MRI features of benign multiple sclerosis: Toward a new definition of this disease phenotype

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ABSTRACT
It is well known that the current classification of patients with benign multiple sclerosis (BMS), i.e., those with absent or minimal locomotor disability several years after disease onset, suffers from not having any prognostic value for the subsequent evolution of multiple sclerosis (MS). The identification of markers predictive of the longer-term course of MS will help define BMS more reliably and would allow better counseling of patients, particularly when advising on the initiation of a disease-modifying treatment. MRI-based evidence suggests that there are three potential, but not mutually exclusive, explanations for the scarce clinical impact of BMS: 1) the paucity of tissue damage within and outside MS lesions; 2) the relative sparing of clinically eloquent regions; and 3) the presence of effective compensatory mechanisms. In addition, the results of correlative MRI/neuropsychology studies underpin the need for a new definition of BMS, which should consider the maintenance of a normal cognitive profile as an additional criterion. Neurology® 2009;72:1693-1701

GLOSSARY
BMS = benign multiple sclerosis; CIS = clinically isolated syndromes; EDSS = Expanded Disability Status Scale; fMRI = functional MRI; Gd = gadolinium; GM = gray matter; ICL = intracortical lesions; MR = magnetic resonance; MS = multiple sclerosis; MT = magnetization transfer; MTR = magnetization transfer ratio; NAA = N-acetylaspartate; NAWM = normal-appearing white matter; RR = relapsing-remitting; RT = relaxation time; SP = secondary progressive; TD = triple-dose.

Multiple sclerosis (MS) is characterized by the occurrence of CNS damage, which is secondary to both inflammatory and neurodegenerative mechanisms.1 A hallmark of MS is the wide intrapatient and interpatient variability of its clinical manifestations. It is recognized that the disease can follow a benign clinical course, which is currently defined as a condition “in which the patient remains fully functional in all neurologic systems 15 years after disease onset.”2 At present, the diagnosis of benign MS (BMS), which is based upon the duration of the disease and the Expanded Disability Status Scale (EDSS) score,3 can only be made retrospectively. Thus, BMS is merely reflecting a (seemingly) low level of (motor) disability observed several years after the clinical onset, but which does not necessarily predict the patient’s subsequent evolution. Also, as of yet it is a purely clinical statement. Furthermore, although numerous clinical features have been proposed as possible prognostic factors for a benign course of MS,4-6 follow-up studies of BMS cohorts have shown that a significant proportion of these patients can still enter a disabling disease phase beyond the 15-year mark.7-10 Moreover, some degree of cognitive dysfunction can be found in up to 45% of patients with BMS,5,11 indicating that the current EDSS-based definition of this disease phenotype, which considers the absence of locomotor disability as the main index of a preserved function, is likely to underestimate the...
functional impact of the disease in patients thus classified. In a large, hospital-based series of patients with BMS, the presence of cognitive impairment was also associated with higher handicap scale scores, thus suggesting that these subjects, albeit fully ambulatory, do have considerable disease-related psychosocial problems. Considering these limitations, the identification of markers associated with a persisting or long-lasting benign course of MS, which may lead to a more reliable definition of BMS, would be very useful for counseling these patients, particularly when advising on the initiation of a disease-modifying treatment.

BMS can also be considered a useful model to be studied when investigating the mechanisms underlying the accumulation of disability, by means of an improved understanding of the reasons why this does not occur in a minority of patients with MS. MRI remains the most used paraclinical tool to investigate in vivo the pathobiology of MS and to monitor the evolution of the disease. Indeed, several quantitative MRI-derived metrics have shown a significant, moderate relationship with the severity of clinical disability in non-benign MS. This article reports the conclusions of a workshop of the European Network Magnetic Resonance in MS, which was held on May 29, 2008, to critically review the main findings of MRI studies conducted in BMS, with the aims to achieve a better understanding of this condition and to move a first step toward a new definition of BMS. In an attempt to address these two aims, evidence from MRI studies are reviewed under four main headings: focal tissue damage, tissue loss, intrinsic lesion damage and diffuse tissue injury and, finally, cortical reorganization.

FOCAL TISSUE DAMAGE IN BMS: SPARING OF STRATEGIC AREAS AND RELENTLESS ACCRUAL OF LESIONS? At one extreme, focal MS-like lesions in the brain can be an incidental postmortem finding. Such clinically silent MS, which has been found in large autopsy series with a prevalence of 0.1%–0.2%, may be considered a prototype of BMS. Interestingly, in asymptomatic first-degree relatives of patients with MS, the occurrence of brain MRI abnormalities indistinguishable from MS lesions has also been described, thus confirming that focal MS lesions can occur without any clinical manifestation. Furthermore, it is also known that a subsequent evolution to established MS does not happen in all subjects with silent brain lesions which were detected on MRI scans performed for medical events other than an episode of neurologic dysfunction.

In patients with BMS, the average burden of T2-visible lesions in the brain can be similar to that found in patients with relapsing-remitting (RR) MS, defined as those having either a shorter disease duration or a higher EDSS score or both, although patients with BMS with higher lesion volumes seem to have an increased risk of clinical worsening at follow-up. The wide interindividual variability in T2-hyperintense lesion load has been emphasized by a recent description of patients with BMS with very long disease duration (more than 20 years). Studies comparing patients with BMS with those affected by secondary progressive (SP) MS (who also have a long disease duration, but are severely disabled) have shown conflicting results (figure 1). Earlier studies did not find any difference in brain lesion load between these two subgroups, whereas a recent study of specifically selected individuals reported that patients with BMS may have a greater average lesion burden than those with SPMS. Conversely, another recent study reported a higher lesion load in SPMS than in BMS in cohorts of patients who were matched for disease duration.

A possible reason for these conflicting findings may be that lesion location in clinically eloquent CNS regions (e.g., cortex, internal capsule, brainstem, and spinal cord) is more important than their overall extent in determining the severity of neurologic disability in patients with MS. Another complementary explanation may be the difference in lesion load accrual rate over time between patients with BMS and those with other, more disabling disease phenotypes. Such a low accumulation rate of disease burden, possibly associated with different genetic susceptibility or environmental factors, might increase the efficacy of the mechanisms of tissue repair and cortical reorganization which follow MS injury. In patients with BMS, however, the disease might also, by chance, become clinically evident earlier than in other cases, thus leading to an overestimation of its actual duration. Consistent with the first explanation, it has been recently reported that patients with BMS do not differ from patients with RRMS on their average brain T2 lesion load, but have a significantly lower number of intracortical lesions (ICL), and fewer new ICL after 1 year of follow-up. Interestingly, two different studies conducted a decade apart both described a significantly
lower infratentorial lesion volume in BMS compared to SPMS.18,27 The presence and features of spinal cord lesions were also compared in patients with BMS and SPMS. The frequency and average size of cervical cord lesions were significantly lower in BMS than in SPMS, even though the former sample included patients with a disease duration of 10 years or longer, i.e., not necessarily fulfilling the more restrictive classification criteria used by recent studies. As regards the second explanation, a long-term follow-up study of patients at the onset of MS showed that the trend for lesion burden growth rates over 20 years was higher in patients with SPMS than in those with BMS, and a significant correlation was found between T2 lesion volume increase during the first 5 years after clinical onset and the severity of neurologic impairment at 20 years.24 It is worth noting, however, that in this cohort the prevalence of BMS (39%) was higher than on average.24

A longitudinal, 6-month study with monthly gadolinium (Gd)-enhanced MRI scans showed that the rate of development of new lesions is lower in BMS than in RRMS.29 In a cross-sectional study, triple-dose (TD) Gd-enhanced MRI of the brain revealed enhancing lesions in 50% of patients with BMS vs 35% when using standard-dose scans.30 This may indicate that, in BMS, the amount of inflammation in macroscopic lesions is mild and heterogeneous. The overall frequency of patients with BMS with active TD Gd-enhanced MRI scans remains, however, lower than that reported for patients with RRMS.31,32

Another study investigating the pattern of evolution of newly formed MS lesions after enhancement ceased showed that, in BMS, the frequency of lesions which become black holes is lower than in SPMS.33 This may indicate that the severity of tissue damage within macroscopic lesions is less pronounced in BMS than in the more disabling MS phenotypes, even though (in another study) no difference in the total T1-hypointense brain lesion load was found between patients with BMS and RRMS.17

TISSUE LOSS IN BMS: SPARING OF THE CORTEX AND INFRATENTORIAL STRUCTURES? A significant reduction of brain volume has been described in patients with BMS compared to healthy subjects in some studies,34 but not others.35,36 In addition, the severity of whole brain atrophy was found not to differ between BMS and SPMS,21,37 even though, in one study, infratentorial atrophy was found to be higher in the latter patients compared to those with BMS.22 The hypothesis that the severity of local atrophy in clinically eloquent brain regions may play a central role in differentiating BMS from nonbenign phenotypes has been confirmed by the results of several recent studies.27,35,38,39 The severity of both gray matter (GM)27 and cerebellar tissue27 loss has been found to be significantly greater in patients with SPMS than in BMS, in contrast with similar global and white matter volumes reported by the same studies. The presence of a significant reduction
in thalamic volume when compared to healthy subjects has been described both in BMS and RRMS, although this finding seems to be a typical feature of all patients with MS, thus possibly reflecting the vulnerability of the thalamus to MS damage, due to the presence of focal lesions as well as that of Wallerian and trans-synaptic degeneration of neurons and axons.

Cervical cord size does not seem to be reduced in patients with BMS compared with age-matched controls. Several cross-sectional studies comparing the severity of cervical cord atrophy in patients with BMS and patients with SPMS showed that the average severity of cord atrophy is significantly greater in the latter group and it becomes significantly more pronounced with increasing degrees of neurologic disability. These findings indicate that the absence or mildness of tissue degeneration in the spinal cord may also play a role in determining a favorable clinical evolution of MS.

**INTRINSIC LESION DAMAGE AND DIFFUSE TISSUE INJURY IN BMS: LESS SEVERE?**

Among quantitative MR-based techniques, magnetization transfer (MT) MRI, diffusion MRI, and relaxation time (RT) measurements enable us to quantify the extent of structural changes both in T2-visible MS lesions and in tissue that appears normal on conventional MR images, with improved pathologic specificity (for demyelination and axonal loss). Proton MR spectroscopy (1H-MRS) can add information on the biochemical nature of such changes. Complementary to these techniques, functional MRI (fMRI) holds promise in its ability to elucidate the possible mechanisms of cortical reorganization underlying the ability of the brain to respond to MS injury.

In a cross-sectional study of patients with different MS phenotypes, BMS patients showed brain MT ratio (MTR) histogram characteristics which were comparable to those of healthy subjects and patients with clinically isolated syndromes (CIS), and significantly more preserved than in patients with RRMS. A recent study of patients with BMS and early RRMS also showed significantly less pronounced MTR abnormalities in the former group across T2-visible lesions, normal-appearing white matter (NAWM), and cortical regions. These group differences were still present when patients were selected for having no disability (i.e., EDSS ≤2.0) or, in the case of BMS, disease duration longer than 20 years, as well as when both groups were matched for high T2 lesion load. When compared with healthy subjects, MT features of BMS revealed significant abnormalities only within lesions and in the perilesional white matter, but not in the NAWM and cortex. In contrast to these two studies, other MT investigations of BMS did not find significant differences between patients with BMS and healthy subjects or patients with RRMS. In a longitudinal MT study of patients with BMS, who were followed for at least 1 year, patients with BMS with higher brain lesion volumes at baseline had more frequent relapses and more new T2 lesions during follow-up. In two patients who developed SPMS, new T2 lesions had lower MTR values and the load of black holes was markedly increased at follow-up. This suggests that in a small proportion of patients with BMS the risk of developing SPMS over a short-term period may be associated with multiple factors reflecting more severe lesional tissue damage. Another 1-year follow-up study of patients with different MS phenotypes found no significant changes in lesion load and MTR histogram-derived metrics of the normal-appearing brain tissue from patients with BMS. The magnitude of these changes was significantly more pronounced in RRMS and SPMS than in BMS, indicating that, in the short term, the speed of accrual of normal-appearing brain damage is lower in the latter group.

In a cross-sectional study measuring T2 decay in lesions and NAWM from patients with BMS and SPMS, a higher proportion of large lesions with biexponential T2 relaxation was found in SPMS than in BMS, indicating a greater degree of axonal loss within lesions in the former group. In contrast, two preliminary diffusion MRI studies failed to detect any difference between patients with BMS and patients with SPMS in the diffusivity patterns within and outside T2-visible lesions.

In two cross-sectional 1H-MRS studies of patients with BMS and patients with SPMS, chronic MS lesions from patients with BMS showed higher N-acetylaspartate (NAA) levels than those from patients with SPMS. In contrast with these findings, two studies using single-voxel 1H-MRS and one using whole-brain 1H-MRS did not find differences in brain tissue NAA concentrations between patients with BMS and patients with SPMS or RRMS. The lack of such a clear-cut difference in the NAA profile of BMS and nonbenign MS seems to be confirmed by the results obtained in a large cohort, where patients with BMS with low T2-hyperintense lesion load showed NAA values similar to those of patients with early RRMS and patients with BMS with high lesion load showed NAA values similar to those of patients with SPMS (N. De Stefano, personal communication, 2008).

Most of the studies using MR-derived markers of irreversible myelin and axonal loss seem, therefore, to indicate that tissue damage both within and outside
T2-visible lesions is significantly less severe in BMS than in SPMS or RRMS, and that the structural features of the normal-appearing brain of patients with BMS may not significantly differ from those of healthy subjects nor change significantly after 1 year. Nevertheless, these findings do not fully account for the observed clinical differences between BMS and the other disease phenotypes. Using a voxel-wise approach to analyze diffusion MRI data obtained with a 3.0 T scanner in patients with RRMS and BMS, significant differences in the topographic distribution of white matter damage were found between the two groups (figure 2), even though no significant differences were evident when the overall extent of white matter diffusivity changes was assessed. In a diffusion MRI study of the cervical cord, when compared with healthy subjects, patients with BMS showed significant diffusivity abnormalities of the cervical cord, which were, however, significantly less pronounced than in age-matched patients with SPMS. Two studies conducted with MT and diffusion MRI have shown that the presence and severity of cognitive impairment are associated with increased brain damage in patients with BMS, particularly in the GM. In the second of these studies, the brain diffusivity features of patients with BMS with cognitive impairment did not differ from those of a group of patients with SPMS, whereas those patients with BMS without cognitive impairment had a significantly higher brain volume (i.e., less brain atrophy) and lower GM diffusivity (i.e., less severe GM damage) than those with SPMS. It is worth reminding that, in patients with BMS, the prevalence and pattern of cognitive deficits seem to be comparable to those generally reported for RRMS, with a prominent involvement of attention and frontal lobe functions, as well as to be associated with a higher prevalence of depression than in those patients with BMS with normal cognition. Taken all together, neuropsychological and MRI data seem, therefore, to indicate that the current definition of BMS underestimates the presence of clinically relevant structural brain damage which, in turn, may be associated with cognitive deficits and, therefore, be in contrast with the concept of a nondisabling disease profile.

Overall, these findings confirm that the selective assessment of clinically eloquent CNS regions using quantitative magnetic resonance (MR)-based techniques might be rewarding to investigate the role of regional damage in determining the clinical manifestations of MS. Furthermore, and more importantly, they suggest that the definition of BMS should include a measure of cognitive functioning, since patients with BMS with cognitive impairment do not seem to have the structural MRI features of a benign disease at all.
CORTICAL REORGANIZATION IN BMS: COPING WITH TISSUE INJURY? An additional factor which can explain the conflicting findings obtained by quantitative MR-based studies of BMS is the interindividual variation in brain plasticity. This phenomenon may generate compensatory responses in the cortex, which, in turn, might limit the impact of tissue damage on patients’ functioning. As shown by fMRI studies, the patterns of activation of cortical networks during motor or cognitive tasks vary across different MS phenotypes and are significantly correlated with the severity of tissue damage, as measured by quantitative MRI-derived parameters. Nondisabled patients with RRMS performing a simple motor task showed an increased activation of a widespread sensorimotor network. It is, therefore, conceivable that adaptive responses with a compensatory effect may also occur in patients with BMS and be one of the reasons why these patients have a long-lasting nondisabling disease course. The saturation of this compensatory process may also explain why some patients subsequently develop disability after an initial benign course. In a recent fMRI study conducted in patients with BMS using a cognitive task, the performance did not differ between patients and healthy controls, but the former had more significant activations of several areas of their cognitive network (figure 3), as well as altered connectivity strengths among these areas. Interestingly, the coefficients of altered connectivity were correlated only with the diffusion properties of cognition-related white matter fiber bundles, suggesting that functional cortical changes in BMS might represent an adaptive response driven by damage to specific brain structures. These preliminary data call for further fMRI studies to better understand the pathophysiology of BMS.

DISCUSSION The current definition of BMS suffers from evident limitations, as it is retrospective and based upon a combination of long disease duration.

**Table** Summary findings from MRI-based studies of BMS

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See the text for references and further details.

BMS = benign multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; GM = gray matter.
and absence of locomotor disability. In addition, it does not consider the presence of other clinical features, particularly cognitive dysfunction. All these factors may contribute to the low reliability of such a definition, which has a suboptimal prognostic value for the evolution of BMS over the longer term, and explain, at least partially, the conflicting findings of BMS studies. As a consequence, we believe that a new definition of BMS is needed, which should be validated formally by future investigations. Such a definition will maintain the present requisites in terms of disease duration (15 years or longer) and disability level (EDSS score 3.0 or lower), but it would necessarily include the absence of cognitive impairment, as assessed by a proper neuropsychological evaluation. This statement is supported by the link between cognitive impairment and increased GM damage shown by MT\textsuperscript{58} and diffusion\textsuperscript{66} MRI studies of BMS, although it remains to be ascertained whether the presence of cognitive dysfunction may represent an unfavorable prognostic feature.

The results of MRI studies indicate that while there seem to be no differences between BMS and RRMS in terms of number of T2 lesions, there are in fact differences in many other MRI metrics (table). In this context, it should be noted that the role played by tissue preservation in clinically eloquent CNS regions, such as the cerebellum and the spinal cord, may merely reflect the current definition of BMS, that is weighted toward the absence of significant impairment of locomotion, which is anatomically linked to these structures. Nevertheless, BMS seems to be, on average, characterized by less severe intrinsic lesion disruption and GM involvement than SPMS. The well-known interindividual differences in the MRI profiles in MS might be more pronounced in individuals with a benign course than in other disease phenotypes and account for the variable BMS patients’ prognosis in the long term. In addition, disease duration and age might play an important role in contributing to the accumulation of permanent tissue damage in MS, but the low progression speed of these processes in BMS may increase the effectiveness of compensatory mechanisms or repair. Thus, in patients with BMS, potential, but not mutually exclusive, explanations for the scarce clinical impact of the disease might include the paucity of tissue damage outside and within macroscopic MS lesions, the relative sparing of clinically eloquent CNS regions, and the presence of effective compensatory mechanisms. It is not possible to establish which MRI aspect may have the best combination of sensitivity and specificity to distinguish between patients with BMS and those with other disease phenotypes, since all available evidence derives from group studies conducted with different methodologies and criteria. We believe that these MRI features should not be used as criteria for BMS and, therefore, be fully translated into the management of individual cases, but rather be viewed as potential red flags pointing to a non-BMS diagnosis. Albeit difficult to plan, medium- to long-term prospective MRI studies of large cohorts of patients classified as having BMS, possibly including other potential prognostic markers, are warranted to validate these hypotheses by ascertaining which features may reliably identify those patients who will maintain a nondisabling disease course during a clinically meaningful period of observation.

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