eNeurologicalSci 7 (2017) 37–43

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: www.elsevier.com/locate/ensci

Review article

Definition, prevalence and predictive factors of benign multiple sclerosis

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ARTICLE INFO

Keywords:
Benign multiple sclerosis
Prediction
Demographic
Clinic
Imaging

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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http://dx.doi.org/10.1016/j.ensci.2017.05.002
Received 23 January 2017; Accepted 12 May 2017
Available online 13 May 2017

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 Disease 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 Colombia* 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.