P726

Is benign MS ‘benign’?

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on behalf of the German Multiple Sclerosis Register by the German MS Society

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1. Background

Benign MS (BMS) was defined as patients that are fully functional in all neurologic systems 15 years after onset (Lublin and Reingold, 1996). Amato et al. (2006) described the most commonly used definition of patients (PwMS) not exceeding an EDSS of 3.0 after 15 years of disease duration (DD). The definition and existence of BMS is still a matter of debate. In the age of earliest possible MS diagnosis, individual prognosis and initiation of DMT - the clinical relevance of a ‘benign’ disease course is a pressing question.

2. Aims and Hypotheses:

This study aims to provide quantitative and qualitative analysis on BMS in Germany.

3. Methods and Material:

- Data [export date: 13.08.2019] of 28,595 PwMS from the German MS-Register was analysed. Subsequently, only PwMS with a DD of ≥15 years were included. These were divided into “benign” with documented EDSS ≤ 3 at any visit later than 15 years disease duration and “non-benign” with EDSS > 3 at all visits after 15 years and beyond.
- Descriptive analyses were performed using Fisher’s exact test (p_F) for categorical data, t-test (p_t) for metric outcomes and Wilcoxon test (p_W) for ordinal outcomes considering p-values $p < 0.05$ as statistically significant. No adjustments for multiple comparisons were made due to the exploratory nature of the study.
- Kaplan-Meier (KM) analyses using interval censored data were used to model and to test time to EDSS > 3. The left side of the interval is the last (sustained) measurement of EDSS ≤ 3 if existing and the right side the first visit with EDSS > 3.

4. Results:

We identified 9,398 PwMS with a disease duration ≥15 years of which 3,794 patients (40.4%) fulfilled the criteria of EDSS ≤ 3.0 at least one visit. Follow-up by exact years of disease duration shows that up to half of PwMS are ‘benign’:

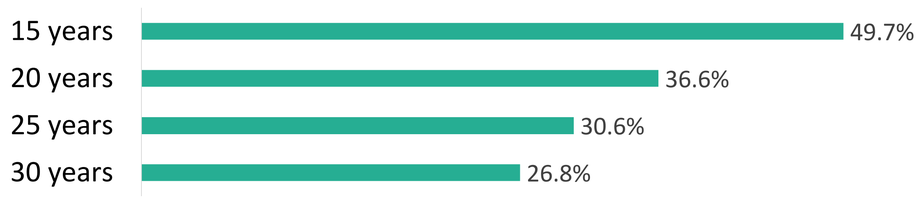


Figure 1: Proportion of EDSS ≤ 3.0 after exactly 15, 20, 25 and 30 years of disease duration.

We analysed the BMS group for survival (defined as EDSS ≤ 3; interval-censored Kaplan-Meier estimation), showing that 57% of the benign PwMS stayed benign for further 10 years, with males having less chances and PwMS with progressive onset (POMS) only being very rarely ‘benign’.

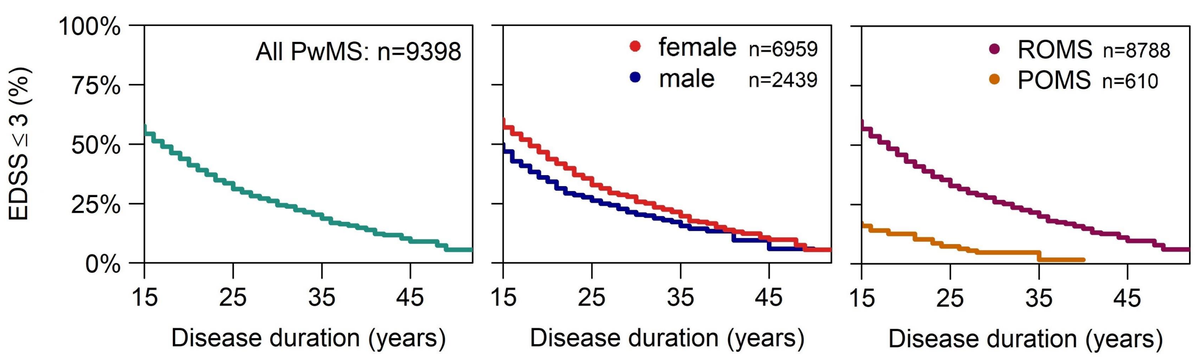


Figure 2: Kaplan-Meier estimates of proportion of PwMS with EDSS≤ 3.0 in the period from 15 to 55 years of disease duration.

5. Conclusions:

- With 40% a high number of the patients did fulfil the most commonly used definition of BMS.
- In contrast, the low number of benign-PwMS with DD of 25 years shows that the time to measure ‘true benignity’ of a MS might no longer be at DD of 15 years.
- In contrast to the low EDSS a high number (30%) of ‘benign’ patients is unemployed (already after 15 years).
- The focus on the EDSS in today´s definition of BMS, which disregards ‘soft/hidden’ symptoms like fatigue, cognition and emotions could be a possible explanation.
- A revision of the definition for ‘benign’ MS is due.

	benign MS	non−benign	benign: 20 y follow−up	benign: 30y follow-up
% (n)	40.4% (n=3798)	59.6% (n=5600)	33.3% (n=1991)	24.2% (n=434)
Females (%)	78.0%	71.3%	79.1%	76.5%
Progress. Onset (%)	1.6%	9.8%	1.9%	1.6%
∅-Age onset	29.0 (±8.5)	31.0 (±9.4)	27.4 (±7.6)	24.2 (±6.7)
∅-Time to diagnosis	4.3	4.1	5.6	9.6
∅-Age (last visit)	50.9 (±9.1)	55.7 (±9.9)	53.6 (±8.2)	59.3 (±7.8)
Employment (%)	68.7%	32.5%	66.2%	58.3%
Highschool grad. (%)	33.8%	30.6%	33.4%	33.8%
DMT (%)	76.7%	61.4%	74.7%	67.2%

Table 1: Comparison of benign and non-benign PwMS, and subgroups of BMS when instead of 15 years DD 20 or 30 years DD are used.

Within the benign group 91% were RRMS, 7% SPMS and 2% PPMS. The levels of SPMS (47%) and PPMS (10%) were higher in the non-benign group. Levels of employment (69%) were higher than in non-benign patients (33%), while school education had only marginal differences.

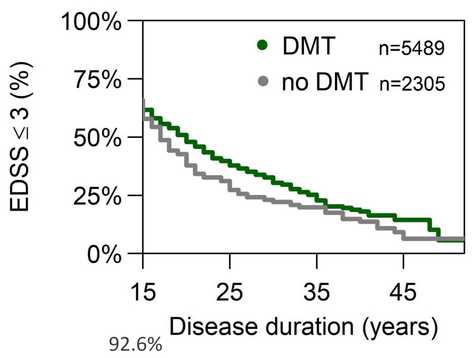
Baseline covariates	**hazard ratio**	**p-value**
female gender	0.819	**<0.001**
age onset (per year)	1.028	**<0.001**
progressive onset	2.004	**<0.001**

Table 2: Kaplan-Meier effect estimates with interval-censored time to EDSS > 3. Besides male gender and prog. onset the age at onset is associated with a faster EDSS progression.

KM-analyses of symptoms at onset show that *weakness* and *cerebellar signs* at onset are associated with a worse prognosis towards EDSS > 3 while *sensory signs* were found to be beneficial in relation to other symptoms.

Symptoms at onset	**hazard ratio**	**p-value**
weakness	1.340	**<0.001**
cerebellar signs	1.112	0.051
sensory signs	0.894	**0.010**
depression	1.023	0.72
visual disturbances	0.962	0.38

Table 3: Effect estimates of symptoms at onset in KM-estimation regarding time-to-EDSS > 3 with adjustment for baseline covariates. Polysymptomatic onset was not found to have a relevant effect.



	hazard ratio	**p-value**
DMD treatment	0.811	**<0.001**

Table 4: KM-estimates for DMT status later than 15 years DD with adjustment for baseline covariates.

Figure 3: Proportion of benign PwMS by DMD treatment in the time period after 15 years DD.

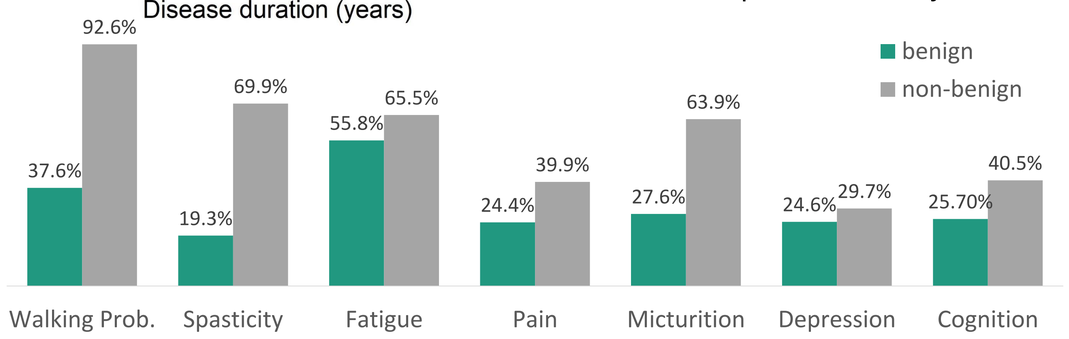


Figure 4: Symptoms upon reaching EDSS > 3 or at last visit when still benign.

6. References

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Abstract

Download

Disclosure – Declaration of Interest

DE, KE, OR: nothing to disclose
PF has received speaker's fees and honoraria for advisory boards from Almirall, Bayer, Biogen, Genzyme, Merck-Serono, Novartis, Roche and Teva. He has participated in pharmaceutical company sponsored trials by Almirall, Biogen Idec and Novartis. None resulted in a conflict of interest.
JH has received compensation from Almirall, Allergan, Biogen, Bayer, HOFFMANN La Roche, Merck, Novartis, Octapharma and Teva. None resulted in a conflict of interest.
CK has received speaker's fees and honoraria for advisory boards from Biogen, Merck Serono, Bayer, Teva, Novartis, Medday, Mylan, Genzyme, Almirall und Roche; None resulted in a conflict of interest.
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