Prevalence and prognostic value of prodromal symptoms in relapsing-remitting multiple sclerosis

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ABSTRACT

Introduction. Several studies have suggested the possibility that disease prodromes might occur months or even years before a multiple sclerosis diagnosis.

Objectives. To describe the profile of prodromal symptoms and the possible relationship between the occurrence of individual symptoms and clinical course characteristics in patients with relapsing-remitting multiple sclerosis (RRMS), and to assess their role as predictors of further disease course.

Material and methods. The cohort included 564 patients with RRMS. Patients were stratified based on their current EDSS score, and the annual EDSS growth rate was calculated. Logistic Regression Analysis was used to study the relationship between prodromal symptoms and disease progression.

Results. The most commonly reported prodromal symptom was fatigue (42%). The following symptoms were significantly more common in women than in men: headache (39.7% *vs.* 26.5%, $p < 0.05$), excessive sleepiness (19.1% *vs.* 11.1%, $p < 0.05$) and constipation (18.0% *vs.* 11.1%, $p < 0.05$).

Prodromal urinary and cognitive disturbances, fatigue and pain complaints were significantly more common in patients with the highest annual EDSS increase ($p < 0.05$).

Multivariate analysis revealed some potential predictors of long-term disability progression: hesitancy in starting urination predicted EDSS increase by 0.6 point ($p < 0.05$), while deterioration in everyday functioning because of cognitive disturbances, and pain complaints, were associated with an EDSS increase of 0.5 ($p < 0.05$), and 0.4 ($p < 0.05$), respectively.

Conclusions. Prodromal pain, urinary and cognitive complaints (especially when these lead to deterioration of everyday functioning) were associated with a higher EDSS increase rate, and may thus be regarded as possible predictors of worse clinical outcomes in RRMS patients.

Key words: multiple sclerosis, prodromes, disease predictors, RIS, preclinical phase

(*Neurol Neurochir Pol 2023; 57 (3): 289–296*)

Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of inflammatory and neurodegenerative aetiology, which mainly affects young adults [1]. Currently, MS diagnosis can only be made at the onset of clinical symptoms typical for MS, when the patient meets the criteria for dissemination in time and space [2]. However, it is vital to diagnose the disease at a very early stage, since starting treatment without delay allows patients to achieve better outcomes [3–6].

Radiologically isolated syndrome (RIS), first described by Okuda in 2009 [7], is a condition wherein the patient has brain

magnetic resonance imaging (MRI) abnormalities suggestive of MS, but with no apparent signs or symptoms of the disease. Approximately 50% of subjects with RIS go on to develop MS within 10 years [8]. Therefore, describing RIS was one of the first arguments to suggest that there was a preclinical phase of MS. If such a phase does in fact exist, then it would be extremely important to be able to identify patients who are still in this very phase, possibly by careful screening for disease prodromes.

A prodrome is defined as a sign or symptom preceding the classical course of a specific disease [9]. One of the best examples of diseases with an evident prodromal phase is Parkinson's disease [10] but it is also features in Alzheimer's disease, depression, rheumatoid arthritis, and Crohn's disease [1, 11, 12].

Clinical rationale for study

Several studies have suggested the possibility that disease prodromes might occur even 5–10 years before MS diagnosis. Such a possibility is implied by a higher number of hospitalisations and visits to psychiatrists and dermatologists, and more frequent recognition of sleep and bowel disturbances, fatigue, pain, migraines or cognitive impairment [1, 13–18].

In this study we aimed to: (I) analyse the profile of prodromal symptoms based on information obtained directly from MS patients; (II) compare this profile to previously published data obtained from healthcare and insurers' registries; (III) analyse the profile of patient-reported prodromal symptoms with regards to gender and age at disease onset; and (IV) finally to assess the possible role of different prodromal symptoms as predictors of the subsequent disease course.

Material and methods

Participants were recruited from the single MS centre at the Department of Neurology, Poznan University of Medical Sciences, Poznan, Poland. Adult patients with relapsing remitting MS (RRMS) were enrolled to take part in the study between November 2021 and April 2022. The data was obtained by neurologists using an original questionnaire called 'ProdroMuS' (see Appendix 1) during the patients' visits to the clinic. In the questionnaire, patients were asked about any symptoms that preceded the onset of their first relapse for up to five years, but were not typical MS relapses. In the questionnaire, we listed the prodromal symptoms mentioned in previously published studies. Additionally, we asked patients about their subjective feelings about their cognitive functions during the time preceding their first MS relapse. The patients were asked to mark the time frame in which they developed symptoms. When asking about fatigue and upper respiratory tract infections, we asked about the increased number of symptoms or severity in comparison with their peers.

Patients were also assessed by their treating neurologists with Expanded Disability Status Scale (EDSS) at the time of enrollment into the study. Clinical data concerning the onset of first MS symptoms, MS diagnosis and all annual EDSS assessments since treatment onset were obtained from patient records, and verified with the data entered by treating neurologists to the central nationwide register under the Polish public healthcare system (the National Health Fund electronic database).

Patients who did not consent to participate in the study were excluded.

This study was approved by the Internal Review Board at Poznan University of Medical Sciences, Poznan, Poland.

Demographics and clinical characteristic of study group

We enrolled 564 patients with relapsing-remitting MS, consisting of 383 women (67.9%) and 181 men (32.1%). The study flow diagram is presented in Figure 1. The mean age (years) was 39.3 ± 10.4; median 39 (range 19–71); IQR 14.8. The mean EDSS at enrollment was 2.0 ± 2.8, median 2.0 (range 0–6.5), IQR 1.5.

The mean age at MS diagnosis (years) was 30.9 ± 9.2; median 29.5 (range 13–66); IQR 12.8.

The mean time from experiencing first MS symptoms to enrollment (years) was 9.9 ± 6.3, median 9.0 (range 0–39), IQR 9. The majority of patients were treated with disease-modifying therapies (N = 562; 99.6%), including 70 (12.4%) on high-efficacy therapies (natalizumab, alemtuzumab, ocrelizumab, cladribine, fingolimod) and 494 (87.6%) on platform therapies (injectables) i.e. teriflunomide or dimethyl fumarate. The relatively small percentage of patients treated with high-efficacy therapies in our centre is a result of the provisions of the National Health Fund that require meeting the appropriate (relatively high) criteria for receiving high-efficacy therapies [19].

Statistical analysis

The results were reported as counts (percentage) for the categorical variables, mean with standard deviation, and median with quartiles for the continuous variables. As appropriate, categorical variables were compared using Chi-square tests (with Yates correction for 2×2 tables) or Fisher's exact tests.

Continuous variables were compared between two groups using a Mann–Whitney test. The comparison of variables in three or more groups was performed using a Kruskal-Wallis test. After detecting statistically significant differences, *post-hoc* analysis with Dunn's test was conducted to determine which groups differed from each other.

A multiple linear regression model was used to investigate the combined effect of all prodrome variables on EDSS value.

A p-value of 0.05 or lower was considered statistically significant. All statistical analyses were performed using R software [R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/].

Results

Frequencies and timing of prodromal symptoms prior to first relapse

Four hundred and sixty-five out of 564 patients (82.4%) had at least one prodromal symptom, and 99 patients (17.6%) had no such symptoms. The mean number of prodromal symptoms per patient was 4.8 ± 4.4, median 4 (IQR = 7), and ranged from 0 to 22.

The period in which patients noticed prodromes was mostly reported as being difficult to assess (N = 142, 25.2%), followed by 2–3 years (N = 120, 21.3%), then within one year (N = 102, 18.1%), then within 4–5 years (N = 99, 17.6%) before the onset of classical MS symptoms (Tab. 1).

Two hundred and thirty-seven patients (42%) experienced fatigue and this was the most commonly reported prodrome. As the definition of fatigue can be vague, we asked specifically about fatigue which hindered everyday functioning and was more pronounced than in their peers.

A total of 65 (11.5%) patients observed new dermatological diseases, such as atopic dermatitis, psoriasis, rash, tinea versicolor or photodermatosis, in the years preceding MS onset. In addition to the symptoms mentioned in the questionnaire, we also asked an open question about any bothersome symptoms occurring in the years preceding the MS onset. Patients typically reported: paresthesia (N = 62, 11%), non-specific visual disturbances (N = 27, 4.7%), or Lhermitte sign (N = 12, 2.1%). Fewer than five patients mentioned other symptoms, such as syncope, Bell's palsy, hearing disturbances, sexual dysfunction, excessive sweating, tinnitus, stammering, or involuntary movements of the upper limbs.

Differences between women and men

A total of 318 women (83%) and 147 men (81.2%) reported prodromal symptoms, which was not significantly different (p = 0.682) However, women reported more symptoms than men (mean 5.1 *vs.* 4.3, p < 0.05).

The following symptoms were significantly more common in women than in men: headache (39.7% *vs.* 26.5%, p < 0.05), excessive sleepiness (19.1% *vs.* 11.1%, p < 0.05), and constipation (18% *vs.* 11.1%, p < 0.05). Gender-related differences were not statistically significant for other symptoms (see Tab. 2).

Prodromal symptoms and age at disease onset

We divided patients into five groups depending on their age when experiencing their first MS symptoms. The largest group constituted patients with a typical age at MS onset, namely 21 to 30 years of age (N = 231, 41%). The frequency of prodromal symptoms was not significantly different between the groups. However, the mean number of the reported prodromal symptoms was higher in the groups of middle age at disease onset (mean 5.3 and 6.1 for 31–40-years and 41–50-years onset respectively) compared to younger patients (mean 4.3 for onset ≤ 20 years and 4.2 for onset at 21–30 years) and to the late onset group (mean 4.8 for disease onset > 50 years), p < 0.05.

Table 1. Prodromal symptoms reported by RRMS cohort in 'ProdroMuS' questionnaire

Symptom	N	%
Fatigue	237	42%
Headache	200	35.5%
Vertigo	173	30.7%
Sleep disturbances	165	29.3%
Bowel disturbances	146	25.9%
Cognitive difficulties at school/work	130	23.1%
Concentration disturbances	123	21.8%
Limb tremor	119	21.1%
Dizziness	112	19.9%
Urinary disturbances	104	18.4%
Spinning	101	17.9%
Excessive sleepiness	93	16.5%
Increased frequency of URTIs	89	15.8%
Constipation	89	15.8%
Insomnia	83	14.7%
Deterioration in everyday functioning due to cognitive difficulties	83	14.7%
Anxiety and depressive disorders	82	14.5%
Dermatological disorders	65	11.5%
Abdominal pain	61	10.8%
Urgent need to urinate	58	10.3%
Diarrhoea	46	8.2%
Incontinence	44	7.8%
Use of antidepressant drugs before diagnosis	36	6.4%
Hesitancy in starting urination	32	5.7%

URTIs — upper respiratory tract infections

We also analysed whether the occurrence of specific prodromes was associated with age at MS onset. Pain complaints, sleep disturbances, vertigo, and fatigue were most common in the group that was diagnosed with MS between the ages of 41 and 50. Nightmares prevailed in the group with disease onset before age 20. Dizziness, urinary incontinence, or urgent need to urinate dominated in the group with late MS onset (after 50 years of age). All the above-mentioned relationships were statistically significant (p < 0.05, see Supplemental Tab. 1).

Prodromal symptoms and EDSS

To assess how and which of the prodromal symptoms were associated with future neurological status, we stratified patients into two groups according to their current EDSS (EDSS < 3 and ≥ 3).

The group with the higher EDSS reported more prodromal symptoms (a mean of 6.1 ± 5 *vs.* 4.4 ± 4.1, p < 0.05), see Figure 1.
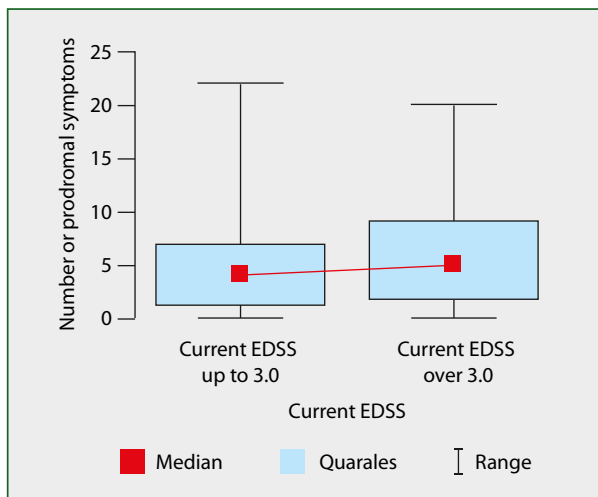
Figure 1. Number of the reported symptoms by the current EDSS score (p < 0.05)

The following prodromes were significantly more frequent in the higher EDSS group: pain complaints, headache, vertigo, dizziness, limbs tremor, diarrhoea, urinary disturbances (incontinence, urgency, hesitancy in starting urination) and deterioration in everyday functioning due to cognitive issues, see Supplemental Table 2.

In multivariate analysis, the following prodromes correlated significantly with the future EDSS score: hesitancy in starting urination (raised EDSS by 0.6, p < 0.05), deterioration in everyday functioning because of cognitive difficulties (raised EDSS by 0.5, p < 0.05), and pain complaints (raised EDSS by 0.4, p < 0.05). The R^2 coefficient for this model was 14.13% (p < 0.05).

Prodromal symptoms and subsequent increase in disability

We adopted the index EDSS increase per year to assess whether and which prodromal symptoms occurred in patients

Table 2. Prevalence of reported prodromal symptoms by gender

Symptom	Sex		p-value
	Women (N = 383)	Men (N = 181)	
Pain complaints	88 (23%)	38 (21%)	0.68
Headache	152 (39.7%)	48 (26.5%)	0.003*
Sleep disturbances	122 (31.9%)	43 (23.8%)	0.06
Insomnia	60 (15.7%)	23 (12.7%)	0.43
Excessive sleepiness	73 (19.1%)	20 (11.1%)	0.02*
Vertigo	128 (33.4%)	45 (24.9%)	0.005*
Spinning	71 (18.5%)	30 (16.6%)	0.65
Dizziness	80 (20.9%)	32 (17.7%)	0.44
Anxiety and depressive disorders	57 (14.9%)	25 (13.8%)	0.84
Limb tremor	78 (20.4%)	41 (22.7%)	0.61
Bowel disturbances	105 (27.4%)	41 (22.7%)	0.27
Diarrhoea	25 (6.5%)	21 (11.6%)	0.06
Constipation	69 (18%)	20 (11.1%)	0.046*
Abdominal pain	42 (11%)	19 (10.5%)	0.98
Urinary disturbances	76 (19.8%)	28 (15.5%)	0.26
Incontinence	34 (8.9%)	10 (5.5%)	0.22
Urgent need to urinate	41 (10.7%)	17 (9.4%)	0.74
Hesitancy in starting urination	21 (5.5%)	11 (6.1%)	0.93
Use of antidepressant drugs before dg	23 (6%)	13 (7.2%)	0.73
Fatigue	168 (43.9%)	69 (38.1%)	0.23
Cognitive difficulties at school/work	94 (24.5%)	36 (19.9%)	0.26
Concentration disturbances	86 (22.5%)	37 (20.4%)	0.67
Deterioration in everyday functioning due to cognitive difficulties	59 (15.4%)	24 (13.3%)	0.59
Increased frequency of URTIs	60 (15.7%)	29 (16%)	1.0

*statistically significant. URTIs — upper respiratory tract infections

with a more aggressive course of the disease. Patients with disease duration of less than one year were excluded from this analysis. Subjects were divided into four numerically similar subgroups (see Suppl. Tab. 3).

The presence and number of prodromal symptoms correlated significantly with a higher increase in index EDSS per year during the course of the disease (see Suppl. Tab. 3).

For several of the analysed prodromal symptoms, we showed statistically significant differences between the groups, with the following prodromes occurring more often in the two groups with the highest annual EDSS increase: urinary disturbances, cognitive complaints, fatigue, and pain (see Suppl. Tab. 4).

Pain complaints, headache, sleep disturbances, cognitive difficulties at school/work and deterioration in everyday functioning due to cognitive complaints were all significantly more frequent in the group with the fastest rate of disability accrual of ≥ 0.35 EDSS per year (p < 0.05 for all correlations).

Discussion

In this study, a great majority of our RRMS cohort (82.5%) presented with at least one prodromal symptom. The following characteristics correlated significantly with the number of reported prodromal symptoms: female sex, disease onset between ages 31 and 50, EDSS score ≥ 3.0 at enrollment into the study, and higher annual EDSS increase. We stratified patients into two groups using a cut-off of EDSS 3.0. This was selected as a generally accepted essential milestone in the course of the disease [20].

The occurrence of individual prodromes differed significantly depending on gender; specifically, headache, excessive sleepiness and constipation were significantly more common among women. The differences between the groups stratified by age at MS onset did not reach statistical significance. Therefore, it seems that the occurrence of the prodromal phase is independent of age at disease onset.

Fatigue, which is common among MS patients, has also been described in subjects with RIS [21], and was the most commonly reported symptom in our population (42%). In a study by Berger et al. [22], 28.9% of MS patients were labelled with chronic fatigue syndrome, malaise or fatigue in the three years preceding the MS diagnosis. In another study, fatigue was significantly more frequent in MS subjects up to five years before their diagnosis, compared to a healthy population [23].

Cognitive impairment in MS tends to progress over time, but might be detected as early as in clinically isolated syndrome [24] and even in up to 27.6% subjects with radiologically isolated syndrome [25]. Notably, almost a quarter of our patients reported that they had noticed problems with concentration and learning even several years before their first relapse. These cognitive disturbances resulted in difficulties at school or work [26] and in almost 15%, these symptoms had affected their everyday life months or even years before MS onset.

Similarly, according to a Norwegian study, impaired cognitive performance was found up to two years prior to the first MS event [27]. In an Argentinean population, it was shown that patients with subsequent MS diagnosis performed worse in their math exams at school compared to the healthy control group, even many years before disease onset [13].

In the current study, we were able to show that the prodromal cognitive complaints were most frequently reported by the group with the fastest rate of disability accrual.

Also, patients with EDSS ≥ 3 at enrollment were more likely to report that prodromal cognitive impairment and fatigue led to deterioration in everyday functioning even before their first MS relapse.

We acknowledge that fatigue could affect cognitive impairment. Importantly, our study participants were specifically asked whether their memory and concentration problems or difficulties in acquiring new information were more severe than in their peers and whether they made it difficult to cope with work or school duties. It was the deterioration in everyday functioning due to cognitive impairment that was a predictor of higher EDSS increase rate. This finding underlines the importance of patients' subjective judgements and patient-reported outcomes in clinical reasoning.

Another clinically significant complaint is pain, which is more prevalent in MS subjects, even as much as 10 years before their first MS relapse [15, 23, 28]. In our study group, pain complaints (usually muscles, joints or back) were a predictor of higher disability (raised EDSS by 0.4 point, p < 0.05) and were reported more commonly in the higher EDSS subgroup (33.6% *vs.* 18.7%, p < 0.05) and in the subgroup with the highest annual EDSS increase (33.8% in ≥ 0.35 EDSS/y group *vs.* 12.1% in ≤ 0.10 EDSS/y group, p < 0.05). However, pain might be more elusive as a potential outcome predictor than cognitive impairment, given that the latter allows for a more reliable quantification.

Interestingly, 6.4% of our patients were treated with antidepressant drugs before their first MS relapse, which is consistent with the data reported for Polish (7%) and European (7.2%) populations [29]. This points to the fact that in the years preceding the disease, future MS patients do not use antidepressant drugs more frequently than the general population, something which has been implied by some studies [14, 15]. Importantly, the number of patients on antidepressants doubled after the diagnosis was made, rising from 6.4% to 12.4%. The frequency of anxiety and depressive disorders did not statistically differ between groups divided based on EDSS outcome or age at onset of disease.

Vertigo was reported by 30.7% of our patients, which is consistent with studies revealing that patients with MS had more prescriptions made out for anti-vertigo drugs in the five years preceding the diagnosis [30]. This was reported more frequently in groups with a higher EDSS score and higher accrual of EDSS per year.

In our study population, gastrointestinal disturbances were observed in 29.1% of patients, which is higher than the numbers reported in Portuguese (17%) [15] and Swiss studies (11.6%) [23]. On the other hand, Almeida et al. [31] revealed that 31.6% of patients with RRMS reported bowel symptoms before the occurrence of clinically isolated syndrome, mostly constipation (50%) and diarrhoea (29.5%). In a Lithuanian population, 36.7% of patients experienced gastrointestinal disorders as prodromes [28]. The differences in the reported numbers may represent regional differences (dietary habits, environmental exposures) or may result from different group size effects.

Urological symptoms are rarely the first presentation of MS (3–10%), but in the course of the disease almost 65% of patients report moderate to severe urinary complaints [32]. Importantly, in our group 18.4% of patients reported them as prodromal signs, mostly in the groups with a higher disability increase rate. We must emphasise that studies based on International Classification of Diseases-10 (ICD-10) codes have also revealed that patients with MS have a significantly higher risk of presenting urinary dysfunction before their MS onset [14] and have a higher hospitalisation rate related to bladder disorders or higher number of prescriptions for urinary anti-spasmodics in the five years before typical MS onset [30, 33].

In the current study, hesitancy in starting urination as a prodromal sign correlated significantly with a higher EDSS at enrollment into the study.

The strengths of our study include its access to a relatively large RRMS population with well-documented disease onset and follow-up EDSS scores, as recorded in the clinical database by the treating neurologists.

So far, the majority of studies concerning the prodromal MS phase have been based on electronic healthcare databases, which does ensure large groups of patients. However, in such databases, MS onset would be reported as the date of the first MS clinic visit [15, 22, 23, 33]. Such an approach could easily be flawed as some of the earlier visits could already be related to MS and not constitute a prodrome. Additionally, symptoms were identified from records by ICD-10 classification, and not reported directly by patients, which we believe to be a limitation. Some complaints, such as fatigue, are rarely coded in ICD-10, especially if they accompany sleep or mood disorders.

Limitations of retrospective approach

Recall bias needs to be addressed as an important limitation of this study. Firstly, our questionnaire was designed to screen a period of only five years before MS onset, which is limiting but reliable (given the fact that it is self-reported). In fact, in most of the available studies on MS prodromes, a 5-year period has been analysed [14–16, 18, 30].

Another limitation is the lack of a control group. However, the aim of our study was rather to assess whether the symptoms were consistent with data available from studies based on ICD-10 databases, and not to compare MS to the general population. Importantly, we attempted to select symptoms that could be predictors of a more severe disease course.

Notably, most patients found it difficult to answer the open-ended questions about the other antecedent symptoms they noticed. This indicates the potential difficulties in accurately estimating prodromal symptoms. Due to their non-specific nature, relatively low intensity as compared to the symptoms of a relapse, and their chronicity, prodromes may sometimes simply be ignored by patients.

It is well established that radiologically isolated syndrome may precede the appearance of clinical symptoms of MS by up to several years [34–36], with levels of serum neurofilament light chain showing increases as much as six years before clinically definite MS [37].

Based on the pattern of radiological abnormalities in RIS and the presence of oligoclonal bands, we can estimate the risk of conversion from RIS to MS [34–36]. It is likely that considering prodromal symptoms would allow physicians a better selection of subjects requiring disease modifying therapies promptly in their care. As we nowadays have a wide range of therapies available, it seems that the biggest problem is still that we introduce them too late [4]. Also, in this specific population, neuroprotective strategies would be especially needed.

In this paper, we have shown that patients with higher EDSS scores reported more prodromal symptoms. Cognitive impairment and urinary disturbances were significantly correlated with a higher rate of EDSS increase in the future. This obviously necessitates further research.

This might be the right moment to change the generally dismissive approach to non-specific, 'mild' symptoms that do not affect a patient's life. This approach is clearly contraindicated by the high percentage of our study population who did experience a significant deterioration in their quality of life years before their first MS relapse.

Clinical implications and future directions

The inclusion of prodromes into the clinical course of MS may change the diagnostic criteria in future, although the use of additional tests/biomarkers, e.g. neurofilament light chain measurements, could be helpful in terms of minimising the risk of misdiagnosis [38]. We suggest that patients with RIS should receive routine assessments on Fatigue Severity Scale, neuropsychological tests, and a detailed history of urinary disturbances.

Since pain and fatigue can be difficult to objectify, we suggest focusing on complaints regarding cognitive impairment, especially since a large group of patients noticed that these deficits worsened their daily functioning, even before manifestation of the typical MS symptoms.

Our study may have important implications for newly diagnosed patients. Specifically, it suggests that screening this population for previous prodromal symptoms could be a factor in considering highly effective therapies (HET) earlier

on, if patients were identified as high-risk for early disability. Interestingly, in a Polish population, it has recently been shown that HET have been used less frequently than anticipated [19].

In the future, we plan to compare the results obtained from the MS population to those of additional comparative study cohorts of patients with other immune-mediated diseases, such as ulcerative colitis.

We conclude that a broader appreciation and deeper understanding of the phenomenon of prodromes will allow us to better apprehend the early stages of multiple sclerosis.

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