noted in 57.32% of the patients, difficulty in walking was noted in 41.46% of the patients, the imbalance was noted in 24.39% of the patients, tingling and numbness were noted in 23.17% of the patients. The following complaints were fatigue (8.94%) and sphincter and sexual dysfunction (8.13%) respectively.

According to the first neurological examination, paraparesis was detected in 27.24% of cases, monoparesis was detected in 25.61%, ataxia in 24.39%, paresthesia in 22.76%, sphincter and sexual dysfunction was detected in 7.72%

When the possible localization was predicted according to the initial symptoms, medulla spinalis involvement was likely in 55.28% of the patients, brainstem and/or cerebellum involvement was in 32.11%, and involvement of a cerebral hemisphere was in 20.33%. The 59.7% of patients had monosymptomatic onset whereas 27.2% of patients had polysymptomatic/multifocal onset and 13% patients had polysymptomatic/monofocal onset. Positive CSF findings were obtained in 77% of the patients.

The 84% of patients were categorized as inactive PPMS and 16% of patients were categorized as active PPMS. 223 patients reached EDSS 3 in a mean time period of 4.21 years. According to disease subtypes, the mean time to reach an EDSS score of 3 was shorter in the patients with active clinical course (3.77 vs 4.48 years, p=0,027)

It was found that 135 patients reached EDSS 6 in a mean time period of 12.87 years. When these patients were grouped according to the disease type, it was found that the active PPMS group reached in 12.19 years and inactive PPMS group reached in 13.93 years. Interestingly, it was found that 135 patients who reached EDSS 6 reached EDSS3 1.5 years earlier than the others.

The effects of age, sex, and factors on course were evaluated. Sex was found to be a significant factor on the course. Men reached EDSS 6 1.23 times faster than the women. When we categorize the age into decades, the time for each decade to reach EDSS 3 and 6 is as follows. The time to reach EDSS 3 was 5.4 years for ≤30y, 4.34 years for 30-<40y, 4.2 years for 40-<50 y and 3.4 years for ≥50 years. And the time to reach EDSS 6 was 13.76 years for ≤30y, 12.85 years for 30-<40y, 11.48 years for 40-<50 y and 8.6 years for ≥50. As the age increased one decade, reaching the EDSS 6 was accelerated 1.25 times. The younger onset patients reached EDSS 6 in a longer time but at a younger age than remaining patients.

There was no difference in terms of reaching EDSS 3 or 6 between patients with and without positive CSF. (p:0.15).) The detection of paraparesis at onset accelerates access to EDSS 3 by 1.24 times (p <0.001) Moreover, patients with paraparesis at onset reached EDSS 6 in 10.96 yrs, and those without paraparesis at onset reached in 13.55 yrs.

Medulla spinalis involvement at onset significantly reduced time to EDSS 3 by 1.46 times and time to EDSS 6 1.66 times (p = 0.001). The presence of pyramidal involvement at onset was also found to have an effect on the course. (p:0.015). Symptom onset including monosymptomatic, polysymptomatic/polyfocal, polysymptomatic/monofocal found to have no effect on the course. (p:0.068)

DISCUSSION

The majority of patients with MS have a relapsing-remitting phase at onset and more than half of them show a transition to progressive phase. Even if beginning with the progressive phase is a rarer entity,it is a major problem because both physicians and the patients face a more reluctant clinical course with less response to the treatment (7). Despite the similar course after the onset of the progressive phase, the initial characteristics of the populations seem to be different between the relapsing onset and progressive onset groups (8). Moreover, the factors affecting the progressive course are not well documented in the literature (9).

In our study, the percentages of females to males was almost equal. It is known that female dominance is observed in RRMS, while PPMS patients had almost equal predominance in female/male ratios (10).

The mean age of the first symptom was 35 years. Previous studies have demonstrated that progressive course at onset started much later than the relapsing-remitting course at the onset. The mean age at first symptom was found to be 37.3 in the study of Confavreux et al., 38.5 in the study of Cotrell et al. 38,5 in the study of Ebers et al. and 41.2 in the study of Andersson et al. (11-14). In our study, the patients were diagnosed on average 3,5 years after the first symptom. Although this time was shorter than that reported for the same population in the literature, it is still longer than the time for diagnosis in relapsing-remitting MS patients. In our opinion, the reason for being shorter than the literature is that the patients are allowed to directly admit to the neurologists in our country. So the patients are able to directly access a neurologist expert in MS. The reason for being longer than the RRMS group may be explained by the wider differential diagnosis list and presence of higher number of accompanying diseases in PPMS group because of the higher age of this population.

Based on the initial symptoms of our cohort, we found that more than half of the initial symptoms may be attributed to the involvement of pyramidal tract. The following most common involvements were brainstem cerebellar and sensory system respectively. This result is in line with the study of Abdelhak et al, which reported pyramidal findings as the most common symptom at onset (15).

Similar to the literature, in our study the most common localization for the initial symptoms was medulla spinalis involvement which has been described as a poor prognostic factor in many previous studies. In our study, patients with spinal cord involvement at onset also reached EDSS 6 and EDSS 3 faster than the others.

In our cohort more than half of the patients reached EDSS 6 within a period of 12 years. According to the study of Ebers, this time period was reported as 8 years. It is difficult to explain these differences but ethnicity or geographical differences may have an impact on the different results (11).

With respect to the second study question, we found clinical activity during the course as a poor diagnostic factor (16). The view that clinically active progressive MS patients reaches severe disability milestones like EDSS 3 and 6 faster than inactive progressive MS patients. Soldan et al also confirmed that superimposed relapses after the progressive phase increased the disabiltiy acumulation (17).

In accordance with the literature, age was found to have an effect on the course. Initially, as the age increased one decade, reaching the EDSS 6 time was faster (18). In addition to our findings Koch et alalso claimed that eventhough the progressive phase is slower in the younger adult patients, they reached EDSS 6 at earliear age than patients with onset at older ages (19). So, young age at disease onset should not be considered a predictive of the better prognosis (20).

Another important finding of this study is defining the male gender as a poor prognostic factor. Previous research findings on poor prognostic factors in PPMS are conflicting. According to some studies, the male gender is represented as a poor prognostic factor (21). Others reported no significant difference in terms of genders.

This study was unable to demonstrate the effect of number of symptoms at onset on the course. No significant differences were found between patients with monosymptomatic onset, polysymptomatic/multifocal onset, and polysymptomatic/monofocal onset. However, polysymptomatic patients tended to reach EDSS 6 faster than the monosymptomatic ones. Initial involvement of two or more systems is accepted as a poor prognostic factor. Moreover, according to Cottrell et al. (14) and Ebers et al. patients with polysymptomatic clinical findings at onset reached EDSS 6 earlier (11).

There was no difference in terms of reaching EDSS 3 or 6 between patients with and without positive CSF. Abdelhak et al. (15) found no correlation between IgG-production and clinical parameters. Our study supported this view.

A recent study has revealed that those patients who reached EDSS 6 reached EDSS 3 earlier than the others. This information may have a clinical impact and may be useful in practice. Those who reached EDSS 3 in 4 years should be followed more carefully for progression and treatment strategies should be adjusted carefully

Several limitations to this study need to be acknowledged. Firstly these findings are limited by the use of retrospective design. The most

important limitation is the lack of imaging data, which was not evaluated due to the unstandardized radiological protocols. However, a key power of the present study was the very high number of patients and exclusion of patients with missing data. Further studies are needed to confirm to validate these findings, and to provide greater insights into the effects of ethnic or geographical differences.

CONCLUSION

In this paper, we aimed to describe the clinical and socio-demographic profiles of the patients with the progressive onset and also to explore the determinants of disability on progression on the course of the disease. The initial socio-demographic and characteristics of the cohort were consisted with the previous studies. Clinical activity during the course, age, male gender, medulla spinalis involvement at onset and detection of paraparesis at initial neurological examination were found as poor prognostic factors. The most practical benefit of our study is to emphasize the issues to be considered in the follow-up of Turkish MS patients.

Ethics Committee Approval: The Medical Ethical Committee of Medical School of Cerrahpaşa University approved the study (18.11.2008/34275).

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - AS, SS, MT; Design - AS, SS, MT; Supervision - AS, SS, MT; Resource - (-); Materials - (-); Data Collection and/ or Processing - AS, SS, MT; Analysis and/or Interpretation - AS, SS, MT; Literature Search - MT; Writing - MsdT, MT, AS; Critical Reviews - MT.

Conflicts of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: No funding bodies were involved in the design, collection, analysis, interpretation, or writing of the manuscript.

REFERENCES

1. Kantarci OH. Phases and phenotypes of multiple sclerosis. Continuum: Lifelong Learn Neurol 2019;25:636–654. [Crossref]
2. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162–173. [Crossref]
3. Montalban X, Sastre-Garriga J, Filippi M, Khaleeli Z, Téllez N, Vellinga M, et al. Primary progressive multiple sclerosis diagnostic criteria: A reappraisal. Mult Scler J 2009;15:1459–1465. [Crossref]
4. Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. N Engl J Med 2000;343:1430–1438. [Crossref]
5. Faissner S, Gold R. Progressive multiple sclerosis: latest therapeutic developments and future directions. Ther Adv Neurol Disord 2019;12:175628641987832. [Crossref]
6. Bahar Kaymakamzade, Ahmet Kasım Kiliç, Aslı Tuncer Kurne, Rana Karabudak Progressive Onset Multiple Sclerosis: Demographic, Clinical and Laboratory Characteristics of Patients With and Without Relapses in the Course Noro Psikiyatr Ars. 2019 Mar; 56(1): 23–26 [Crossref]
7. Ontaneda D, Thompson AJ, Fox RJ, Cohen JA. Progressive multiple sclerosis: prospects for disease therapy, repair, and restoration of function. Lancet 2017;389:1357–1366. [Crossref]
8. Tutuncu M, Tang J, Zeid NA, Kale N, Crusan DJ, Atkinson EJ, et al. Onset of progressive phase is an age-dependent clinical milestone in multiple sclerosis. Mult Scler J 2013;19:188–198. [Crossref]
9. Ferreira Vasconcelos CC, Santos Thuler LC, Cruz Dos Santos GA, Alvarenga Marcos P, Alvarenga Marina P, Camargo SMGG, et al. Differences in the progression of primary progressive multiple sclerosis in Brazilians of African descent versus white Brazilian patients. Mult Scler J 2010;16:597–603. [Crossref]
10. Weinshenker BG. The natural history of multiple sclerosis. Neurol Clin 1995;13:119–146. [Crossref]
11. Ebers GC. Natural history of primary progressive multiple sclerosis. Mult Scler J 2004;10:S8–S15. [Crossref]
12. Confavreux C, Vukusic S. Natural history of multiple sclerosis: A unifying concept. Brain 2006;129:606–616. [Crossref]
13. Weinshenker BG, Bass B, Rice GP, Noseworthy J, Carriere W, Baskerville J, et al. The natural history of multiple sclerosis: A geographically based study: 2 PREDICTIVE value OF the EARLY clinical course. Brain 1989;112:1419–1428. [Crossref]
14. Cottrell DA, Kremenchutzky M, Rice GPA, Koopman WJ, Hader W, Baskerville J, et al. The natural history of multiple sclerosis: A geographically based study. 5. The clinical features and natural history of primary progressive multiple sclerosis. Brain 1999;122:625–639. [Crossref]
15. Abdelhak A, Hottenrott T, Mayer C, Hintereder G, Zettl UK, Stich O, et al. CSF profile in primary progressive multiple sclerosis: Re-exploring the basics. PLoS One 2017;12:e0182647. [Crossref]
16. Marrodan M, Bensi C, Pappolla A, Rojas JI, Gaitán MI, Ysrraelit LMC, Negrotto L, et al. Disease activity impacts disability progression in primary progressive multiple sclerosis. Mult Scler Relat Disord 2020;39:101892. [Crossref]
17. Soldán MMP, Novotna M, Zeid NA, Kale N, Tutuncu M, Crusan DJ, et al. Relapses and disability accumulation in progressive multiple sclerosis. Neurology 2015;84:81–88. [Crossref]
18. Koch M, Kingwell E, Rieckmann P, Tremlett H. The natural history of primary progressive multiple sclerosis. Neurology 2009;73:1996–2002. [Crossref]
19. Scalfari A, Neuhaus A, Daumer M, Ebers GC, Muraro PA. Age and disability accumulation in multiple sclerosis. Neurology 2011;77:1246–1252. [Crossref]
20. Vukusic S, Confavreux C. Natural history of multiple sclerosis: Risk factors and prognostic indicators. Curr Opin Neurol 2007;20:269–274. [Crossref]
21. Kantarci O, Siva A, Eraksoy M, Karabudak R, Sutlas N, Agaoglu J, Turan F, Ozmenoglu M, Togrul E, Demirkiran M; The Turkish Multiple Sclerosis Study Group (TUMSSG). Survival and predictors of disability in Turkish MS patients. Neurology 1998;51:765–772. [Crossref]