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Original article

Is benign MS really benign? What a meaningful classification beyond the EDSS must take into consideration

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ABSTRACT

Background: Multiple sclerosis (MS) is a neuroinflammatory and neurodegenerative disease with an unpredictable course that has a broad clinical spectrum and progresses over time. If a person with MS (PwMS) shows overall mild to moderate disability even after a long duration of disease, the term benign MS (BMS) is used. However, there is currently no generally accepted definition of BMS. Most definitions are based on EDSS in connection with disease duration, i.e. EDSS ≤ 3.0 after 15 years' disease duration. The question arises whether focusing on EDSS alone is adequate for classifying the disease course taking into account that 'hidden' or 'soft' symptoms are not sufficiently covered by this instrument. The aims of the study are to assess the prevalence of BMS in one of the largest patient cohorts, to describe the prevalence of patients without disabilities and to assess the further disability progression of these patients over another 15 years.

Methods: Based on data exported from the German MS Registry, PwMS with a disease duration of 15 years or more were included in the analyses. PwMS were divided into BMS (EDSS ≤ 3.0) or non-benign (NBMS, EDSS > 3.0).

Results: Out of 31,824 PwMS included in the German MS Register, we identified 10,874 patients with a disease duration ≥ 15 years of whom 4,511 (42%) showed an EDSS ≤ 3.0 fulfilling the criterion of benign MS. In the subgroup with EDSS measured exactly at 15 years' disease duration, the proportion was 54%. This proportion decreased continuously with increasing disease duration and fell to 30% after 30 years. Female sex (hazard ratio [HR]: 0.84) was associated with BMS, while a progressive (HR: 2.09) and late disease onset (HR: 1.29) were associated with NBMS ($p < 0.001$). With a more rigorous definition of BMS (EDSS ≤ 1.0, absence of disability, and active employment), only 580 (13%) of the initial BMS remained 'benign'.

Conclusion: Our data propose an alternative definition (EDSS ≤ 1.0, absence from any disability, and the ability to work after 15 years of disease duration) which might truly reflect BMS.

1. Introduction

Multiple sclerosis (MS) is a neuroinflammatory and neurodegenerative disease that primarily affects young adults. The disease follows an unpredictable course with a broad clinical spectrum and progresses over time (Krieger et al., 2016; Reich et al., 2018; Zettl et al., 2012). The search for prognostic factors to predict the course of the disease is essential, especially in view of the initiation and choice of disease-

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modifying therapies (DMT) which have increasingly emerged over the last decades (Rommer et al., 2019). In general, more efficacious DMT have higher risks for severe adverse events, such as opportunistic infections, secondary autoimmune complications, or infusion reactions. Therefore, there is a need for the definition of 'benign MS' that could allow to identify early predictive factors or biomarkers. A person with MS (PwMS) may show slight/moderate disabilities and limitations even after a long period of illness (Weinshenker et al., 1989). These patients usually are classified as benign, but currently, there is no generally accepted definition of this type of MS. Most definitions are based on EDSS (<3.5 or <4.0) in conjunction with a disease duration of 10–15 years (Reynders et al., 2017). In this regard, it is important to note that a mere EDSS based definition has a strong focus on the patient´s mobility, and the fact that 'hidden' or 'soft' symptoms such as fatigue, depression, cognitive dysfunction, and pain are not sufficiently covered (Meyer-Moock et al., 2014; Paul, 2016; Penner, 2016; Penner and Paul, 2017; von Bismarck et al., 2018). In particular fatigue is a disabling and frequent symptom even in early disease stages and one of the most common across all stages of the disease (Rommer et al., 2019). These soft symptoms have a major impact on the patients' well-being and work ability. The aims of the study are to assess the prevalence of BMS in one of the largest cohorts of patients worldwide, to describe symptoms and sociodemographic data, to assess patients without disabilities who are still able to work after 15 years of illness, and to investigate subsequent progression of the disease once a patient has fulfilled the common definition of BMS.

2. Material and methods

Based on data exported from the German MS Register (GMSR, www.msregister.de/en; March 2020), people with MS (PwMS) having a disease duration of 15 years or more were included in the analyses. Based on clinically assessed Expanded Disability Status Scale (EDSS) (Kurtzke, 1983), BMS classification was done as interval-censored time-to-event endpoint defined by the event of EDSS >3.0 (Amato et al., 2008). The left side of the censoring interval is the last visit when the sustained EDSS was still ≤3.0 or zero if not observed. The right side is the first visit when the EDSS was sustained >3.0 or infinity if not observed. Disease duration was calculated from the onset of the disease, but in cases where the onset of the disease is unknown, the date of diagnosis was used.

The progression of disability, measured by EDSS and duration of the disease, was examined in regard to the association with other clinical as well as sociodemographic variables from the register. For longitudinal variables, the first visit after at least 15 years within the censoring interval was chosen as the reference visit. For BMS this is the last visit (>15 years) when the (sustained) EDSS was still ≤3.0, and for NBMS, the first visit after at least 15 years of disease duration when the (sustained) EDSS was >3.0. For data reconciliation, we allow an additional two months' difference in time points. This approach allows the most coherent and real-world based comparison of the two (sub)cohorts, and the resulting difference in average disease duration was small.

MRI activity is rated by a neurologist based on new T2 lesions and gadolinium enhancing lesions. Updating of MRI status in patients is often unregularly done, especially in older cohorts, and its extent of missingness in GMSR was reported.

The GMSR collects the working status of PwMS and part-time and full-time employment were considered as employed, while early retirement and unemployment were considered as unemployed. Payments or notifications from/in statutory pensions, education, domestic work, or parental leave were treated as unclear / missing values in the analyses. Furthermore, to measure effects of early treatment exposure, the time to first DMT was analyzed. This analysis was only performed in patients who had complete DMT documentation in the GMSR available, a relapsing course, and an initiation of DMT within the first 15 years after disease onset. The absence of a disability was defined when no current symptoms that impair the patient were observed by a clinician. To investigate a more rigorous definition of truly benign MS, the absence of disability is used in conjunction with the ability to work, and an EDSS ≤1.0, which indicates abnormalities in neurological examination without suffering from symptoms (Kurtzke, 1983).

Analyses on the time to EDSS >3.0 were done using univariable as well as multivariable interval-censored Cox proportional hazard model according to Pan, 1999. Descriptive figures and all analyses were performed using R 3.6 (R core Team, Vienna), and group comparisons were done using 95% confidence intervals (CI), including Clopper-Pearson CI, chi-squared tests, or t-tests considering p-values of less than 5% statistically significant. Scatterplots of EDSS follow-up of BMS use beeswarm plot clustering whenever points would overlap and interpolation splines are estimated by generalized additive models for metric and binomial data. The GMSR has been registered at the German Clinical Trials Register (DRKS, Deutsches Register Klinischer Studien, No. DRKS00011257), and initial ethical approval was gained by the IRB at the University of Würzburg.

3. Results

Out of 31,824 PwMS from the German MS Register with an updated entry since 2014, we identified 10,874 PwMS with a disease duration ≥15 years having a median date of onset in 1996 (IQR: 1990–2000). Of these, 4511 PwMS (41.5%) had an EDSS ≤3.0 after at least 15 years, as shown in Fig. 1. When considering discrete points in time, the proportions with an EDSS ≤3.0 were 54% after exactly 15 years (n = 5082; rounded to whole years), and 30.0% after 30 years (n = 1195), see Fig. 2.

3.1. Demographics

BMS patients were younger at the onset of the disease and more often had a relapsing-remitting course. The employment level in the BMS cohort was higher (75%) than in the NBMS cohort (36%), the educational level showed higher rate of high school diploma in the BMS cohort (33.9%) than in the NBMS cohort (30.4%, p = 0.002). The average disease duration at the reference visit (last visit with EDSS ≤3.0 after at least 15 years of disease) was 22.0 years in the BMS group compared to 23.7 years in the NBMS group at the reference visit (first visit with sustained EDSS >3.0 after 15 years). Table 1 provides an overview of the demographics of the PwMS analyzed. Data on treatment status during the first 15 years after onset of the disease were

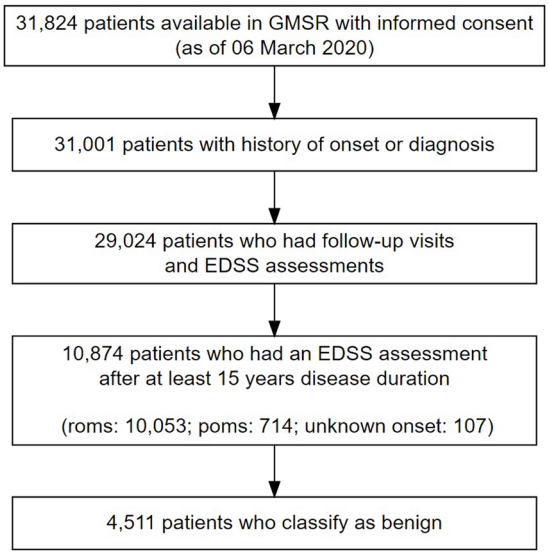

Fig. 1. Flowchart of patients of the study.

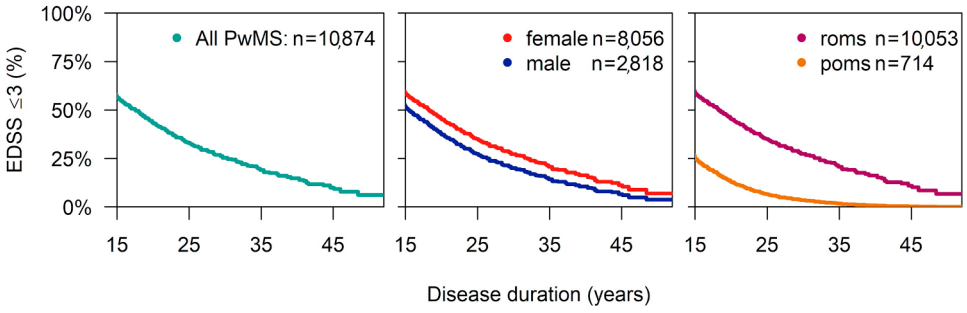

Fig. 2. Cox-estimates of proportion of PwMS with EDSS ≤3.0 in the period from 15 to 50 years of disease duration. Numbers of patients that are 'at risk', i.e. not having been documented with either sustained EDSS >3.0 or been lost to follow-up, given by disease duration in years (y) are: 6103 (20y), 3410 (25y), 1714 (30y), 796 (35y), 338 (40y), 131 (45y), 48 (50y). Covariables gender and type of onset are added in univariable analyses. For 107 PwMS the type of onset is unclassifiable to relapsing onset MS (roms) or progressive onset MS (poms).

Table 1
Comparison of benign and non-benign PwMS and subgroups of BMS when instead of 15 years, 20 or 30 years disease duration were examined. Proportions along with Clopper-Pearson 95% confidence intervals or mean (± sd) are reported. *Mean (median) time to diagnosis as the delay from manifestation of first symptoms to diagnosis of MS in years is given (p=0.14). **Time to first DMT is restricted to patients with complete DMT documentation, an observation period of up to 15 years after onset and calculated for RRMS only (p=0.04). All other statistical comparisons between BMS and NBMS were significant with p<0.01.

	benignMS	non-benign	benign: >20 years follow-up	benign: >30 years follow-up
% (of total)	41.5%	58.5%	34.4%	25.1%
n (subgroup)	n=4511	n=6363	n=2348 (/6824)	n=503 (/2002)
Females (%)	77.6% [76-39%]	71.6% [70-73%]	78.7% [77-80%]	77.5% [74-81%]
Prog. onset (%)	1.9% [1.5-2.3%]	9.9% [9.1-10.6%]	1.8% [1.3-2.3%]	2.2% [1.1-3.9%]
∅-Age onset	28.8 (± 8.4)	30.7 (± 9.4)	27.2 (± 7.6)	24.2 (± 6.7)
∅-Time to diagnosis*	4.0 (0.7)	3.7 (0.6)	5.3 (1.0)	9.0 (5.0)
∅-Disease duration (reference visit)	22.0 (± 6.2)	23.6 (± 7.8)	26.3 (± 5.7)	35.1 (± 5.0)
∅-Age (last visit)	51.3 (± 9.1)	56.0 (± 9.8)	53.9 (± 8.3)	59.7 (± 7.7)
MRI active (reference visit)	17.7% [15.7-19.8%] (n = 1353)	25.0% [22.7-27.2%] (n = 1445)	13.8% [11-16%] (n = 683)	13.9% [8-19%] (n = 151)
Employment (%)	74.9% [73-76%]	35.7% [34-37%]	71.9% [70-74%]	64.9% [60-70%]
Highschool grad. (%)	33.9% [32-35%]	30.4% [29-32%]	33.0% [31-35%]	32.5% [28-37%]
∅-Time to first DMT**(years)	6.5 (± 4.8) (n=1287)	6.9 (± 4.9) (n=1243)		

available for 2530 patients. The time to first DMT was slightly shorter in the BMS cohort than in the NBMS cohort (6.5 ± 4.8 vs. 6.9 ± 4.9 years, $p = 0.04$).

In order to look at the whole cohort of patients with disease duration >15 years and associations with covariates, we analyzed the time to EDSS >3.0 (as event; interval-censored Cox proportional hazard model), with male PwMS and those with progressive onset (POMS) being less often benign (Fig. 2b/c).

3.2. Predictive factors at onset of the disease

Multivariable estimates of the Cox model showed that female sex was more likely to be associated with BMS, while a progressive and later disease onset is associated with NBMS (Table. 2).

Cox model of symptoms at onset of disease showed that initial symptoms, such as paresis, bladder dysfunction, and cerebellar signs, were associated with a worse prognosis, while sensory signs or depression may be considered beneficial and were associated with a higher probability of BMS (Table 2).

Table 2
Multivariable Cox regression effect estimates (HR) with interval-censored time to EDSS >3.0. Male gender, progressive onset, and later age at onset are associated with a faster EDSS progression. Multivariable models with adjustment for the three baseline covariates also are calculated for symptoms at onset of disease: pyramidal, cerebellar, brainstem, sensory, bladder, visual, depression, polysymptomatic.

Baseline covariates (at onset of the disease)	hazard ratio (HR) [95%-CI]	p-value
female gender	0.84 [0.79–0.89]	**<0.001**
age onset (10 years)	1.29 [1.25–1.34]	**<0.001**
progressive onset	2.09 [1.87–2.34]	**<0.001**
pyramidal	1.51 [1.37–1.66]	**<0.001**
cerebellar	1.10 [1.00–1.21]	0.05
brainstem	1.04 [0.96–1.14]	0.3
sensory	0.84 [0.78–0.90]	**<0.001**
bladder	1.39 [1.20–1.61]	**<0.001**
visual	1.01 [0.93–1.08]	0.9
depression	0.86 [0.77–0.96]	**0.009**
polysymptomatic	0.90 [0.81–1.00]	0.05

3.3. Association with other measurements of burden of disease

Fig. 3 shows current symptoms in patients when they were still benign (reference visit; last visit after 15 years and EDSS ≤3.0) or first EDSS >3.0 in NBMS patients. It is evident that BMS differed from NBMS mainly in terms of walking problems, spasticity, and bladder dysfunction, which were more common in NBMS patients, while the differences in depression, fatigue, and cognition were smaller but still present.

Taking all above-mentioned factors together, we defined truly benign MS as follows: EDSS ≤1.0 after 15 years disease duration, absence from any disability (symptoms), and the ability to work. Applying these strict criteria, we identified 580 PwMS (13% of the original 'benign MS' cohort), PwMS, which can be described as truly benign (Fig. 4).

3.4. EDSS progression within the BMS subgroup

A crucial question when looking at the concept of BMS is how many PwMS remained benign for the next couple of years, and whether reaching the status of BMS might be a predictor for the subsequent disease course. Fig. 5 shows that 60% of PwMS with BMS and an age <50 years remained benign for another decade after the first date of being classified as benign. In older PwMS (age >50 years) this proportion decreased significantly but was still around 40% (Fig. 5). Applying the strictest criteria (EDSS ≤1.0, absence of symptoms, and ability to work), about 70% of these patients remained benign for another decade.

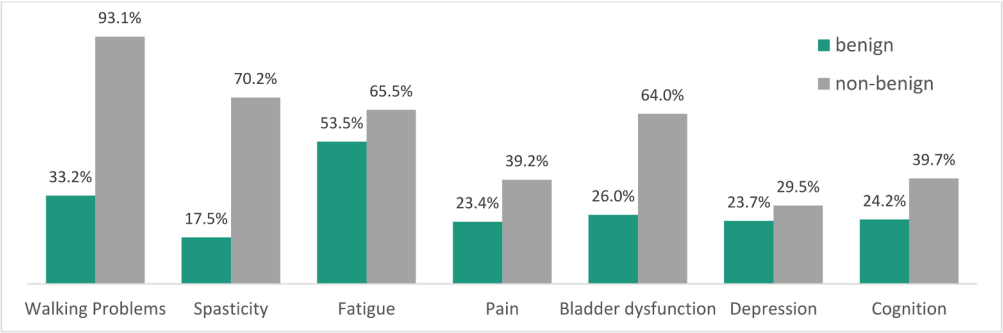

Fig. 3. Symptoms at reference visit, i.e. upon reaching EDSS >3.0 (gray) or at last visit when still benign (green). All symptoms were more frequent in the non-benign group than in the benign group ($p < 0.001$).

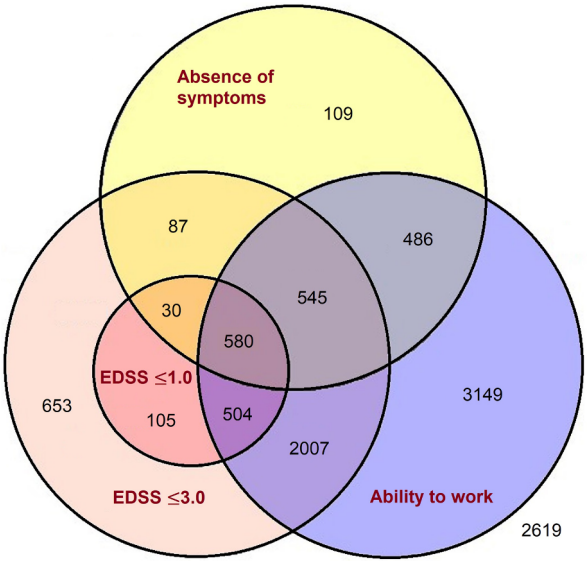

Fig. 4. Venn-diagram of number of patients that might be truly benign.

4. Discussion

One of the most striking findings of our analysis is that although half of patients with a disease duration of 15 years and an EDSS ≤3.0 were classified as benign if the most common definition of BMS was followed (Amato et al., 2008). One in four of these patients was unemployed compared to 5% national unemployment rate in Germany (as of March 2020). Moreover, the proportion of BMS in the overall sample decreased over time, and only about one in three remained benign after 30 years. Thus, this definition seems not to truly reflect a benign course of the disease and underscores the need for an alternative definition.

'Benign' MS was originally defined by Lublin and Reingold (Lublin and Reingold, 1996) as patients who are fully functional in all neurological systems 15 years after onset. The concept of BMS is not uniformly defined in the literature and is still a matter of debate (Reynders et al., 2017), and discussions are emerging whether or to what extent MS can be described as benign at all. Nevertheless, the clinical spectrum of MS is broad and there are certainly patients who are mobile and able to work after 15 years of disease (Weinshenker, 1994).

The factors that tend to indicate a favorable or benign course in our analyses were a relapsing course, female sex, and earlier onset of the disease. Paresis and cerebellar symptoms at the onset of the disease were negative predictors, while sensory disorders were more likely to indicate a benign course. This is consistent with the literature, where female gender, younger age, and a relapsing disease course also indicate a more favorable course, while dysfunction of the pyramidal tract and cerebellar involvement are associated with a more severe course (Bsteh et al., 2016; Confavreux et al., 2003; Weinshenker et al., 1989).

Age was a decisive factor in the long-term prognosis in patients with BMS, similarly as described in the Swedish cohort (Crielaard et al., 2019). At an age of less than 50 years and 10 years additional follow-up, 60% of patients with BMS remained at EDSS ≤3.0, while at an age of over 50 years the proportion was below 40%. There are many reasons for the role of age in disease progression. On the one hand, it might be that with increasing age and disease duration, the probability of suffering a progressive course increases (Mahad et al., 2015). On the other hand, it has recently been shown that with advancing age, physical symptoms occur that can be confused with MS symptoms even in individuals without any neurological disorder (Azevedo et al., 2019; Lynch et al., 2019).

The already mentioned relatively high number of unemployed BMS patients, despite the rather low level of EDSS, makes the definition of BMS additionally come to the fore. The focus on EDSS in the current definition of BMS, which ignores soft or hidden symptoms such as fatigue, cognition, and emotional disorders, may be a possible explanation for this discrepancy. For example, Amato et al. showed that out of 47 patients who met the definition of BMS, 11 patients suffered from cognitive impairment. In addition, Bsteh et al. (2016) demonstrated that neuropsychological disorders have a negative long-term influence on the disease outcome. These neuropsychological symptoms and fatigue (Patejdl et al., 2016) may be present early in the course of the disease (von Bismarck et al., 2018), but are not adequately covered by the EDSS (Rommer et al., 2019).

For this reason, the currently used definition of BMS is too broad, and the percentage of more than 50% in our sample and in other studies seems to be too high. We propose to introduce the following criteria for defining 'truly' benign MS: EDSS ≤1.0, absence of any disability, and able to work at least part-time. These criteria were chosen based on of the importance of employment in BMS patients (McAlpine, 1961) and the original definition that patients are fully functional in all neurologic systems 15 years after onset (Lublin and Reingold, 1996). Applying these criteria to our sample, the proportion of patients from the original 4511 patients with BMS were reduced to only 580 patients (13%). Tallantyre et al. (2019) also aimed at describing truly benign MS patients. BMS patients were defined as having MS for at least 15 years; an EDSS <3.0; no significant fatigue, mood disturbance, cognitive impairment, or disrupted employment; and had not received DMT. They found that only about 15% of their original population meet these criteria and the main reasons for the reduction were effects on employment and neuropsychological symptoms. Our figures showed a similar decrease in the proportion of BMS patients with the additional criteria, although we did not select for the absence of DMT. In agreement with Tallantyre et al. (2019), we did not see a relevant effect of time to first DMT in our analysis. The reason for this may be limited treatment options at manifestation for our cohort of patients whose

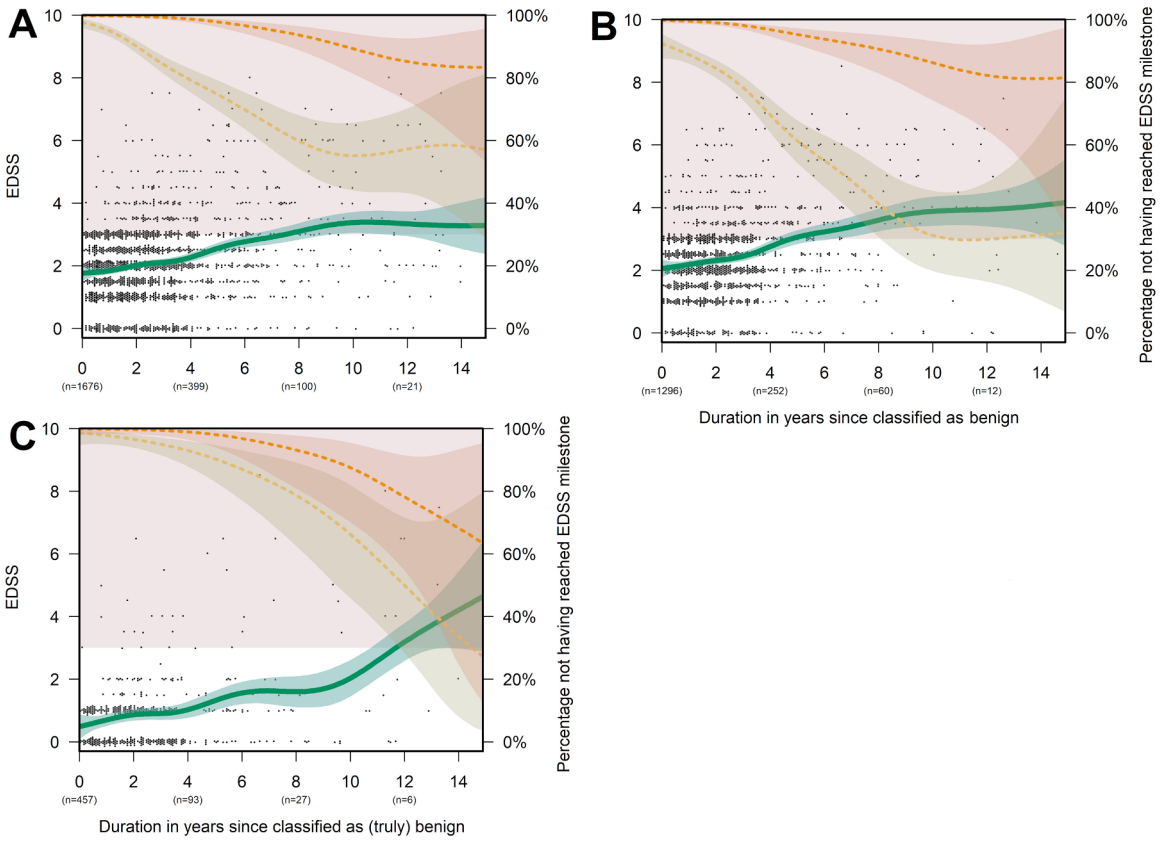

Fig. 5. Scatterplot of EDSS progression in the benign subgroup after 15 years of disease duration (n = 2972). Using generalized additive models for interpolation, solid green lines show the mean EDSS. Dotted lines show the percentage of PwMS with EDSS ≤3.0 (yellow) and EDSS ≤6.0 (orange). X-axis shows the time from first fulfilling the criteria of a benign MS in years. (A) under age 50 at first fulfilling benign MS; (B) above age 50; (C) truly benign MS (EDSS ≤1.0, absence of symptoms, ability to work).

disease onset was predominantly in the 1990s. Also, it remains unclear on whether a benign course would have caused the avoidance of DMT or whether an early DMT would have caused the course to be benign. Long-term availability of crucial time-varying confounders is needed to address this (Trojano et al., 2017).

Limitations regarding the comparability of the NBMS group and the BMS group may apply. However, our choice of reference visit >15 years disease duration, i.e. the last visit when BMS or the first visit when NBMS, resulted in a much higher similarity of both groups regarding disease duration and year of disease onset, compared to other studies (Crielaard et al., 2019). The question on how to classify a BMS patient who starts rapidly progressing after e.g. 20 or 25 years remains open. Most BMS were found to be stable, but Fig. 5 also reveals a certain amount of cases that may have lost their benignity in a relatively short amount of time. This may suggest that BMS could also be considered a status that could be lost (after being attained) or that is in general time-varying over the course of the disease.

Our figures may indicate that employment status can be considered one of the most important indicators to classify BMS versus NBMS. Conversely, the factor with greatest impact on employment in MS patients is disability, which ranks ahead of education level, age and gender (Salter et al., 2020).

5. Conclusion

Approximately half of all MS patients suffer from BMS according to the most commonly used criteria. These criteria largely neglect neuropsychological symptoms. With stricter application of BMS criteria (ability to work, absence of disability, and EDSS ≤1.0), the number of BMS patients decreased strongly to 13% of the original BMS cohort. Several reports and our data call for a redefinition of BMS. We propose a definition that includes an EDSS ≤1.0, absence from disability, and employment status (taking into account the employment market and age of the patients) after 15 years of disease duration.

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CRediT authorship contribution statement

David Ellenberger: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing, Visualization. **Peter Flachenecker:** Conceptualization, Writing - review & editing. **Judith Haas:** Conceptualization, Writing - review & editing. **Kerstin Hellwig:** Writing - review & editing. **Friedemann Paul:** Writing - review & editing. **Alexander Stahmann:** Conceptualization, Software, Data curation, Writing - review & editing, Project administration, Funding acquisition. **Clemens Warnke:** Writing - review & editing. **Uwe K. Zettl:** Writing - review & editing, Supervision. **Paulus S.**

Rommer: Conceptualization, Writing - original draft, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

PF has received speaker's fees and honoraria for advisory boards from Almirall, Bayer, Biogen Idec, Celgene, Genzyme, Novartis, Merck-Serono, Roche and Teva. He has participated in pharmaceutical company sponsored trials by Roche.

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