



Determining the Prognostic Characteristics of People with Multiple Sclerosis with Bowel and Bladder Dysfunction as the Initial Presentation: A Cohort Study

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Abstract

Objective: This study's first aim is to assess the prognostic characteristics of people with multiple sclerosis (pwMS) who initially had bowel-bladder dysfunction and to present their relationship with the transition to secondary progressive MS (SPMS). The second aim of the study is to show the frequency of relapses that affect bowel-bladder functions as one of the first reasons for hospital admission among pwMS. The third aim is to present the frequency of relapses affecting bowel-bladder functions in pwMS throughout the disease process.

Materials and Methods: Study data of this retrospective cohort study were obtained from longitudinal follow-up data of pwMS who were followed up since 1996 in an Dokuz Eylul University Hospital MS Unit. A total of 3448 pwMS were assessed for eligibility, and those who met the eligibility criteria were included in the study. Included pwMS were assessed for relapse affecting bowel and bladder functions and transition from the Relapsing-Remitting MS (RRMS) course to the SPMS course.

Results: A total of 459 (13.3%) pwMS experienced at least one relapse affecting their bowel-bladder functions at any point in their disease process, and these bowel-bladder functions were affected in 129 of 3,448 (3.7%) patients during their first relapse. Affected bowel and bladder functions during the first relapse were ineffective in predicting the transition to the SPMS course ($p>0.05$). The initial Expanded Disability Status Scale score ($p=0.001$), age of disease onset ($p<0.001$), age at the start of progression ($p=0.035$), and spinal cord involvement in the functional systems affected at first admission ($p=0.013$) effectively predicted the transition to the SPMS course.

Conclusion: Bowel and bladder dysfunction is a common but poorly-addressed clinical presentation. It is observed even at the onset of the disease. Although the affected bowel and bladder function at first relapse is not effective in predicting the transition from the RRMS course to the SPMS course, the onset of the disease at a young age, severe disability at the beginning, and the spinal origin of the first symptom are promising predictors. Bowel and bladder dysfunction and factors predicting the transition to the SPMS course should be addressed in many ways.

Keywords: Multiple sclerosis, bowel, bladder, relapse, prognostic, progression

Introduction

Multiple sclerosis (MS) is a chronic, neurodegenerative disease characterized by its autoimmune origin and transected inflammatory demyelination affecting the central nervous system (CNS) (1). Around 2.8 million people worldwide and 58,401 people in our country live with MS (2,3). Although the exact cause of MS is still unknown, it is thought that various

genetic, environmental, and immunological factors play a role in the etiology of this complex disease (4).

The clinical course of MS is defined under three main headings: clinically isolated syndrome (CIS), relapsing MS, and progressive MS (5). CIS is the first neurological picture in which inflammation and demyelination are observed in the CNS. CIS is used to describe the first clinical event of acute or subacute onset, which peaks quickly, in which a patient has symptoms and signs

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Received: 08.08.2022 **Accepted:** 02.12.2022

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suggestive of an inflammatory demyelinating disorder of the CNS (6). Relapsing-Remitting MS (RRMS) is the most common course of MS. It progresses with recurrent relapses of varying severity and frequency (relapse, exacerbation), followed by a period of complete or nearly-complete recovery (remission) (5). Studies have shown that most untreated RRMS patients eventually progress to secondary progressive MS (SPMS) (7). It has been reported that 62% of RRMS patients switch to the SPMS course by the age of 75 years (8). SPMS is a course of MS in which exacerbations are seen in addition to progressive clinical worsening (5). The mean age of onset of progression has been reported as 45 years (8). Advancing age and the longer duration of MS are the most important risk factors for progressive disease. Other clinical risk factors for the early onset of SPMS include incomplete recovery from the first MS relapse, multifocal clinical manifestations of relapses, and the presence of brainstem and/or infratentorial lesions (9). Oh et al. (7) identified early symptom recognition as a key step in the transition from the RRMS course to the SPMS course.

Among the most important signs and symptoms of MS are fatigue, impaired balance and decreased mobility, neuropathic pain, bowel and bladder dysfunction, cognitive impairment, and mood disorders (4). Bowel and bladder dysfunctions are common in MS, affecting the bowel in 39-73% of the population and urinary function in more than 80% of the population (10,11). Nortvedt et al. (12) reported that bowel and bladder involvement is present at an early stage of MS (within 2-5 years after diagnosis). Given that these symptoms worsen with disease progression in MS and those treatments and preventive strategies are available, they recommended focusing on these aspects of MS in patient interviews from the early stages of the disease (12).

This study has three aims; the first is to assess the prognostic characteristic of people with MS (pwMS) who initially had bowel-bladder dysfunction and to present their relationship with the transition from the RRMS course to the SPMS course. The second aim of this study is to determine the frequency of relapses that affect bowel-bladder functions as one of the first reasons for admission among pwMS. The third aim of this study is to determine the frequency of relapses affecting bowel-bladder functions among pwMS throughout the disease process.

Materials and Methods

Study Design

This is a retrospective cohort study. Ethical approval was obtained from the Non-Invasive Clinical Research Ethics Board of Dokuz Eylul University (decision no: 2022/31-04, date: 28.09.2022). The strengthening the reporting of observational

studies in epidemiology statement was followed for this retrospective cohort study (13).

Participants and Procedures

Data collection was done in July 2022. Study data were obtained from longitudinal follow-up data of pwMS since 1996 in the MS Unit of the Dokuz Eylul University Hospital Neurology Department. A total of 3,448 pwMS followed in our MS unit were assessed for eligibility, and those who met the eligibility criteria were included in the study. Inclusion criteria were: (i) being over the age of 18 years, (ii) being definitively diagnosed with MS per the Poser or the McDonald diagnostic criteria (14-18). We excluded pwMS with missing data from the study. For the first aim, the whole cohort was screened, and people with the SPMS course were included in the study. For the second and third aims, the whole cohort was screened for relapse affecting bowel and bladder functions, and those identified were included. The first relapse was defined as an episode of worsening reported at disease onset, lasting at least 24 hours, and presenting with one or more clinical signs in the absence of fever or infection, without any clinical features of encephalopathy. A standardized form was applied for data records.

Outcome Measures

Demographic and Clinical Measurement

Age, sex, MS course, disease duration, first and last Expanded Disability Status Scale (EDSS) (19) scores, first MS treatments, age at the start of disease progression, age at the onset of the disease, disease duration from the RRMS course to the SPMS course, functional systems affected at first admission (by the first clinical event), functional systems involved during the first relapse, and medical history were obtained from the related medical records.

EDSS

It is the most commonly used scale to assess the disability of pwMS, and it was developed by Kurtzke (19,20). Scoring based on neurological examination findings takes a value between 0-10. Normal neurological findings are represented by 0 and death due to MS is represented by 10. In this scale, in which pyramidal, cerebral, cerebellar, visual, sensory, brainstem, bladder, and bowel functions are scored, the best performance is evaluated without the patient making any special effort. Scores of 1-4.5 indicate full ambulation, scores of 5-6.5 indicate ambulation with assistance, and scores ≥ 7 indicate the need for a wheelchair for mobilization. EDSS scoring of the patients was done by a specialist neurologist.

Statistical Analysis

The Kolmogorov-Smirnov test and histograms were used to assess the normal distribution of data. Descriptive analyses were presented using the mean and standard deviation for

continuous variables and frequencies and percentages for categorical variables. Linear logistic regression models were structured to understand the factors affecting the duration transition from the RRMS course to the SPMS course. The first and last EDSS scores, age at the start of disease progression, age at the onset of the disease, sex, functional systems affected at first admission, relapse involving bowel and bladder functions during the first admission, and first MS treatment were included in the model. The threshold for statistical significance was set at $p < 0.05$. Data were analyzed using IBM SPSS (Version 25.0. Armonk, NY: IBM Corp).

Results

In this study, 3,448 pwMS followed up at the MS Unit of Dokuz Eylul University were screened in terms of having the SPMS course and having a relapse that affects their bowel-bladder functions. It was determined that 459 (13.3%) pwMS experienced at least one relapse involving their bowel-bladder functions at any point in their disease course and that bowel-bladder functions were affected in 129 (3.7%) of these people during their first relapse. As a result of the screening, it was determined that 358 pwMS had the SPMS course, and 17 of these individuals had their bowel-bladder function affected during their first relapse. Twelve participants were excluded due to missing data and could not be included in the analysis. (Figure 1). Demographic and clinical characteristics of pwMS included in the study are presented in Table 1.

The linear logistic regression model is presented in Table 2. The first EDSS score and the age at the onset of the disease were found to have a negative correlation with the duration of the transition from the RRMS course to the SPMS course (respectively, $p = 0.001$; $p < 0.001$). Moreover, while the increase in the age at the start of disease progression increases the duration of the transition from the RRMS course to the SPMS course ($p = 0.035$), spinal cord involvement among the functional systems affected during the first admission decreases this duration ($p = 0.013$).

Discussion

The predictors of SPMS remain uncertain and heterogeneous. In addition, there are no clear clinical, imaging, immunological, or pathological criteria to define the transition to the SPMS course (5). Although the risk of conversion to SPMS is challenging to determine, older age, longer disease duration, and cumulative CNS lesions are the most significant clinical risk factors (9). Information on potential biomarkers of progression is promising but limited (21). The detection of transition to the SPMS course is a complex and challenging process for patients, caregivers, and healthcare professionals, and its detection is important for clinical care (7). Determining the predictors of the transition to the SPMS course is crucial. Therefore, this study aimed to evaluate the prognostic features of pwMS who initially had bowel and bladder dysfunction and their relationship with the transition to the SPMS course. We identified the young age of disease onset,

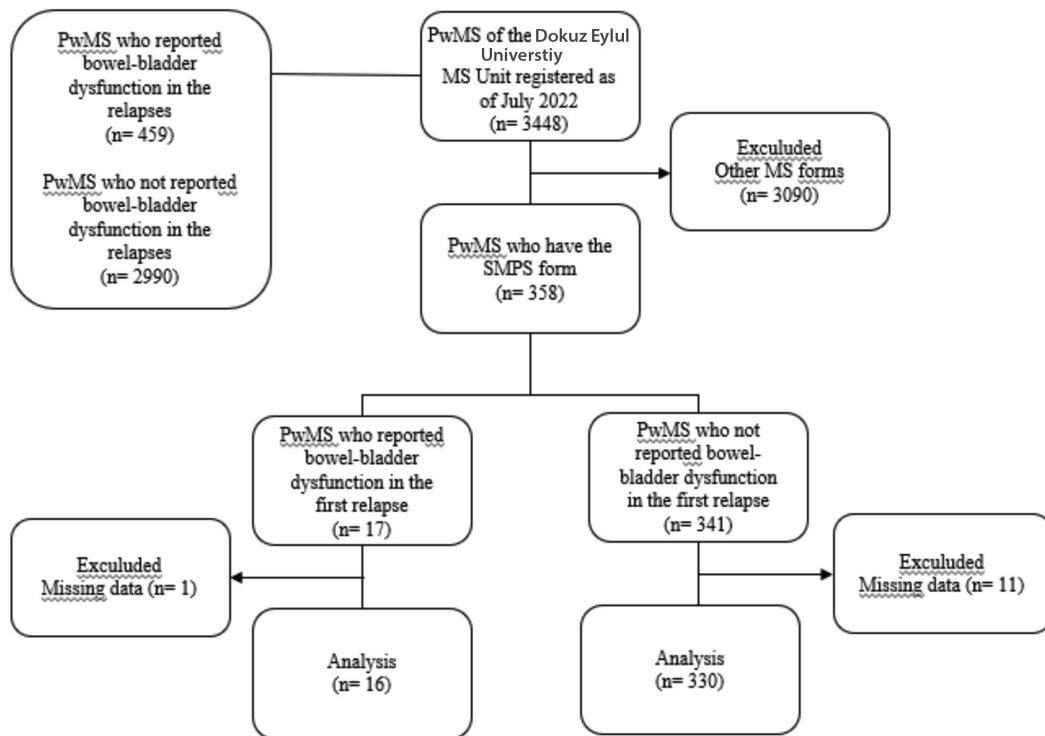


Figure 1. Flow chart
MS: Multiple sclerosis, PwMS: People with MS

severe disability at the beginning, and the spinal origin of the first symptom as effective predictors of the transition time from the RRMS course to the SPMS course. However, sex, first MS treatment, and bowel and bladder function involved in the first relapse were ineffective predictors. The other aims of this study were to demonstrate that the frequency of relapses affecting bowel and bladder function throughout the disease process was one of the first reasons for referral among pwMS. Relapse involving bowel and bladder functions was identified as one of the first reasons for admission in 3.7% of pwMS and at any time point in 13.3% of pwMS.

Bowel (39-73%) and bladder (>80%) functions are frequently affected in pwMS (10,11). However, in this study, we found that bowel and bladder functions were involved in the first relapse (3.7%) or subsequent relapses (13.3%) of a small number of patients. The low frequency of relapses affecting bowel and bladder functions suggests that dysfunctions in these systems occur due to progression and was independent of relapses. Although the first relapse involving bowel and bladder functions fails to predict the transition to the SPMS course, the

| Variables | mean (SD)/n (%) |
|---|-----------------|
| First EDSS score | 4.9 (1.9) |
| Last EDSS score | 6.3 (1.2) |
| Age of start of progression | 42.7 (10.6) |
| Disease onset age | 30.3 (9.9) |
| Transition time to SPMS | 14.7 (49) |
| Sex | |
| Female | 225 (65%) |
| Male | 121 (35%) |
| Functional systems affected at first admission-supratentorial | |
| Yes | 99 (28.6%) |
| Functional systems affected at first admission-optic pathways | |
| Yes | 71 (20.5%) |
| Functional systems affected at first admission-brainstem and cerebellum | |
| Yes | 124 (35.8%) |
| No | |
| Functional systems affected at first admission-spinal cord | |
| Yes | 139 (40.2%) |
| Relapse affecting bowel and bladder functions in the first admission | |
| Yes | 16 (4.6%) |
| First MS treatment | |
| None | 69 (19.9%) |
| First line treatments | 277 (80.1%) |

EDSS: Expanded Disability Status Scale, SD: Standard deviation, SPMS: Secondary progressive multiple sclerosis, pwMS: People with MS

involvement in these functions may suggest the transition to the SPMS course. This should be taken into account in the clinic. Future studies focused on this point will illuminate the situation.

Similar to our results, it has been reported in the literature that the onset of the disease at a young age and the presence of an initial severe disability may increase the risk of developing the SPMS course. It has been stated that this can be explained by the fact that the inflammation or CNS destruction accumulated in the early period may lead to an irreversible point when it reaches a certain level (9).

Disease-modifying drugs (DMDs) used in MS are associated with a slight delay in conversion to SPMS by preventing the additional disability burden due to relapses; however, they do not seem very effective in delaying the transition to SPMS course (8,9). Similarly, in this study, we found that any DMD used

Table 2. Risk factors on the duration transition from the RRMS course to the SPMS course

| Risk factors | OR | 95% CI | p-value |
|---|--------|-------------------|------------------|
| First EDSS score | -3.215 | (-1.086)-(-0.262) | 0.001 |
| Last EDSS score | 0.293 | -0.598-0.807 | 0.770 |
| Age of start of progression | 2.119 | 0.001-0.032 | 0.035 |
| Disease onset age | -5.478 | (-0.294)-(-0.139) | <0.001 |
| Sex | | | |
| Female (references) | | | |
| Male | -0.927 | -2.352-0.845 | 0.355 |
| Functional systems affected at first admission-supratentorial | | | |
| Yes (references) | | | |
| No | 1.129 | -0.777-2.870 | 0.260 |
| Functional systems affected at first admission-optic pathways | | | |
| Yes (references) | | | |
| No | 0.560 | -1.522-2.732 | 0.576 |
| Functional systems affected at first admission-brainstem and cerebellum | | | |
| Yes (references) | | | |
| No | 1.714 | -0.230-3.344 | 0.088 |
| Functional systems affected at first admission-spinal cord | | | |
| Yes (references) | | | |
| No | 2.498 | 0.521-4.381 | 0.013 |
| Relapse affecting bowel and bladder functions in the first admission | | | |
| Yes (references) | | | |
| No | -0.310 | -4.292-3.125 | 0.757 |
| First MS treatment | | | |
| None (references) | | | |
| First line treatments | 0.412 | -1.524-2.330 | 0.681 |

Significant p-values are presented in bold.

EDSS: Expanded Disability Status Scale, CI: Confidence interval, OR: Odds ratio

at the onset of the disease did not affect the transition time to the SPMS course. In addition, we found that the male sex was not an additional risk factor for the transition to the SPMS course, a finding that aligns with those of Tutuncu et al. (8).

Sexual dysfunction is also a common and very stressful problem in MS. The prevalence of sexual dysfunction among pwMS is higher than that in the general population and among people with other neurological diseases (22,23). In addition, Nortvedt et al. (12) reported that sexual dysfunction, such as bladder and bowel dysfunction, was present within 2-5 years after the diagnosis of MS. Drulovic et al. (24) emphasized that although the importance of sexual function problems is known, it has not been adequately addressed, and more focus should be placed on this aspect of the disease during follow-up. Since bowel and bladder function is a component of EDSS and their bowel and bladder dysfunctions are recorded in the relapse, they are relatively easier symptoms to follow up than sexual dysfunction. We found that we could not adequately address sexual dysfunction during our study period. We recommend that sexual dysfunction be handled in detail and followed up in clinical practice from the moment of the initial diagnosis. This issue could be investigated in future studies.

Study Limitations

Our study has some strengths and limitations. The main strength of this study is that it is a cohort study. Data were obtained from the longitudinal follow-up of a large cohort of patients. In addition, these data were collected in a standardized single center. The major limitation of this study is that a few patients could not be included in the study due to missing data. Another rule is that current bowel and bladder function conditions are not presented. Considering these limitations, we think that studies on this topic that consider different functions, such as sexual function, will contribute significantly to the literature in the future.

Conclusion

We found that the onset of the disease at a young age, severe disability at the beginning, and the spinal origin of the first symptom were effective determinants of the transition time from the RRMS course to the SPMS course. However, sex, initial MS treatment, and affected bowel and bladder functions at the first relapse were ineffective predictors of the transition to the SPMS course. Bowel and bladder dysfunction is a common condition that is often overlooked but is also indicated at the onset of the disease.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Non-Invasive Clinical Research Ethics Board of Dokuz Eylul University (decision no: 2022/31-04, date: 28.09.2022).

Informed Consent: This is a retrospective cohort study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.K., Concept: I.Y., Design: I.Y., A.T.O., Data Collection or Processing: I.Y., E.K., A.T.O., Analysis or Interpretation: I.Y., A.T.O., Literature Search: I.Y., E.K., Writing: I.Y., A.T.O.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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