Truly benign multiple sclerosis is rare: let’s stop fooling ourselves—Yes

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Multiple sclerosis (MS) affects young adults during the most productive period of life. The disease course is highly heterogeneous and includes a subgroup of patients who show little or no disease progression and minimal disability decades after the clinical onset, the so-called benign MS (BMS). In a 1996 consensus meeting, BMS was defined as a ‘disease in which the patient remains fully functional in all neurological systems 15 years after disease onset’. However, in the literature, the definition of BMS has been mainly focused on the preservation of motor abilities of the patients, usually relying on the Expanded Disability Status Scale (EDSS) that is particularly influenced by ambulation and lacks sufficient association with important manifestations of MS, such as inability to perform daily living activities, reduction in quality of life, loss of gainful employment, hopelessness and cognitive dysfunction. Recently, BMS has been defined as an EDSS score <2.0 after a disease duration of at least 10 years. Over the past few years, BMS has been studied more systematically due to the current trend to treat patients early with disease-modifying therapies which would largely be unnecessary for benign patients. Recent research findings lead us to reconsider both the definition criteria and the frequency of truly BMS.

BMS frequency has been overestimated

In the literature, the estimated frequency of BMS varies from 6% to 64% of the whole MS population. The two main factors accounting for this variability of estimates are differences in definition criteria and duration of the follow up. Indeed, when stringent criteria are used and observation is prolonged over time, the prevalence of BMS declines substantially both in population-based and clinic-based studies. In a Canadian study that defined BMS as an EDSS ≤3.0 after at least 10 years, 169 BMS patients (representing approximately the 15% of the whole cohort of MS patients diagnosed between 1978 and 1984) were followed up for 20 years. Nearly 50% of these BMS subjects progressed to ‘no longer benign status’ by 20 years of observation, with more than 21% becoming severely disabled (EDSS ≥6.0). This would result in a prevalence of BMS of nearly 7–8% after 20 years, using traditional criteria of definition that only rely on motor functioning. BMS therefore appears to represent just a temporary descriptor of the disease status rather than a permanent condition.

Over the past few years, the results of accurate neuropsychological assessment associated with quantitative MR metrics have contributed to reshaping the definition of truly BMS.

In a study on 163 BMS subjects, significant cognitive disability was found in about 45% of patients fulfilling traditional criteria for BMS (disease duration ≥15 years, EDSS ≤3.0). Depression and fatigue were also detected in a sizeable proportion of the patients. Results were confirmed in a subgroup analysis using a more stringent EDSS cut-off score of 2.0 or less. In this sample of ‘pseudo-benign’ subjects, cognitive dysfunction negatively affected everyday activities, work and social life, despite complete preservation of motor functioning. Limitations of classifications based on the EDSS have been recognized in an experts’ consensus that has highlighted the need to include cognitive assessment in the modern definition of BMS.

Benign MS can only be defined ‘a posteriori’

Even if truly BMS exists in a strict minority of patients, who exhibit substantial motor and cognitive preservation decades after the clinical onset of the disease, we are left with the practical problem of how to accurately identify these subjects in the early stages of the disease, when faced with prognostic prediction and therapeutic decision-making.

In fact, extensive searches dealing with clinical, laboratory and genetic features have produced no single reliable prognostic marker that enables clinicians to predict the disease course in the individual patient with sufficient accuracy.

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Over the past decade considerable effort has been dedicated to better characterizing BMS through MRI studies. While using conventional MRI techniques lesion loads in BMS can be similar to those measured in secondary progressive (SPMS), a few studies using newer quantitative techniques have highlighted differences that point to lesser degree of tissue damage and/or higher reparatory and compensatory abilities in BMS compared with other disease subtypes. Sparing of brainstem and spinal cord, less pronounced cortical changes, changes within the lesions and in ‘normal appearing brain tissue’ detected through magnetization transfer, diffusion and spectroscopic MRI have been reported in BMS.

A more accurate classification of the BMS population can be achieved by considering both neuropsychological and imaging findings. In particular, cognitive impairment in ‘pseudo-benign’ MS subjects has been related to higher T2 and T1 lesion volumes and higher cortical damage, assessed through atrophy and magnetization transfer measures. Consistent findings were reported in a study using diffusion MRI. Cognitive dysfunction and MRI parameters may also play a prognostic role. In fact, patients who exhibited cognitive impairment and higher T1 lesion loads at baseline assessment had an increased risk of progression over a 5-year follow up. Again, however, these aspects can be identified only after a long-term observation and they do not apply to the early disease stages for prediction of subsequent disease course.

Benign MS in summary: what it was, what it is and what it is not

Previous definitions of BMS were highly influenced by motor abilities and overlooked other important disease aspects, such as neuropsychological dysfunction and quality of life, so that BMS frequency has probably been overestimated in the past.

As a consequence, there is increasing consensus that a modern, more accurate definition of BMS should maintain the present criteria in terms of disease duration (≥15 years) and disability level (EDSS ≤3.0), but also include the absence of cognitive impairment, assessed by proper neuropsychological tools. Using these criteria, BMS defines only a strict minority of patients who are extremely unlikely to be encountered and followed up in everyday clinical practice.

When coupled with the current inability to reliably identify these subjects, the consideration of BMS is useless for patient counselling, prognostic prediction and therapeutic decision-making. The majority of patients with MS will go on to develop significant disability over time. Partially effective disease-modifying drugs are available that are more useful in the early stages of the disease; the logical consequence is to carefully consider offering therapy to every patient with MS.

Ultimately, BMS should be regarded as a rare condition that represents an intriguing model for the investigation of disease heterogeneity and the physiopathology of brain tissue damage and repair.

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