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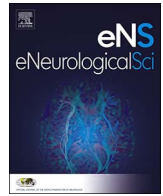
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## Review article

## Definition, prevalence and predictive factors of benign multiple sclerosis

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## ABSTRACT

**Background:** Multiple sclerosis (MS) is characterized by a great inter-individual variability in disease course and severity. Some patients experience a rather mild course, controversially called 'benign MS' (BMS). The usefulness of this entity in clinical practice remains unclear.

**Methods:** We performed a literature search in PubMed, Web of Science and Cochrane Library databases from November 1980 to December 2015, using the following key words: *benign multiple sclerosis, diagnosis, imaging, prognosis, predictive, natural history* and predefined inclusion criteria.

**Results:** Our search yielded 26 publications. Most definitions were based on the Expanded Disease Status Scale (EDSS), which is heavily weighted towards physical disability. Between 30 and 80% of relapsing-remitting MS patients have EDSS < 3 or 4 at 10 years after onset. Having only one relapse in the first 5 years and EDSS ≤ 2 at 5 years or EDSS ≤ 3 at 10 years appears to be predictive for a prolonged benign disease course, without protecting against disease progression at a later stage. Evidence on the predictive value of MRI parameters remains limited.

**Conclusions:** Current BMS definitions have some predictive value for future physical disability, but do not take into account the age at EDSS and the potentially disrupting effects of non-EDSS symptoms and cognitive impairment. It appears to correspond to mild RRMS in the first decades and its prevalence varies. Since early and accurate prediction of BMS is not yet possible, the clinical relevance is limited. Research approaches are suggested.

## 1. Introduction – background

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating and neurodegenerative disease with an unpredictable course and substantial heterogeneity. Most patients start with a relapsing-remitting (RR) course, which may be followed by a secondary progressive phase (SPMS). A minority of subjects present with an insidious progression of disability from onset, or primary progressive (PPMS).

MS is the most important non-traumatic cause of neurological disability in young adults. Nevertheless, a mild course is common, especially in the early stages. Recent cohort studies use the McDonald diagnostic criteria and therefore include patients at an earlier stage of disease when compared to older studies using the Poser's criteria [1]. This skews the overall outcome towards better results when considering progression from onset or from diagnosis.

Definitions and estimates of BMS frequency vary considerably.

Whether benign MS (BMS) really exists, has even become a matter of debate [2,3]. Because MS patients with a benign disease course are not in need of aggressive treatments, adequate recognition is clinically meaningful.

The aim of this review is to summarize data on BMS and evaluate its definitions, prevalence and predictors in clinical practice.

## 2. Methods

English language articles and reviews from November 1980 to December 2015 were identified through searching the PubMed, Web of Science and the Cochrane Library databases with queries: "*benign multiple sclerosis*" AND ("*diagnosis*" OR "*imaging*" OR "*prognosis*" OR "*predictive*" OR "*natural history*"). Based on the reference lists, a further search was undertaken. Using the inclusion criteria proposed by Langer-Gould [4], we only considered articles that (1) defined a BMS

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phenotype, (2) included at least 40 MS patients in total or 15 patients per group for cross-sectional studies, (3) contained enough relevant data to ascertain the level of possible bias and (4) reported at least 5 years of longitudinal follow-up for 80% of the studied population for cohort studies.

The qualification of evidence scheme for prognostic accuracy developed by the American Academy of Neurology [5] was used to assess the methodological quality of studies. We considered relevant clinical questions and analysed the strength of evidence for a number of statements, using previously published criteria [6]. Well-conducted systematic reviews were considered to have a high level of evidence. To avoid duplication and reduce bias, we included these results and not those of the original studies [7]. When a predictor was studied at several occasions in the same population, we used the most recent publication for this predictor. The risk of bias was judged for each statement. Two reviewers independently assessed the identified articles. Consensus was achieved in case of disagreement.

### 3. Results

#### 3.1. Study selection

The PubMed/Medline search yielded 59 eligible articles. 42 were excluded because they did not correspond to the inclusion criteria. In the Web of Science database, we extracted another 4 articles of 40 entries. No new entries were found in the Cochrane Library. Based on the reference lists, 23 more papers were included, resulting in 44 articles.

After correcting for double or outdated data, 29 articles were used: 10 papers on 8 *population-based studies* [1,8–16], 16 papers on 12 *clinical cohort* [17–27], 5 *cross-sectional studies* [28–32], 1 *review* [33] and 2 *systematic reviews* [4,34]. Details are shown in Table 1.

#### 3.2. Definitions

Since its first mention in medical literature, no strong consensus has been reached in criteria that define BMS [12]. Most definitions are based on the Expanded Disability Status Scale (EDSS), which is non-linear and heavily weighted towards physical disability [11]. Having EDSS or less at a disease duration of 10, 15 or more years is used to classify those MS patients who seem to have a less severe disease course. No definition addressed the issue of previous or current treatment, nor excluded patients under immunomodulating treatment. The oldest definitions of BMS by McAlpine and Bauer included the ability to remain active or employed after 10 or 20 years of disease as the only criterion [35,36].

#### 3.3. Prevalence

A systematic review on population, community and hospital-based BMS cohorts, estimated a prevalence ranging from 6% to 64% of the total MS population [34,37], illustrating the large variability in BMS definitions and methodology in these studies. Part of this variation could also be explained by geographical differences.

Table 2 summarizes prevalence data in population-based longitudinal cohorts. Between 30 and 80% of studied RRMS patients were reported to have EDSS < 3 or 4 after a disease duration of 10 years or more, as opposed to 9 to 20% in PPMS and 10 to 36.2% in mixed MS populations. Non-population-based prevalence ranges from 0 to 70% and is less contributory because of selection bias in clinic-based populations (*online only*) [14,15,17,18,20,22–26]. Between 34 and 74% of RRMS patients have EDSS ≤ 3 or 4 after a disease duration of 10 years, as opposed to 0–14% of PPMS patients.

#### 3.4. Clinical characteristics

Based on cross-sectional and clinic-based studies, patients with EDSS-based definitions of BMS may have mental symptoms and cognitive impairment [21,29,30,38]. While common MS symptoms such as fatigue, anxiety and depression often impact daily functions but do not change EDSS [12]. Cognitive difficulties can be considered in specific functional systems of the EDSS (cerebral or mental), grading possibilities are limited and subjective.

Among BMS patients, better scores for patient reported outcomes on quality of life (QoL), fatigue and depression have been reported in patients with lower disability (EDSS ≤ 1.5) when compared with higher disability (EDSS ≤ 3) [30,38]. Even though BMS patients have slightly better scores for quality of life and patient reported outcomes than non-BMS patients, they still score worse than healthy controls [28,30]. Up to one half of BMS patients (EDSS ≤ 3.0 after ≥ 10 years) may suffer from fatigue, depression or cognitive impairment when asked [29].

#### 3.5. Demographic and clinical predictors of BMS

Six publications focused on predictors of BMS: 2 population-based studies [11,12], 3 clinical cohorts [16,19,20] and 1 systematic review [34] (Table 3).

##### 3.5.1. Clinical phenotype at onset

A progressive disease course from onset is a strong predictor of future disability (Table 3; not corrected for EDSS at onset). BMS usually presents as a relapsing-remitting phenotype [11], but has occasionally been described in PPMS [9,20]. Because PPMS is often diagnosed *after* significant irreversible disability has developed, selection bias cannot fully be excluded. Within 20 years of disease duration, no BMS cases (EDSS ≤ 3 after 10 year) with a PP course were found [8,20].

##### 3.5.2. Relapse phenotype and frequency

There is inconclusive evidence on the predictive effect of the relapse phenotype (i.e. sensory, motor, cerebellar, etc.) at onset on having BMS (EDSS ≤ 3 after 10 years) (Table 3). The *Groningen* study group found that having mono-regional versus poly-regional onset symptoms is not independently predictive for BMS in RRMS patients [20]. Having only 1 relapse in the first 5 years after MS diagnosis increases the probability of having BMS [34].

##### 3.5.3. Age at onset and gender

We did not find conclusive evidence for an effect of age at onset on the probability of having BMS (Table 3) [16,20,34], or staying benign after a disease duration of 20 years [12]. Similarly, gender does not appear to be an independent predictor of BMS in multivariate analyses (Table 3), correlating with age at onset, phenotype at onset and relapse phenotype [12,16,20,34].

##### 3.5.4. Early disability scores and prognosis

The *Olmsted County* population-based cohort study with a follow-up of 20 years showed that having an EDSS of ≤ 2 after 10 years was predictive for the disease course in the following 10 years (7% chance of developing significant disability) [11]. In the *British Columbia* cohort, about half of BMS patients (EDSS ≤ 3 at 10 years) did not surpass the limit of EDSS 3 after another decade, and two thirds of BMS patients with EDSS ≤ 2 at 10 years were still considered benign after 20 years of disease duration [12]. In *Iceland*, the proportion of BMS patients declined from 91% at 10 years to 69% at 20 years from disease onset in the RRMS onset group [8]. Whether the EDSS score increased due to relapses or progression was not specified. Longitudinal data is shown in Table 4.

**Table 1**  
Characteristics of articles included in this review.

| N    | Author; year; research group             | Cohort size; cohort type                         | MS phenotypes (number of patients)   | Diagnostic criteria | Proportion treated with DMT | Duration of follow-up                        | Proportion censored | Quality assessment |
|------|--|--|--|---------------------|-----------------------------|--|---------------------|--------------------|
| [1]  | Tedeholm; 2015; <i>Gothenburg</i>        | 298; population-based; retrospective-prospective | RR-SPMS (71.1%), CIS (14.1%), PPMS (14.8%)                                       | Poser               | 0%                          | 1950–2012<br>1964–2012                       | 11.4%               | Class I            |
| [8]  | Benedikz; 2002; <i>Iceland</i>           | 372; population-based; prospective               | RRMS (75.3%), PPMS (24.7%)   | Poser               | 0%                          | 1950–1999                                    | 0%                  | Class II           |
| [13] | Skoog; 2012; <i>Gothenburg</i>           | 255; population-based; prospective               | RRMS (79.2%), PPMS (17.3%), Undefined (3.5%)                                     | Poser               | 0%                          | 1950–2010                                    | 10.6%               | Class II           |
| [11] | Pittock; 2004; <i>Olmsted County</i>     | 49; population-based; retrospective-prospective  | RRMS (100%)  | Not mentioned       | 0%                          | 1991–2001                                    | 0%                  | Class II           |
| [12] | Sayao; 2007; <i>British Columbia</i>     | 200; population-based; retrospective-prospective | RRMS (98%), PPMS (2%)  | Poser               | 23%                         | 1978–2006                                    | 5.5%                | Class II           |
| [10] | Phadke; 1990; <i>Scotland</i>            | 1055; population-based; retrospective            | Relapsing onset (91%), Progressive onset (9%)                                    | Poser               | 0%                          | 1970–1981                                    | NA                  | Class II           |
| [9]  | Koch; 2009; <i>British Columbia</i>      | 424; population-based; retrospective             | PPMS (100%)  | Poser               | 1.9%                        | 1980–2003                                    | NA                  | Class II           |
| [15] | Weinshenker; 1989; <i>London Ontario</i> | 1099; mostly population-based; prospective       | RRMS (65.8%), PRMS (14.8%), PPMS (18.7%), Undefined (0.9%)                       | Poser               | 0%                          | 1972–1984                                    | 6.6%                | Class III          |
| [16] | Glad; 2009; <i>Hordaland County</i>      | 230; population-based; retrospective-prospective | RRMS (80.4%), PPMS (19.6%)   | McDonald            | 16.5%                       | 1976–1995<br>1976–2003                       | 0%                  | Class III          |
| [14] | Hirst; 2008; <i>UK</i>                   | 379; population-based; retrospective             | Not mentioned  | Poser               | 0.3%                        | 1985, up to 20 years follow-up               | 2.4%                | Class III          |
| [27] | Calabrese; 2013; <i>Italy</i>            | 140; clinical cohort; prospective                | BMS <sup>a</sup> (32.1%), non-benign RRMS (67.9%)                                | Not mentioned       | Not mentioned               | 2005–2012                                    | 0.7%                | Class II           |
| [20] | Ramsaransing; 2007; <i>Groningen</i>     | 496; clinical cohort; retrospective-prospective  | RRMS (72.4%), PPMS (27.6%)   | Poser               | 19.4%                       | 1985–2005                                    | 89.5%               | Class II           |
| [24] | Amato; 2000; <i>Italy</i>                | 224; clinical cohort; prospective                | RRMS (85.3%), PPMS (14.7%)   | Poser               | Not mentioned               | 1983–1990                                    | Not mentioned       | Class III          |
| [21] | Portaccio; 2009; <i>Italy</i>            | 63; clinical cohort; prospective                 | BMS <sup>a</sup> (100%)  | Poser               | 30%                         | 5 years                                      | Not mentioned       | Class III          |
| [22] | Trojano; 1995; <i>Italy</i>              | 309; clinical cohort; retrospective-prospective  | RRMS (58.3%), PRMS (22.3%), PPMS (19.4%)   | Poser               | Not mentioned               | 1976–1991                                    | NA                  | Class III          |
| [26] | Kantarci; 1998; <i>Turkey</i>            | 1259; clinical cohort; retrospective-prospective | RRMS (62%), SPMS (12.2%), PPMS (25.8%)   | Poser               | 9.5%                        | 1994–1997                                    | 74%                 | Class III          |
| [25] | Hawkins; 1999; <i>Northern Ireland</i>   | 181; clinical cohort; retrospective-prospective  | BMS <sup>b</sup> (19.9%), RRMS (72.4%), PPMS (7.7%)                              | Poser               | Not mentioned               | 1987–1996                                    | 61.3%               | Class III          |
| [17] | Leray; 2012; <i>Rennes</i>               | 874; clinical cohort; retrospective-prospective  | BMS (73.9%, 57.7%), RRMS (26.1%)   | Poser               | 8.4–15.4%                   | ≥ 20 years<br>≥ 30 years                     | 61%<br>86.4%        | Class III          |
| [23] | Moreira; 2000; <i>Brazil</i>             | 302; clinical cohort; retrospective              | Relapsing onset (72.8%), Progressive onset (27.2%)                               | Poser               | Not mentioned               | 1980–1997                                    | NA                  | Class III          |
| [18] | Confavreux; 2003; <i>Lyon</i>            | 1844; clinical cohort; retrospective             | RR-SPMS (84.7%), PPMS (15.3%)  | Poser               | 49%                         | 1957–1997                                    | NA                  | Class III          |
| [19] | Mandrioli; 2008; <i>Italy</i>            | 64; clinical cohort; retrospective               | BMS <sup>b</sup> (59.4%), non-benign RRMS (40.6%)                                | Poser               | 70.3%                       | 2003–2004 with ≥ 10 years retrospective data | NA                  | Class III          |
| [31] | Rovaris; 2011; <i>Italy</i>              | 369; cross-sectional; retrospective-prospective  | BMS <sup>a</sup> (49.3%), RRMS (50.7%)   | McDonald            | 41.7%                       | 7–104 months                                 | 20.9%               | Class II           |
| [28] | Bueno; 2015; <i>British Columbia</i>     | 61; cross-sectional; prospective                 | BMS <sup>c</sup> (100%)  | Poser               | 36.1%                       | 1978–2010                                    | 34.4%               | Class III          |
| [29] | Amato; 2006; <i>Italy</i>                | 163; cross-sectional; NA                         | BMS <sup>a</sup> (100%)  | Not mentioned       | 57%                         | 2002–2004                                    | NA                  | Class III          |
| [30] | Hviid; 2011; <i>USA</i>                  | 1265; cross-sectional; NA                        | BMS <sup>a</sup> (14.6%), early RRMS (16.7%), late RRMS (4.6%), low EDSS (64.1%) | McDonald            | Not mentioned               | 2000–2009                                    | NA                  | Class III          |

(continued on next page)

Table 1 (continued)

| N    | Author; year; research group     | Cohort size; cohort type  | MS phenotypes (number of patients)                 | Diagnostic criteria | Proportion treated with DMT | Duration of follow-up | Proportion censored | Quality assessment |
|------|----------------------------------|---|--|---------------------|-----------------------------|-----------------------|---------------------|--------------------|
| [32] | Calabrese; 2009; Italy           | 144; cross-sectional; NA  | BMS <sup>a</sup> (33.3%), early RRMS (66.7%)       | Poser               | 77.1%                       | 2005–2006             | NA                  | Class III          |
| [33] | Tremlett; 2010; British Columbia | Review: 10,298 population and clinic-based  | Relapsing onset (85.6%), Progressive onset (14.4%) | Poser               | Not mentioned               | 11–20.1 years         | Not mentioned       | Class II           |
| [34] | Ramsaransing; 2001; Groningen    | Systematic review: 2204 population and clinic-based                                     | BMS <sup>b</sup> (26.7%), non-benign MS (73.3%)    | Poser               | Not mentioned               | 1961–1999             | NA                  | Class II           |
| [4]  | Langer-Gould; 2006; Stanford     | Systematic review: 475 population-based, 384 non-population-based, 7767 cross-sectional | Relapsing onset (86.4%), Progressive onset (13.6%) | Poser and McDonald  | Not mentioned               | 1950–1997             | NA                  | Class II           |

BMS: benign multiple sclerosis, defined as MS with <sup>a</sup> EDSS ≤ 3 and a disease duration of ≥ 15 years (<sup>b</sup> ≥ 10 years, <sup>c</sup> ≥ 20 years), or <sup>d</sup> DSS ≤ 3 (<sup>e</sup> ≤ 2) ≥ 10 years from onset.

CIS: clinically isolated syndrome.

DMT: disease modifying treatment.

EDSS: expanded disease status scale.

NA: not applicable.

PPMS: primary progressive multiple sclerosis.

PRMS: progressive relapsing multiple sclerosis.

RRMS: relapsing-remitting multiple sclerosis.

SPMS: secondary progressive multiple sclerosis.

### 3.6. Prognostic MRI measures in BMS

While there is a substantial amount of descriptive MRI data, evidence on the prognostic value for BMS is scarce. Most originate from cross-sectional studies.

In a retrospective, multicentre BMS and RRMS cohort, a high T2 brain lesion volume was associated with worsened locomotor disability at short-term (median follow-up of 29 months) [31]. The number of T1 brain lesions in BMS patients (EDSS ≤ 3 after ≥ 15 years) was found to predict having EDSS ≤ 3.5 after another 5 years (hazards ratio 1.3) [21].

Two clinic-based MRI studies compared cortical lesions in a shared cohort of 48 BMS (EDSS ≤ 3 after ≥ 15 years, 50% treated) to 96 early RRMS patients (EDSS ≤ 3 at ≥ 5 years, 95% treated) [27,32]. A low number of intra-cortical lesions, cortical lesion volume at baseline, cortical lesion volume change over 6 years and higher cortical thickness of selected gyri appeared to be independent predictors of BMS (cross-validated) [27].

While we found many studies on MRI spectroscopy, magnetization transfer ratio histogram analysis and atrophy rate in MS and their correlation with disease activity, disability and cognition, none of these studies were aimed at predicting BMS.

## 4. Discussion

BMS is a challenging concept. Based on our systematic review of 29 articles, using stringent criteria, a substantial proportion of *untreated* patients with RRMS appear to have a mild disease course over the first 10 to 20 years of the disease. Most study groups use EDSS 3 or lower at a disease duration of 10, 15 or more years to classify those MS patients who seem to have BMS. While not protecting against disease progression at a later stage, current EDSS-based BMS definitions have some predictive value for future disability.

However, the EDSS scale is skewed towards ambulation and underestimates the impact of less visible symptoms such as fatigue and

Table 2

Chronological view of BMS prevalence estimations, based on EDSS definitions in population-based cohorts.

| Study group           | Time frame for inclusion (follow-up) | Population size | MS phenotype (number of patients)                    | Definition           | BMS prevalence                               |
|-----------------------|--------------------------------------|-----------------|--|----------------------|--|
| Iceland [8]           | 1950–1999 (up to 50 years)           | 372             | RRMS/SPMS (n = 280), PPMS/PRMS (n = 92) (Poser)      | EDSS < 4 at 15 years | 80% relapsing onset<br>20% progressive onset |
| Scotland [10]         | 1970, 1981, 1987 (up to 60 years)    | 1055            | Relapsing onset (n = 960) Progressive onset (n = 95) | EDSS < 3 at 10 years | 26%<br>5%                                    |
| British Colombia [9]  | 1980–2003 (up to 23 years)           | 552             | PPMS (Poser)   | EDSS ≤ 3 at 10 years | 9%   |
| UK [14]               | 1985 (up to 20 years)                | 379             | Definite of probable MS (Poser)                      | EDSS ≤ 4 at 10 years | 22.1%  |
| Olmsted County [11]   | 1991–2001 (up to 20 years)           | 162             | RRMS   | EDSS ≤ 4 at 10 years | 30.25%                                       |
| Hordaland County [16] | 1976–1986 (up to 27 years)           | 230             | RRMS (n = 185)<br>PPMS (n = 45)<br>(McDonald)        | EDSS ≤ 3 at 10 years | 1995: 37.6%<br>2003: 24.2%                   |

BMS: benign multiple sclerosis.

EDSS: expanded disease status scale.

RRMS: relapsing-remitting multiple sclerosis.

SPMS: secondary progressive multiple sclerosis.

PPMS: primary progressive multiple sclerosis.

PRMS: progressive relapsing multiple sclerosis.

**Table 3**  
Demographic and clinical predictors in BMS (EDSS ≤ 3 after 10 years).

| Variable                              | Statement  | Rating of studies   | Evidence classification  |
|---------------------------------------|--|---|--|
| Disease phenotype at onset            | A <i>relapsing</i> phenotype at onset increases the probability of having BMS by roughly threefold [20].   | <u>Confirmed</u> : 2 high quality [20,12], 1 low quality [16]   | <b>Strong evidence</b> that a relapsing phenotype at onset increases the probability of having BMS |
| Age at onset in RRMS                  | Younger onset age increases the probability of having BMS, when compared to an older age at onset.   | <u>Confirmed</u> : 1 systematic review [34], 1 low quality [16]<br><u>Not confirmed</u> in multivariate analysis of 1 high quality [20]   | <b>Inconclusive evidence</b>   |
| Gender in RRMS                        | Female gender increases the probability of having BMS, when compared to male gender.   | <u>Not confirmed</u> : 1 systematic review [34], 2 high quality [20,12], 1 low quality [16]   | <b>Strong evidence</b> that gender has <i>no</i> predictive effect for BMS in RRMS patients        |
| Relapse phenotype at onset in RRMS    | Onset with <i>afferent</i> symptoms increases the probability of having BMS, while onset with <i>efferent</i> symptoms decreases this probability in RRMS. | <u>Both confirmed</u> : 1 systematic review [34]<br><u>Motor symptoms confirmed</u> : 1 high quality [11]<br><u>Both not confirmed</u> : 2 high quality [20,12], 1 low quality [16]<br><u>Afferent not confirmed</u> : 1 low quality [19] | <b>Inconclusive evidence</b>   |
| Early relapse rate                    | Having only 1 relapse in the <i>first 5 years</i> increases the probability of having BMS.   | <u>Confirmed</u> : 1 systematic review [34], 1 high quality [20]  | <b>Strong evidence</b>   |
| EDSS at 5–10 years from onset in RRMS | EDSS ≤ 2 at 5 years or EDSS ≤ 3 at 10 years increases the probability of still having EDSS ≤ 3–4 after another 10 years.                                   | <u>Confirmed</u> : 3 high quality [11,20,12]  | <b>Strong evidence</b>   |

Bold and underlined words signifies aesthetics.

BMS: benign multiple sclerosis.

RRMS: relapsing-remitting multiple sclerosis.

PPMS: primary progressive multiple sclerosis.

EDSS: expanded disease status scale.

cognitive impairment. Assessment of these symptoms is not routinely integrated in clinical practice, even though they have been associated with immune-related processes [39] and brain atrophy [38], respectively. The fact that disease activity in MS may be hidden, adds to the controversy surrounding BMS. The same holds true for current defini-

tions of the “no evidence of disease activity” status, as more than half of the treated RRMS patients who receive this status showed cognitive worsening [40].

While not all population-based studies included BMS as a separate entity and some BMS patients may not seek medical attention, the

**Table 4**  
Proportion of BMS patients that stay benign at different follow-up intervals.

| Population (number of BMS at start of follow-up) | 18 years since MS diagnosis (BMS/still in follow-up) | 20 years since MS diagnosis (BMS/still in follow-up) | 30 years since MS diagnosis (BMS/still in follow-up) | 50 years since MS diagnosis (BMS/still in follow-up) |
|--|--|--|--|--|
| <i>Iceland</i> [8] <sup>a</sup>                  |  |  |  |  |
| Relapsing onset (n = 218)                        |  | 81% (86/165)   | 69% (56/81)  |  |
| Progressive onset (n = 72)                       |  | 16% (9/58)   | 0% (0/27)  |  |
| <i>Olmsted County</i> [11] <sup>b</sup>          |  |  |  |  |
| RRMS (n = 49)                                    |  | 72.3% (34/47)  |  |  |
| <i>British Colombia</i> [12] I                   |  |  |  |  |
| BMS <sup>a</sup> (n = 200), of which:            |  | 52.1% (88/169)                                       |  |  |
| Relapsing onset (n = 196)                        |  | (all relapsing onset)                                |  |  |
| Progressive onset (n = 4)                        |  |  |  |  |
| <i>Groningen</i> [20] H                          |  |  |  |  |
| BMS <sup>a</sup> (n = 151), of which:            |  | 69% (35/51)  | 22.9% (8/35)   |  |
| Relapsing onset (n = 142)                        |  |  | (all relapsing onset)                                |  |
| Progressive onset (n = 9)                        |  |  |  |  |
| <i>Norway</i> [16] HH                            |  |  |  |  |
| BMS <sup>a</sup> (n = 86)                        | 65.1% (56/86)  |  |  |  |
| <i>Italy</i> [21] HHH                            |  |  |  |  |
| BMS <sup>c,d</sup> (n = 63)                      |  | 68.3% (43/63)  |  |  |
| <i>Gothenborg</i>                                |  |  |  |  |
| RRMS (n = 202) [13] <sup>a</sup>                 |  |  |  | 5.4% (11/202)  |
| PPMS (n = 44) [1] <sup>a</sup>                   |  |  |  | 0% (0/44)  |

BMS: benign multiple sclerosis, defined by <sup>a</sup> (EDSS ≤ 3) or <sup>b</sup> (EDSS ≤ 4) at ≥ 10 years disease duration, or <sup>c</sup> (EDSS ≤ 3) or <sup>d</sup> (EDSS ≤ 3.5) at ≥ 15 years disease duration.

RRMS: relapsing-remitting multiple sclerosis.

PPMS: primary progressive multiple sclerosis.

I 23% treated by an immunomodulatory drug (43/46 after diagnosis of BMS). Results for the untreated population were “in the same direction as for the main analysis”. Data not specified.

H 14.5% was ever treated by Interferon beta. Data not specified.

HH Unclear whether participants are treatment naïve.

HHH 31.7% treated by an immunomodulatory drug at start of follow-up, 32.6% of those that stayed BMS.

estimated prevalence ranges from 30 to 80% when considering RRMS patients who have EDSS < 3 or 4 at 10 years or more after onset. About half on them maintains this status up to 20 years, suggesting up to one third of MS patients maintains EDSS < 4 over several decades [8–11,15,16]. Recent prevalence data on BMS are lacking. However, based on the progressively lengthening time from diagnosis to EDSS 6 [33], the recognition of milder cases using the new McDonald criteria and changing temporal trends, there is no evidence to suggest that the incidence of BMS may be decreasing.

The treatment era has changed our view on MS. The variable length of the interval to (E)DSS 3 in RRMS, as shown in Leray's Figure 1 [41], is often presented as the therapeutic window to delay the onset of secondary progression and to motivate early and aggressive treatment. After having reached the first disability milestone, the second phase of DSS progression appears to run in parallel over the whole population, and demographics and initial disease characteristics no longer seem to affect disability progression [41]. A longlasting first phase (up to several decades) may correspond to BMS. Similar to RRMS being followed by SPMS, this does not entirely protect against future disability progression.

Ideally, predictors should enable us to distinguish those patients who may be in need of early and aggressive treatment from those who are not. This is not the case for BMS. Nevertheless, having a relapsing-remitting onset, only one relapse in the first five years and an EDSS of 2 or less at 5 years or EDSS of 3 or less at 10 years of disease duration are strong predictors for having BMS and remaining BMS for another 10 years. The age at onset appears not to be an independent predictor, which could be explained by recall bias, the difficulties in assessing the true onset of disease, methodological issues and the relatively low number of included studies. Similarly, there is no evidence for gender to independently predict BMS [12,16,20,34] in multivariate analysis [16,20]. In view of the strong effect of age at onset and gender on the clinical phenotype and probability of disease progression [42], we assume that both age at onset and gender are interacting with the clinical disease phenotype [1]. While a younger age at onset is often reported as indicative of a better prognosis, these patients reach ambulatory landmarks at a younger age when compared to patients older at onset [43].

We found only limited data on early MRI predictors, probably because of our stringent inclusion criteria. Most MRI studies on BMS were either cross-sectional, had a short duration or small sample sizes. Prognostic properties of advanced and quantified MRI measures are promising, but currently insufficient on an individual level.

Our review has the strength of focusing on BMS, using predefined criteria for inclusion and quality assessments [4–6]. However, a direct comparison between published studies and cohorts was not possible. We were not able to control for systematic methodological differences between studies. Also, the low number of natural history studies and population-based cohorts with a defined BMS subpopulation may have limited the validity of our findings. Furthermore, most studies contain a certain degree of treated MS patients, making it difficult to attribute conclusions to a benign disease course or treatment response. Solely selecting untreated MS patients could result in small population sizes and possibly a selection bias, as not all BMS patients seek medical attention. Finally, the potential contribution of lifestyle and environmental factors has not been taken into account in these studies. There is increasing evidence that these factors contribute to the risk and course of MS [44].

As neurological disability appears to evolve more slowly than estimated from older natural history cohorts [33,45,46], further prospective, long-term studies are needed to find valid predictors of the long-term disease course in MS. In addition to demographics, clinical and MRI characteristics, we propose to include neuropsychological assessments and to investigate the contributory role of lifestyle and environmental factors. Considering the age at early disability milestones may provide more useful information than the time from disease

onset to these milestones. The recently developed age-related MS Severity Score may be a good start to measure the relative severity of disability [39]. The ideal study population may consist of patients with a clinically isolated syndrome (CIS), which are not necessarily treated from the start. Finding predictors of BMS in those patients who eventually develop multiple sclerosis may be the mission [47]. Searching for predictors that delay the onset of secondary progression in treated and untreated RRMS patients may be an even greater challenge.

## 5. Conclusion

Benign multiple sclerosis appears to correspond to mild RRMS in the first decades and is part of the whole spectrum of MS. In view of the potential burden of less visible symptoms, the limited predictability and uncertain contribution of age-related and lifestyle factors, further prospective studies are needed to increase our understanding of this entity. This area of research is challenging as recent temporal trends suggest a more slowly evolving neurological disability over time. We propose to extend BMS prediction studies to CIS patients in order to find earlier and more accurate predictors.

## Conflicts of interest

None.

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No conflicts of interest are to be declared for any of the authors.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ensci.2017.05.002>.

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