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REVIEW

Benign multiple sclerosis: aspects of cognition and neuroimaging

A esclerose múltipla benigna: aspectos cognitivos e de neuroimagem

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ABSTRACT

The existence of a benign multiple sclerosis (BMS) form is a controversial subject. Recent studies of these patients reveal different levels of cognitive impairment, despite the apparent preservation of motor function. The objective of this study was to review and analyze a number of publications that discuss the general aspects of this disease form, such as the definition criteria, prevalence, and clinical and neuroimaging markers. A systematic review of published data on BMS up to October 2015 was performed. Thirty-one published articles were analyzed. The estimated frequency of BMS varied between 6% and 73%. Cognitive impairment was recognized as affecting 17% to 47% of the subjects and presented significant correlation with neuroimaging, such as brain atrophy, increased lesion volume in T2 magnetic resonance assay, and regional grey matter atrophy. The current criteria overestimated the frequency of BMS and, for that reason, this highlights the importance of validating the diagnostic methods practiced.

Keywords: multiple sclerosis; cognition; neuroimaging.

RESUMO

A existência real de uma forma benigna da esclerose múltipla (EMB) é um tema controverso. Ampliar o número de publicações que abordam os aspectos gerais do subtipo da doença, tais como os critérios de definição utilizados, análise de prevalência e da presença de marcadores clínicos e de neuroimagem. Foi realizada uma revisão sistemática dos dados publicados até outubro de 2015, relativa à EMB. Os dados encontrados foram dicotomizados em gráficos e, posteriormente, analisados. Foram analisados 31 artigos publicados. A frequência estimada EMB oscila entre 6% a 73%. O comprometimento cognitivo foi reconhecido em 17–47% dos sujeitos, apresentando correlação significativa com os aspectos de neuroimagem, como a atrofia cerebral global, aumento do volume lesional em T2 e atrofia regional da substância cinzenta. Os critérios atualmente utilizados superestimam a freqüência de EMB, e, por essa razão, destaca-se a importância da validação dos métodos de diagnóstico praticados.

Palavras-chave: esclerose múltipla; cognição; neuroimagem.

Multiple sclerosis (MS) is referred to as a chronic neurodegenerative disease that affects the central nervous system (CNS)[1]; it is initially inflammatory and demyelinating, with a variable neurodegenerative component. The evolution of MS is heterogeneous, with different levels of progression and clinical overlap[1,2,3].

Most MS patients present with a clinical profile of outbreaks and remissions. After a few years, most of these patients experience a gradual progression of deficit symptoms[1].

However, there is a subgroup of patients, unlike those with primary and secondary progressive MS, who show little or no disease progression and a minimum level of disability, after decades of the first clinical manifestation. This is called benign MS (BMS) progression[1,2,4].

The actual existence of a benign form of MS is a controversial topic and its exact definition has been subject to change over time; to date, there is no official consensus on the subject[2,5].

METHODS

A systematic review of the literature was conducted, searching for studies published between October 1964 and October 2015 in the Cochrane, PubMed and Lilacs databases using "benign multiple sclerosis" as the search term, without language restriction.

The search included descriptive and analytical observational cross-sectional and cohort studies, as well as prospective and retrospective case-control studies, which addressed general aspects of the disease, such as defining criteria, prevalence rate and clinical markers, and also included those that mentioned the current theme with cognitive and neuroimaging assessments. Editorials, systematic reviews, meta-analysis and case reports were excluded.

The following databases were used: Cochrane, PubMed and Lilacs. One of the authors (Ton, A.) manually selected the

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articles in the reference list, to confirm their compliance with the inclusion criteria. The descriptor used was "benign multiple sclerosis." Summaries of the selected articles were evaluated for inclusion or exclusion in the systematic review.

RESULTS

Seventy-two articles were found in the PubMed database using the established patterns with the descriptor "benign multiple sclerosis", while in the Cochrane database only one article was found. The Lilacs database did not have any articles. Initially, due to similarity, one article was excluded; however, after further reading of the abstracts, another 58 articles were excluded. Articles that did not add data to the proposed theme were also excluded. Next, through a manual search, 13 articles that did not have the descriptor applied but had relevant data were identified. After the selection, 36 articles were selected for a thorough reading. Subsequently, the reference list was used to define other relevant articles. In total, 31 articles were included and rated as follows: one descriptive study[2], 23 cross-sectional studies[3,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26], two longitudinal case-control studies[4,27] and six cohort longitudinal studies[27,28,29,30,31,32].

As regards the definition of the term benign MS, eight studies show conflicting concepts[2,3,4,5,7,13,28,29]. With regard to the frequency of BMS in the monitored cohorts, eight studies presented this information[2,3,4,5,7,11,13,29] (Table 1).

Regarding the cognitive aspects of BMS, seven studies examined the prevalence of cognitive impairment[6,13,14,15,16,17,19,27], with values varying from 19% to 45% in the patients. Only six studies evaluated the relationship between the degree of cognitive impairment with specific neuroimaging alterations[6,13,15,16,17,18] in one study no relation was found[6], and in others, positive associations were observed (Table 2).

Regarding the different neuroimaging methods used in patients classified as having BMS, Table 3 shows the evaluation techniques and their findings.

In addition, six studies investigated whether there was a relationship between cognitive abnormalities and neuroimaging in patients with BMS[6,13,15,16,17,19] (Table 4).

DISCUSSION

Several follow-up studies have shown, with statistically significant results, that most patients who initially met the criteria for benign MS, invariably evolved to a secondary progressive MS, with accumulating motor and cognitive dysfunction[2,5,29]. Moreover, neuroimaging techniques mostly showed a structural pattern similar to that found in non-benign forms of the disease, although there were conflicting results[1,6,13].

Definition and frequency

In 1952, for the first time, McAlpine systematically described the benign MS profile and suggested a definition as "patients who, after 10 years of the disease, have no restriction of labor or domestic activity, however are not totally symptom free"[1,2,5]. In the discussion, the benign progress was characterized as "a mild or severe initial attack, with good recovery, mild and infrequent or even absent relapses, with the possibility of permanent cure"[1]. In 1996, the definition by the National Multiple Sclerosis Society was given as: disease in which the patient remains fully functional in all neurological systems after 15 years from the onset of symptoms[33].

Table 1. Frequency and definition of benign multiple sclerosis, according to the authors.

Author	Year	Population (n)	Country	Definition	Frequency (%)	Frequency after		
						5 years (%)	10 years (%)	20 years (%)
Hawkins & Mc Donell[2]	1999	131	Ireland	3	19.90	-	9.30	-
Thompson et al.[3]	1986	240	Ireland	3	42.00	-	-	-
Pittock et al.[4]	2004	162	Ireland	4	30.24	-	20.93	-
Glad et al.[5]	2010	138	Norway	2	14.50	-	-	-
				3	26.30	-	-	-
				4	40.80	-	-	-
McAlpine[7]	1954	241	London	1	32.36	25.72	-	-
Costelloe et al.[11]	2008	355	Ireland	-	14.32	-	-	11.00
Correale et al.[13]	2012	342	Argentina	3	12.50	-	-	-
Sayao et al.[28]	2007	169	England	3	-	-	-	52.10
Leray et al.[29]	2013	374	France	2	57.70	-	12.01	2.63
				3	73.90	-	18.53	5.03

[1]No restriction to labor and domestic activities, however, not necessarily without symptoms; [2]EDSS ≥ 2 with duration of disease exceeding 10 years; [3]EDSS ≥ 3 with duration of disease exceeding 10 years; [4]EDSS ≥ 4 with duration of disease exceeding 10 years. EDSS: Expanded Disability Status Scale.

Table 2. Cognitive aspects, according to the authors.

Author	Year	Population (n)	Cognitive impairment (%)	Cognitive assessment
Pagani et al.[6]	2008	60 BMS 35 SPMS 21 healthy volunteers	20	Nonspecified neuropsychological tests exploring memory, attention and frontal lobe cognitive domains
Correale et al.[13]	2012	47 BMS 299 NBMS	47	Neuropsychological battery containing PASAT- 3 seconds, DST, 7/24 SPART, WCST and VFD.
Bester et al.[15]	2013	26 BMS 24 healthy volunteers	38	Neuropsychological battery containing VFT, CVLT-II, SDMT, PASAT-3 seconds, D-KEFS and CWIT.
Rovaris et a.l[16]	2008	62 BMS 32 SPMS 19 healthy volunteers	19	Neuropsychological battery containing PASAT, TMT, CST, SST, DST, WLT, ROCF-recall, Token Test, VFT and WCST.
Amato et al.[17]	2008	47 BMS	23	SRT, 10/36 SRT, PASAT, SDMT and WLG.
Mesaros et al.[19]	2009	54 BMS	17	Neuropsychological battery containg PASAT, TMT, AMT, DSP, SST, CST, WLG, ROCF-recall, Raven Test, Token Test, WCST and ROCF-copy.
Amato et al.[27]	2006	163 BMS 111 healthy volunteers	45	SRT, 10/36 SRT, PASAT, SDMT, WLG and Stroop Test.

BMS: benign multiple sclerosis; SPMS: secondary progressive multiple sclerosis; NBMS: non-benign multiple sclerosis; PASAT: paced auditory serial addition test; DST: digit span test; SPART: spatial recall test; WCST: Wisconsin card sording test; VFD: visual form discrimination test; VFT: verbal fluency test; SRT: selective reminding test; CVLT-II : California verbal learning test II; SDMT: symbol digit modalities test; D-KEFS: Delis–Kaplan executive function system; CWIT: color-word interference test: inhibition and inhibition switching; TMT: trail making test; CST: Corsi span test; SST: short story test; WLT: word list test; ROCF-recall: Rey Osterrieth complex figure test; WLG: word list generation; AMT: attentive matrices test; DSP: digit span test; SST: short story test; ROCF-copy: Rey Osterrieth complex figure test copy. SPMS: secondary progressive multiple sclerosis

Table 3. Neuroimaging aspects, according to the authors.

Author	Year	Population (n)	Country	Neuroimages findings
Filippi et al.[21]	1995	13 BMS 13 SPMS	Italy	Lower lesional charge (p = 0.03) -
De Stefano et al.[23]	2008	50 BMS 50 RRMS 32 healthy volunteers	Italy	Lesional and perilesional inferior MTr to the healthy controls (p < 0.0001) and bigger than the patients with RRMS NAWM of MTr and cortical similar to the controls (p > 0.05) and bigger than the patients with RRMS (p < 0.0001) -
Gauthier et al.[24]	2006	39 BMS 40 RRMS	USA	Lower rate of brain atrophy (p = 0.02) -
Strasser-Fuchs et al.[25]	2007	13 BMS 15 SPMS	England	No differences in relation to the lesional charge in T2 (p = 0.19) -
Calabrese et al.[32]	2009	48 BMS 96 RRMS	Italy	Inferior number of intracortical lesions (p < 0.001) -

BMS: benign multiple sclerosis; SPMS: secondary progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; MTr: magnetization transfer ratio; NAWM: normal appearing white matter.

Currently, it is proposed that BMS is reported as multiple sclerosis in patients with a disease duration greater than or equal to 10 years and the Kurtzke Expanded Disability Status Scale (EDSS) score less than or equal to 2.0[4]. In addition, the improvement in neuroimaging analysis has allowed the introduction of new diagnostic criteria that provides a methodological basis for the early diagnosis of multiple sclerosis after a single attack, by incorporating evidence from MRI scans. The McDonald criteria were introduced in 2001[34] and revised in 2005 and 2010[35]. This latest revision improves sensitivity from 46% to 77% with a slight trade-off in specificity, with an overall accuracy of 86%[36], facilitating the diagnosis of MS in patients who have a low EDSS score and increasing the estimated frequency of MS over the same follow-up duration.

In the systematic review, two studies classified their population of MS patients using McDonald's criteria[3,11], nine studies made MS diagnoses according to Poser's criteria[5,8,11,13,20,26,28,29,31] and McAlpine classified clinical MS using his own proposed definitions published in 1961[7].

Table 4. Relation of cognitive assessment and neuroimaging findings, according to the authors.

Author	Year	Population (n)	Country	Cognition and neuroimages
Pagani et al.[6]	2008	60 BMS	Italy	There's no difference between the grey matter atrophy level and the patients with, or without, cognitive loss
		35 SPMS		-
		21 healthy volunteers		-
Carreole et al.[13]	2012	47 BMS	Argentina	BMS patients without a cognitive loss present less progression in the lesional charge related to others
		299 BMS		When compared to BMS patients with cognitive loss, there's no difference
Rovaris et al.[16]	2008	62 BMS	London	BMS patients without a cognitive commitment were associated with a less lesional charge in T2 (p = 0.03), normalized brain volume (p = 0.006) and diffusion average of inferior grey matter in relation to SPMS controls (p = 0.03).
		32 SPMS		BMS patients without a cognitive commitment did not show differences in neuroimaging related to others
		19 healthy volunteers		-
Amato et al.[17]	2008	47 BMS	Italy	The cognitive commitment was associated with an increase in lesional charge in T1 (p = 0.001) and T2 (0.05). BMS patients with cognitive commitment presented with a pronounced cortical atrophy (p = 0.005) and a reduction of cortical MTr (p = 0.02)
Mesaros et al.[19]	2009	54 BMS	Italy	The cognitive commitment was associated with a greater lesional charge in the corpus callosum (p = 0.02) and diffusion average of superior NAWM to others (P = 0.02)
Bester et al.[32]	2013	26 BMS	USA	The cognitive commitment was associated with an increase of lesional volume in T2 in the anterior thalamus region (p < 0.001)

BMS: benign multiple sclerosis; SPMS: secondary progressive multiple sclerosis; MTr: magnetization transfer ratio; NAWM: normal-appearing white matter.

In the general literature, the estimated frequency of BMS varied between 6% and 73.9% (Table 1). The two main factors for this variability were the different definition criteria used and the follow-up duration[1,5], in addition to the population base included in the study and the inclusion or exclusion of the mortality index[5].

However, for some authors, BMS is only a temporary descriptor of the disease's status, denying its permanent character[5]. According to Sayao et al.[28], BMS was defined as an EDSS score less or equal to 3.0 after at least 10 years of disease. The same authors evaluated 169 patients with BMS and found that after 20 years of follow-up, approximately 50% had progressed to the status of secondary progressive MS (SPMS), with more than a 21% chance of becoming seriously disabled. Costelloe et al.[11] evaluated a group of 436 patients for 21 years, including 397 patients initially diagnosed as BMS. Among the latter, only 15% kept the same diagnosis at the end of the time period. Likewise, Leray et al.[29], in their work with 874 patients classified as having BMS due to the EDSS being less than 3, found that approximately half of the patients were no longer considered to have the benign form after a decade of disease evolution.

Furthermore, there were divergent therapeutic decisions regarding the administration of disease-modifying drugs in patients with BMS. Among the 18 authors who mentioned drug therapy, only five reported that the patients with BMS did not receive any medications during the follow-up period[4,20-22,31]. Glad et al.[5], Sayo et al.[28], Leray et al.[29], Gauthier et al.[24] and Correale et al.[13] reported that some subjects were given unspecified drug therapy, at the respective frequency of 9.04%, 23.00%, 8.74%, 71.79% and 48.93%. Haase and Faustmann[8] used only azathioprine in 17.07% of the patients included in the sample. Strasser-Fuchs et al.[25] used only interferon beta in 30.76% of subjects. Bester et al.[15], Rovaris et al.[18], Mesaros et al.[19], and De Stefano et al.[23] administered interferon beta and glatiramer acetate in 20.96%, 24.07% and 100% of patients with BMS, respectively. Moreover, Amato et al.[17] and Amato et al.[27] analyzed, respectively, 47.85% and 44.68% patients with BMS using azathioprine, glatiramer acetate or interferon beta in their follow-up research.

Cognitive aspects

Among the nonmotor symptoms, cognitive impairment is increasingly recognized as a manifestation of MS and may occur relatively early in the course of the disease, affecting 40% to 65% of patients and impacting their quality of life. Interestingly, cognitive dysfunction and the degree of progression do not have parallel paths[18,19,24,33,37].

Failure on neuropsychological tests seemed to be an important prognostic index, showing that 90% of patients with cognitive preservation remained within the BMS criteria after five years of follow up, proving that neuropsychological functioning is an important measure of brain integrity[33].

In the study by Amato et al.[27], which evaluated 163 patients with BMS, the authors found cognitive dysfunction in 45% of patients, leading to a negative impact on social activities and work with levels similar to those presented for patients not

having BMS. The cognitive performance was assessed through the Brief Repeatable Neuropsychological Battery incorporating tests of verbal memory acquisition and delayed recall (Selective Reminding Test), visual memory acquisition and delayed recall (10/36 Spatial Recall Test), attention, concentration and speed of information processing (Paced Auditory Serial Addition Test); Symbol Digit Modalities Test and verbal fluency on semantic stimulus (Word List Generation), and the Stroop Test[27]. Gonzales-Rosa et al.[20], in their study of 10 patients with BMS and 17 patients with relapsing-remitting MS (RRMS), found that the BMS group of patients had a poorer performance on the cognitive tests, especially regarding the reaction time analysis and a greater number of errors when compared to patients with RRMS.

Another study conducted by Mesaros et al.[19], which evaluated 54 patients with BMS, and found cognitive dysfunction in 17% of patients, included the cognitive assessment using the Paced Auditory Serial Addition Test, Trail Making Test, Attentive Matrices Test, Digit Span Test, Short Story Test, Corsi Span Test, Word List Generation, Rey Osterrieth Complex Figure Test Recall Task, Raven Test, Token Test, Verbal Fluency Test, Wisconsin Card Sorting Test and the Rey Osterrieth Complex Figure Test Copy Task.

In a prospective analysis of neuroimaging in patients with BMS, Correale et al.[13] showed that 47% who met the criteria for the benign form of MS had significant cognitive impairment. All patients included in the study underwent neuropsychological evaluation with the neuropsychological battery containing the Paced Auditory Serial Addition Test 3-seconds, Digit Span, 7/24 Spatial Recall Test, Wisconsin Card Sorting Test and the Visual Form Discrimination Test. Bester et al.[15] found cognitive impairment in 38% of BMS patients using a neuropsychological battery containing the Visual Form Discrimination Test, California Verbal Learning Test II, Symbol Digit Modalities Test, Paced Auditory Serial Addition Test 3-second, Delis-Kaplan Executive Function System, and the Color-Word Interference Test: Inhibition and Inhibition Switching.

In addition, all studies that evaluated cognitive assessment also required a fatigue and depression assessment, using the Fatigue Severity Scale[27,33], Hamilton Rating Scale[27] and Beck Depression Inventory[33] to clarify the results. Furthermore, Correale et al.[33] excluded the participants requiring psychoactive drugs or other substances potentially affecting neuropsychological performance, while Amato et al.[27] asked the patients who were taking psychoactive drugs to cease the treatment at least one month prior to being tested.

Other studies analyzed alternative methods of cognitive assessment by psychophysiological techniques such as event-related potentials and quantitative electroencephalograms. Gonzales-Rose et al.[38] observed that BMS patients presented with a higher cognitive deterioration when compared with RRMS patients after an event-related potentials assessment. Vazquez-Marrufo et al.[39] published a study analyzing the physiological differences detected by a quantitative electroencephalogram assessment of patients with RRMS and BMS, concluding that BMS and RRMS patients exhibited different physiological patterns. Indeed, the BMS group showed the higher degree of cognitive impairment, and the quantitative electroencephalogram scores remained in the normal range, probably due to cerebral adaptative responses.

Neuroimaging aspects

Over the past decade, the use of new technologies in clinical trials of MS has been presented as an important contribution to *in vivo* evaluation of clinical and pathological manifestations of the disease[18,33]. Currently, there is no clinical prognostic, genetic or laboratory marker that can predict the benign course of MS. However, the use of radiological markers associated with a permanent benign course of MS can lead to a more reliable definition of BMS.

In his analysis of BMS, Ramsaransing et al.[1] found that several MRI studies were not able to show major differences in the number of brain lesions in patients with SPMS and BMS, despite the important clinical differences[1,6,18,24,33].

Correale et al.[13] confirmed this fact, showing that the average impact of the lesion T2 in BMS patients may be similar to that found in RRMS patients with a short disease duration, or with a larger EDSS score, or even in both cases. However, they stated that patients with BMS may have a more selective topographic distribution of the lesions, with a more relative distribution in clinically eloquent regions and a slower accumulation of injuries as a result of cortical reorganization and tissue repair mechanisms.

Calabrese et al.[32] studied 48 patients with BMS and 96 controls with RRMS. Those with BMS showed a lower number of intracortical lesions in relation to those with RRMS. Fisniku et al.[31] corroborated this finding in 107 patients, where the lesion load was higher in patients with SPMS compared to those with BMS.

According to Rovaris et al.[18], many studies comparing patients with BMS and SPMS, present conflicting results, with some showing no difference in the lesion loads and others reporting that patients with BMS have a higher average lesion load than those with SPMS.

One possible reason to explain the practical significance of these contradictory results may be the location of the injury in medically important regions of the CNS, such as the cortex, internal capsule, brain stem and spinal cord, is more eloquent than the total load in determining the severity of the developed neurological disorders. A second explanation is the difference between the lesional accumulation rate over time in patients with BMS and those with other clinical MS phenotypes, possibly different factors associated with genetic and environmental susceptibility[18].

Furthermore, according to Rovaris et al.[18], in a study investigating the pattern of evolution of newly-formed lesions in BMS patients, the frequency of lesions that become designated as black holes in these patients is lower than that found in patients with SPMS. This may indicate that the severity of

tissue damage in macroscopic lesions is less pronounced in BMS than in the disabling phenotypes of MS.

Additionally, some studies showed a significant reduction of the brain volume in patients with BMS compared to healthy subjects[6,18,24]. Using voxel-based morphometry studies, Pagani et al.[6] showed predominant subcortical and cortical atrophy in these patients. However, according to Rovaris et al.[18], the severity of cerebral atrophy was not different when individuals with BMS and SPMS were compared, although Filippi et al.[21] showed in their study that the latter had more severe atrophy in infratentorial regions.

Rovaris et al.[16] compared patients with BMS without cognitive impairment to patients with SPMS and found greater lesion loads, as well as more cerebral atrophy, in the latter group, as opposed to the findings of other studies, suggesting that only patients with preserved cognitive functions may represent those with truly benign MS.

In another study published by Rovaris et al.[18] in 2009, the presence of a significant reduction in thalamic volume compared to healthy subjects was described in both individuals with BMS and those with RRMS. However, according to Gauthier et al.[24], this finding may be a typical characteristic of all MS patients, reflecting the vulnerability of the thalamus to specific damage by the disease because of the presence of focal lesions.

Metric MRI analyses showed that the magnetization transfer ratio (MTr) of the gray matter was significantly higher in BMS patients compared with those with RRMS, despite having a similar load of white matter lesions, suggesting that the scarcity of damage to the gray matter is a trademark of BMS[32].

Other studies have shown lower MTr values in all areas, including in the normal appearance white matter (NAWM) and cortical regions in RRMS patients, suggesting that the brain damage can be milder in BMS patients, even those with long-term disease[23]. Interestingly, patients with cognitive impairment and BMS, show lower MTr values when compared with those with cognitive preservation[27], suggesting that differences in cognition are associated with diffuse neocortical injury.

In addition, according to Pagani et al.[6], damage to the spinal cord is a major determinant of disability in MS patients. However, the macroscopic aspect of the quantification of cervical spinal lesion was not significantly different between BMS and SPMS patients. Cervical spinal atrophy was predominantly observed in SPMS patients, but not in BMS.

Fisniku et al.[31], also compared and evaluated the damage to the spinal cord between the two groups of patients. Frequency, and the average size of the cervical spinal cord lesions, were significantly lower in BMS patients than those with SPMS. In addition, the latter have a greater aggravation tendency of the lesions after 20 years of disease progression.

Cognition and neuroimaging

Cognitive impairment in MS compromises sustained attention, processing speed, abstract reasoning, verbal fluency and visuospatial perception. According to Gonzalez-Rosa et al.[20], the pattern of cognitive impairment must somehow be related to anatomopathology and the number and location of the lesions. However, the discrepancy between the cognitive-behavioral functioning and MRI findings has promoted the use of other techniques to objectively explore the relationship between brain disorders and neuropsychological deterioration[20,33].

Available data suggest that focal lesions in white matter play some kind of role, but the effect of the total load of T2 lesions on cognitive impairment related to MS is limited. The location of lesions in critical brain areas seems to be important and in this context, the ability to improve detection of cortical lesions is essential[15,17,37].

The irreversible loss of brain tissue, measured in terms of global and regional atrophy, is strongly associated with cognitive deficits[37]. In addition, other components of the MS pathology, such as diffuse damage to the NAWM and gray matter may play a decisive role in the development of the cognitive profile[15,17,33,37].

A significant correlation was found between the increase in T2 injuries during the first five years of the disease and the severity of cognitive disorders[31].

Pagani et al.[6], in their study of 60 BMS patients, reported that 12 patients (20%) of this subgroup had abnormal performance in three or more neuropsychological tests. In addition, these patients showed a reduction in gray matter volume in subcortical and frontoparietal regions. However, there was no difference in the regional atrophy pattern in BMS patients with or without cognitive impairment.

These findings were corroborated by Amato et al.[17] in their study evaluating 47 patients with BMS, and the MRI results were compared with the results of 24 healthy controls. Only 23% of the patients showed detectable cognitive impairment. Compared to the group with cognitive impairment, patients with preserved cognition showed a lower lesion load on T2 and T1, as well as higher cortical volumes and MTr values.

Data presented by De Stefano et al.[23] are similar to the previous studies, showing that the brain tissue injury, as assessed by quantitative nuclear magnetic resonance was milder in patients with BMS than those patients with RRMS.

According to Rovaris et al.[18], the brain diffusion characteristics of the BMS and cognitive impairment patients do not differ from a group of patients with SPMS, while the image analysis of individuals with BMS and cognitive preservation showed higher brain volume, i.e., less brain atrophy and decreased diffusion rate in gray matter compared to subjects with SPMS. In 2008, the same authors concluded that 19% of 62 patients with cognitive impairment had BMS. These patients showed an increase in water diffusion abnormalities in both the gray matter and in NAWM compared to healthy individuals. When BMS patients without cognitive impairment were compared with the control group of SPMS patients, increased lesion loads and a more pronounced brain atrophy were found in the SPMS group of patients, in contrast to the findings of other studies[16].

According to Bester et al.[15], previous tractography studies in BMS patients identified lesional and diffuse damage of the

corpus callosum as one of the main findings related to cognitive impairment. The study evaluated 26 BMS patients defined by an EDSS score less than or equal to 3 for at least 15 years. The analysis of the patients' cognitive profile showed that 38% of subjects with BMS had cognitive dysfunction. The specific analysis of the corpus callosum showed the widespread presence of abnormalities, specifically in the knee, body and splenium. However, when patients with cognitive impairment were compared to those with preserved cognition, there were statistically significant differences only relative to the average fractional anisotropy and diffusion of the corpus callosum splenium.

The volume of T2 lesions of the anterior thalamus was higher in patients with cognitive impairment than those with preserved cognition. Finally, they found a moderate correlation between verbal learning and executive function deficits with damage to tracts that connect the knee and the corpus callosum trunk to the prefrontal and supplementary motor areas of the two hemispheres[15].

The demonstration of a link between damage to the corpus callosum and cognitive dysfunction agrees with the hypothesis that the cognitive impairment in MS is probably a result of a multiple disconnection syndrome[19].

Mesaros et al.[19] evaluated 54 BMS patients and 21 healthy controls, and found that only 17% of BMS patients showed cognitive impairment, predominantly in memory and executive capacities. The analysis of the entire brain lesion load showed an increase in lesions in patients with cognitive impairment compared to those with cognitive preservation, although this difference was not statistically significant. However, the volume of T2 lesions in the corpus callosum was significantly higher in patients with cognitive impairment. This study also defined the topographic distribution through a morphometry-based study in the voxel of the corpus callosum lesions, showing that patients with cognitive impairment had a significantly higher frequency of lesions in the splenium and right trunk of the corpus callosum. Together, these results supported the idea that T2 lesions in the corpus callosum can serve as a marker of cognitive dysfunction in BMS.

These findings were confirmed by Amato et al.[26] in a study with magnetization transfer techniques, which have shown that these structures are heavily damaged in MS and cognitive impairment patients.

Mesaros et al.[19] also showed that, among those examined, the medical diffusion values of the NAWM and the T2 lesion volume of the corpus callosum were the only variables that differed between patients with cognitive impairment and those with preserved cognition. The results support the role of the extent and location of the lesion load on cognitive performance, in regard to attention and speed of information processing, suggesting that the evaluation of structural damage and regional clinical function may be a strategy for identifying patients with truly benign MS. Furthermore, it supports the inclusion of a cognitive profile assessment of patients as an additional criterion in defining disease phenotypes.

Correale et al.[33] found functional changes shown by nuclear magnetic resonance in BMS patients. The abnormalities were mainly characterized by increased recruitment areas normally activated in healthy patients, as well as the bilateral activation in cognitively-preserved patients.

In conclusion, the great variability in determining the true frequency of BMS reflects, predominantly, the multiplicity of study designs and the absence of a conceptual consensus. Moreover, the lack of prognostic, clinical, demographic, laboratory or genetic markers prevents reliable prediction of the development of a benign course of the disease.

When considered together, the data of neuropsychological tests and MRI seem to indicate that the current diagnosis of BMS underestimates the presence of clinically relevant structural brain lesions, which, in turn, may be associated with cognitive deficits, and which contrast with the concept of a nondisabling disease profile. The selective evaluation of the CNS regions using quantitative nuclear magnetic resonance techniques may serve as a strategy to investigate the role of regional lesions in determining the clinical manifestations of MS, including cognitive deficit. The definition of BMS should include an objective measure of cognitive functions, since patients with a benign subtype and cognitive impairment do not appear to show structural differences from those who are completely asymptomatic.

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