RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 3, pages: 282–288
DOI: 10.5603/PJNNS.a2023.0031

ISSN: 0028-3843, e-ISSN: 1897-4260

Brain volume loss in multiple sclerosis is independent of disease activity and might be prevented by early disease-modifying therapy

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ABSTRACT

Introduction. Neurodegeneration is likely to be present from the earliest stages of multiple sclerosis (MS). MS responds poorly to disease-modifying treatments (DMTs) and leads to irreversible brain volume loss (BVL), which is a reliable predictor of future physical and cognitive disability. Our study aimed to discover the relationship between BVL, disease activity, and DMTs in a cohort of patients with MS.

Material and methods. A total of 147 patients fulfilled our inclusion criteria. Relevant demographic and clinical data (age, gender, time of MS onset, time of treatment initiation, DMT characteristics, Expanded Disability Status Scale (EDSS), number of relapses in the last two years prior to MRI examination) were correlated with MRI findings.

Results. Patients with progressive MS had significantly lower total brain and grey matter volumes ($p = 0.003$; $p < 0.001$), and higher EDSS scores ($p < 0.001$), compared to relapsing-remitting patients matched by disease duration and age. There was no association between MRI atrophy and MRI activity ($c2 = 0.013$, $p = 0.910$). Total EDSS negatively correlated with the whole brain ($r_s = -0.368$, $p < 0.001$) and grey matter volumes ($r_s = -0.308$, $p < 0.001$), but was not associated with the number of relapses in the last two years ($p = 0.278$). Delay in DMT negatively correlated with whole brain ($r_s = -0.387$, $p < 0.001$) and grey matter volumes ($r_s = -0.377$, $p < 0.001$). Treatment delay was connected with a higher risk for lower brain volume ($b = -3.973$, $p < 0.001$), and also predicted a higher EDSS score ($b = 0.067$, $p < 0.001$).

Conclusions. Brain volume loss is a major contributor to disability progression, independent of disease activity. Delay in DMT leads to higher BVL and increased disability. Brain atrophy assessment should be translated into daily clinical practice to monitor disease course and response to DMTs. The assessment of BVL itself should be considered a suitable marker for treatment escalation.

Key words: multiple sclerosis, brain volume loss, atrophy, neurodegeneration, disability

(*Neurol Neurochir Pol 2023; 57 (3): 282–288*)

Introduction

Multiple sclerosis (MS) is an inflammatory and degenerative disorder of the central nervous system (CNS) with complex and not yet fully-understood disease mechanisms [1, 2]. In addition, MS has a heterogeneous presentation and a wide range of onset age. This diversity can lead to a delayed diagnosis and result in more complicated management. Although the clinical course of MS is variable, in the vast majority of cases it starts with reversible episodes of neurological

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Received: 11.03.2023 Accepted: 3.04.2023 Early publication date: 5.05.2023

disability — as the relapsing-remitting (RR) form with dominant inflammatory pathogenesis. Later in the course of the disease, continuous and irreversible neurological decline due to neurodegeneration prevails (this is secondary progressive MS — SPMS) [3]. When exactly the progressive phase of MS begins is still the subject of debate. A minority (10–15%) of patients have primary progressive MS (PPMS), in which the progression of disability is present from the very onset [4]. Whether the clinical subtypes of MS are pathologically distinct from each other — or possibly even different disease entities — is still open for discussion. Some authors consider MS *per se* (all types) to be an asynchronously progressive disease from the very beginning [5]. Nevertheless, MS classification is still based on the clinical phenotype [6].

In the context of reserve capacity, progression occurs in all patients, but remains unrecognised by clinicians. Numerous magnetic resonance imaging (MRI) features — i.e. brain volume, spinal cord atrophy, and T2 lesion volume — are predictive of disability worsening and are variably present in both the relapsing and the progressive forms of MS [7, 8]. Brain volume loss (BVL) is relatively independent of lesion load, and, as a predictor of the evolution of disability, has become a critical biomarker of neurodegeneration [9]. Irreversible brain atrophy is clinically relevant, correlating with future physical and cognitive disability in MS patients [10]. Brain volume loss, reflecting the real tissue damage in MS patients, occurs from the preclinical stage of the disease and progresses up to five times faster than natural ageing [11]. Axonal damage accounting for brain atrophy may be acute due to inflammation or chronic due to pathogenic mechanisms primed by the preceding inflammation and later perpetuated with disease progression [12]. Brain atrophy assessment is substantial in MS, making BVL a relevant marker to diffuse CNS damage, leading to clinical disease progression, and serving as a useful parameter in evaluating the effects of MS therapies [13].

The definition for efficacy of MS treatment has become more comprehensive over the last decade. With the introduction of more effective types of disease-modifying therapies (DMTs), the disease-free period or "no evidence of disease activity" (NEDA) became a new measured outcome. Although NEDA status may strongly predict favourable long-term outcomes, its absence is not necessarily a poor prognostic sign. Daily clinical practice indicates that patients may experience a new relapse and/or new MRI lesion, and yet remain stable from a long-term point of view [14].

Three basic components — an absence of clinical relapses, no progression measured by expanded disability status scale (EDSS), and a lack of new T2 and/or enhancing lesions on brain MRI — represent NEDA-3. Cognitive state assessment and monitoring of neuroaxonal damage (measuring BVL or plasmatic levels of neurofilament chain) became the basis for NEDA-4 [15]. The concept of NEDA-4 has the potential to capture the impact of therapies on both inflammation and neurodegeneration. NEDA-4 deserves further evaluation across different compounds and long-term studies [16].

Clinical rationale for study

Our study aimed to analyse the clinical relevance of brain atrophy in a cohort of patients with MS. According to observations from clinical practice and our preliminary data [17], we postulated the following hypotheses:

- Brain atrophy is independent of MRI activity.
- Disability is more affected by brain volume loss than by disease activity (number of relapses and/or new T2 lesions on brain MRI).
- Delay in DMT initiation leads to worse outcomes in MS patients.

Material and methods

Patients

Inclusion criteria for study enrollment were:

- diagnosis of MS according to the 2017 McDonald criteria,
- minimum age of 18 years,
- having valid results from brain MRI and volumetry exams at the MRI Centre, Dr. Magnet Ltd, Bratislava, Slovakia.

Data collection was carried out between April 2017 and December 2020. We collected data from 150 patients; three of them were excluded due to incomplete information.

Methods

This was a retrospective, cross-sectional, single-centre study approved by the Ethical committee of Derer University Hospital, Comenius University, Bratislava, Slovakia under approval number 03/2017.

All MRI examinations were performed using the same hardware and software throughout the whole study duration. Data was assessed by neuroradiologists trained in MS. Visual evaluation of the brain focused on detecting lesions (Flair/T2 hyperintensities, T1 hypointensities) and distribution in space, the detection of new Flair/T2 lesions, and contrast-enhancing T1 hyperintensities to evaluate disease activity — distribution in time, according to the 2017 McDonald criteria. Description of atrophic changes was assessed using visual rating scales. Simultaneously, MRI scans (3D Flair, 3D T1) were analysed by Icobrain MS software (Icometrix, Leuven, Belgium). Icobrain MS software can detect, quantify and track the evolution of MS lesions (Flair, T1) and distribution in space and time. The software provides metrics that can assess the volume of the whole brain and grey matter, tracking annualised brain volume changes to evaluate disease progression. Additionally, the software compares brain volume and volume changes to age — and sex — having matched a normative reference population. The calculated volumes can be used to interpret the subjects' measurements concerning a normative population.

Table 1. Relevant demographic and clinical data of all included patients

	Mean	Median	SD	IQR	Min	Max
Age (years)	42.13	42.00	11.03	15.50	20.00	71.00
MS duration (years)	10.70	8.500	7.458	9.850	0.3000	46.70
Treatment duration (years)	6.128	5.700	4.263	5.600	0.000	20.90
Number of DMTs	2.007	2.000	1.089	2.000	0.000	5.000
EDSS	3.500	3.000	1.417	2.250	1.000	7.000

MS — multiple sclerosis; DMT — disease-modifying therapy; EDSS — expanded disability status scale; SD — standard deviation; IQR — interquartile range

Relevant demographic and clinical data was collected from the information system at the Centre for MS Treatment at the Second Department of Neurology, Faculty of Medicine, Comenius University in Bratislava. Data was obtained at the timepoint corresponding with the date of the brain MRI examination, and included:

- age,
- gender,
- time of MS onset,
- time of treatment initiation,
- DMT characteristics (escalation versus induction; 1st line versus 2nd line),
- Expanded Disability Status Scale (EDSS),
- number of relapses in the two years prior to MRI examination.

Statistical analysis

We determined the required minimum sample size based on a *a priori* power analysis [18] using the G*Power 3 program [19]. The data was analysed by JASP Team (2021) JASP (Version 0.16) software. Statistics were used to evaluate demographic and clinical data. For normality evaluation, individual variables were first tested with the Lilliefors modification of the Kolmogorov-Smirnov test. Continuous parametric data satisfying normal distribution were described as mean ± standard deviation. If the data was non-normally distributed, it was described as median values with corresponding interquartiles. Categorical parametric data was presented as percentages. Parametric data was compared by the Student T-test, non-parametric data by the Mann-Whitney U-test; the chi-square test was used for categorical variables. Using the Bonferroni approach to control Type I errors, a p-value ≤ 0.008 was required for statistical significance. Correlation analysis of the data was conducted with the Spearman correlation test and linear regression. In cross-sectional analysis, a binary logistic or linear regression model was used to estimate probability and 95% confidence intervals (CI) for the risk factors.

Results

Description of patients

We collected complete data from 147 patients with MS, of whom 68.7% were female. The mean age was 42.13 ± 11.03 years and mean disease duration was 10.70 ± 7.46 years. By far the most common MS subtype in our group was relapsing-remitting (n = 123; 83.7%), followed by the secondary progressive (n = 21; 14.3%) and then the primary progressive subtypes (n = 3; 2.0%). The median of EDSS was 3.0 (IQR 2.250, min 1.0, max 7.0). The mean duration of MS treatment was 6.13 ± 4.26 years; 36.7% patients were treated by their first DMT (n = 54), 34.0% (n = 50) by the second DMT, 17.0% by the third (n = 25), 6.8% (n = 10) by the fourth, and 3.4% (n = 5) by the fifth DMT in their medical history. Only three patients (2%) did not take any DMT. Demographic and clinical data is summarised in Table 1.

Both whole brain volume ($r_s = -0.409$, $p < 0.001$) and grey matter volume ($r_s = -0.747$, $p < 0.001$) negatively correlated with age; there were no significant differences between genders.

According to age, whole brain volume negatively correlated with MS duration ($r_s = -0.270$, $p < 0.001$). Progressive MS (both primary and secondary) patients had significantly lower whole brain and grey matter volumes ($p = 0.003$ and $p < 0.001$, respectively) compared to RRMS patients matched by disease duration and age.

Whole brain volume also negatively correlated with treatment duration ($r_s = -0.177$, $p = 0.037$).

There was no significant difference in whole brain volume when comparing patients treated by different treatment lines ($p = 0.384$), different therapy modes (induction versus escalation, $p = 0.552$), or the number of previous treatments ($p = 0.228$). We did not find any significant correlation with grey matter volume in these specific parameters (data available upon request).

MRI atrophy and MRI activity

There was no association between MRI atrophy and MRI activity ($\chi^2 = 0.013$, $p = 0.910$).

Comparing patients with and without MRI activity, there was a significant difference in age ($p = 0.006$) and the number of relapses in the last two years ($p = 0.008$). There was no significant difference in either MS or therapy duration ($p = 0.533$, and $p = 0.113$, respectively) or total brain and grey matter volume ($p = 0.533$, and $p = 0.113$, respectively).

Comparing patients with and without MRI atrophy, there was a significant difference in both whole brain volume ($p < 0.001$) and grey matter volume ($p < 0.001$), and in MS duration

Table 2. Comparison of patients with and without MRI activity, or MRI atrophy, respectively

		MRI activity			MRI atrophy		
	Group	Mean	SD	p-value	Mean	SD	p-value
Age (years)	No	43.577	10.889	0.006	40.527	9.923	0.027
	Yes	37.667	10.398		44.732	12.285	
MS duration (years)	No	10.639	6.833	0.533	9.291	6.501	0.005
	Yes	10.872	9.232		12.979	8.362	
Treatment duration (years)	No	6.356	4.017	0.113	5.384	4.019	0.004
	Yes	5.425	4.943		7.338	4.406	
Relapses in last two years (n)	No	0.360	0.569	0.008	0.429	0.635	0.680
	Yes	0.722	0.815		0.482	0.687	
Whole brain volume (mL)	No	1,509.586	75.779	0.314	1,548.132	64.039	< 0.001
	Yes	1,510.972	89.679		1,447.839	59.607	
Grey matter volume (mL)	No	904.135	48.802	0.038	927.297	46.476	< 0.001
	Yes	925.806	58.206		880.429	47.245	

MRI — magnetic resonance imaging; SD — standard deviation; MS — multiple sclerosis

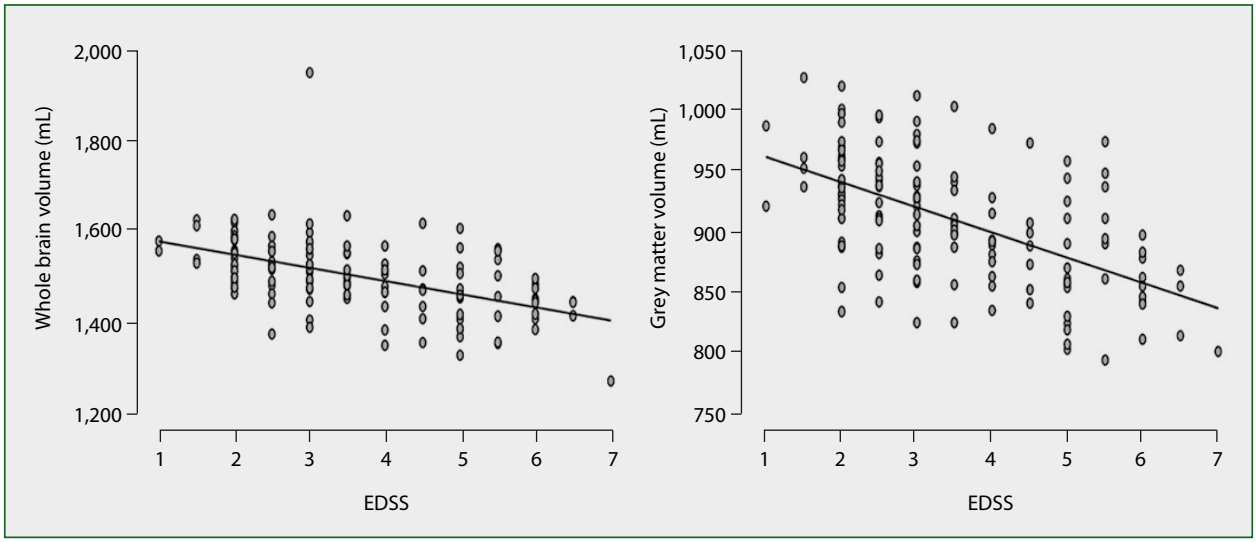

Figure 1. Negative correlation between expanded disability status scale (EDSS) and both whole brain volume (r_s = –0.368, p < 0.001) and grey matter volume (r_s = –0.308, p < 0.001)

(p = 0.005) and treatment duration (p = 0.004). All data is set out in Table 2.

Disability

Total EDSS score correlated positively with MS duration (r_s = 0.457, p < 0.001) and treatment duration (r_s = 0.329, p < 0.001), but was not associated with the number of relapses in the last two years (p = 0.278). Comparing patients with and without MRI activity, there was no significant difference in EDSS (p = 0.01). Comparing patients with and without MRI atrophy, patients with atrophy had higher EDSS scores (p < 0.001). EDSS negatively correlated with whole brain volume (r_s = –0.368, p < 0.001) and grey matter volume (r_s = –0.308, p < 0.001) as shown in Figure 1. Progressive MS patients had significantly higher EDSS scores (p < 0.001) compared to RRMS patients matched by MS duration and age.

Treatment delay

The number of years from MS onset to DMT initiation (treatment delay) negatively correlated with whole brain volume (r_s = –0.387, p < 0.001) and grey matter volume (r_s = –0.377, p < 0,001). Treatment delay was connected with a higher risk for lower brain volume (b = –102, p < 0.001).

There was no significant correlation between treatment delay and MRI activity or the number of relapses (p = 0.943, and p = 0.591, respectively).

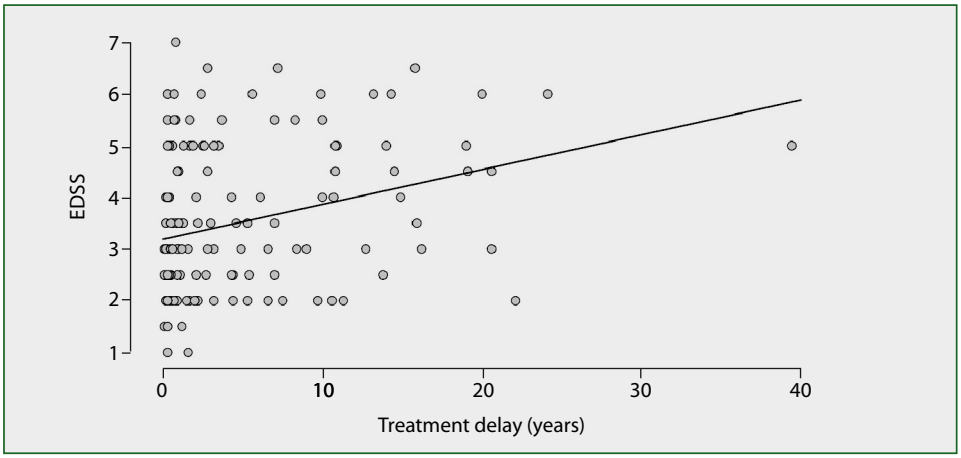

Figure 2. Positive correlation between treatment delay and expanded disability status scale (EDSS) score (r_s = 0.322, p < 0.001)

Discussion

Neuroimaging is of the utmost importance in both the diagnosis and the differential diagnosis of MS — especially in borderline, undetermined and atypical cases [20]. Multiple sclerosis used to be considered a white matter inflammatory disease, whereas brain volume loss was previously regarded as being present in more severe or advanced stages of the disease. This belief has been refuted in the last decade by numerous studies demonstrating that brain atrophy begins to occur from the preclinical stage of MS, and continues (at least partially) independently of inflammation [21]. This has been proved not only by volumetric studies; progressive neurodegeneration was recently confirmed by measuring the peripapillary retinal nerve fibre layer (pRNFL) by optical coherence tomography (OCT) [22].

MRI activity versus MRI atrophy and brain volume loss

Our results confirm that total brain volume is negatively correlated with MS duration. In addition, patients with progressive forms have significantly lower whole brain volume and grey matter volume compared to patients with RRMS (matched by disease duration and age). Previously published data showed that grey matter volume is lower in secondary-progressive disease compared to relapsing-remitting disease [10].

Regarding DMT, brain volume is negatively correlated with treatment duration, but it is not affected by current therapeutic approaches (i.e. the first versus the second line, escalation versus induction scheme). This supports the above-mentioned hypothesis that the neurodegenerative process is not significantly influenced by inflammation and/or immunomodulatory medication.

We found no association between MRI activity and brain volume changes on MRI (atrophy, total brain volume or grey matter volume). We proved that patients with confirmed activity on brain MRI — compared to patients with stable MRI findings — were significantly younger and had a higher number of relapses in the past two years — very probably being still in the inflammatory-predominant stage of MS. Here, MRI activity can predict the effects of immunomodulatory treatment on relapses of over two years [23]. This is important for clinicians' decisions about the escalation of DMT in a patient without manifest clinical worsening, as the predictive value of a new T2 MRI lesion counting as a predictor of longer-term effects on relapses has been assessed [24].

On the other hand, we found that the presence of brain atrophy on MRI did not correlate with disease activity (neither the number of relapses, nor new lesions on MRI). These patients had longer MS duration, as well as longer duration of DMT, compared to patients with no atrophy. All these findings underline that atrophy and activity are independent of each other.

Assessment of atrophy helps to distinguish between clinically and cognitively deteriorating patients and predicts those who will have a less favourable clinical outcome in the long term. Atrophy can be measured from brain MRI scans due to the many technological improvements made over the last few years. Despite this, measuring brain atrophy is not yet established as a routine clinical practice [12]. Early identification of patients with MS — accumulating future irreversible clinical disability in the long term — could help with therapeutic decision-making and patient management [25].

Impact of MRI findings on disability

In our study, EDSS score positively correlated with MS duration. However, it was not associated with disease activity assessed by the number of relapses in the last two years.

In addition, the difference in EDDS scores between patients with and without MRI activity was not significantly different. On the other hand, patients with brain atrophy had significantly higher EDSS scores, and this disability indicator negatively correlated with both whole brain and grey matter volume. An association between brain volume loss and

disability progression has been recently confirmed [12, 25]. These findings support previous research revealing that grey matter atrophy and T2 lesion volume are independent and mirror distinct pathological processes in a specific stage of MS [10].

Progressive MS patients had significantly higher EDSS scores, and lower total brain and grey matter volumes, than RRMS patients matched by disease duration and age.

Grey matter volume loss explains physical disability (as measured by the EDSS) better than white matter volume loss and/or T2 lesion volume [26]. Recent reports have confirmed that the rate of BVL is relatively stable throughout the course of RRMS. Accelerated BVL is weakly associated with concurrent higher disease activity [27]. Brain atrophy might also have a higher predictive value than conventional MRI findings in preventing physical disability progression (T2 lesion load) [21]. Our results are in agreement with the hypothesis that the neurodegenerative components of the progressive aspects of MS pathology, characterised by worsening disability, are independent of relapses [28].

Effect of treatment delay on outcomes

We found no significant correlation between treatment delay and MRI activity or the number of relapses in the last two years. This is not surprising, as the role of effective DMT is to decrease the activity of MS. On the other hand, a higher number of years from MS onset to DMT initiation was associated with lower brain volumes and higher EDSS scores. This has been referred to as the 'therapeutic window': if anti-inflammatory drugs are started late, too much damage has already accrued to prevent the consequences of previous focal inflammatory activity. Patients with SPMS show sustained accumulation of disability due to uncontrolled progression attributable to brain volume loss. The rate of cerebral atrophy is most significant in patients with established cerebral atrophy and a higher inflammatory lesion burden before DMTs [29]. Available DMTs are of only marginal benefit for patients already in the progressive stage of the disease [3]. Therefore, preventing patients from converting from the relapse-remitting to the progressive form of MS might be the only way of slowing down the irreversible neurological deterioration caused by axonal loss. Uher et al. [7] found that early initiation of adequate treatment helps halt the rate of BVL [27]. Randomised controlled trials and recent observational studies suggest that the initiation of early-intensive therapy is associated with decreased accumulation of overall disability. Understanding risk factors associated with disability progression is helpful in enhancing the clinician's availability to provide optimal treatment recommendations. There is clear evidence that a higher reduction in brain atrophy leads to a reduction of disability amelioration, but disease-modifying therapies (DMTs) can only partially slow down the rate of brain atrophy progression in MS patients [11, 21, 24]. Over the past decade, new DMTs with various secondary neuroprotective properties impacting on axonal survival have been implemented. Moreover, treatment delay is now shorter. All this might have contributed to the changes in the course of multiple sclerosis — which is apparently milder nowadays.

Our study has some limitations. The vast majority of our patients were treated with DMTs; therefore, the effect of pseudo-atrophy may have been present [30]. In our study, we did not assess the volume of T2 lesions, which, together with magnetisation transfer ratio (MTR) lesions, correlate with mean grey matter volume loss [31–33].

We did not include healthy controls; nevertheless, our data was statistically analysed, controlling for age and gender. We are aware that EDSS is not sensitive to signs of progression such as cognitive impairment, severe fatigue etc., but despite its limitations, this scoring system for disability evaluation is still the gold standard [6, 12, 28, 33]. Various volumetric software has been used in different reviewed studies compared to ours. However, the majority of results are still consistent [10, 27, 31–33].

Clinical implications / future directions

Our results have validated that brain atrophy manifests progressively in MS patients, and independently of clinical and MRI activity. Brain volume loss is a major contributor to disability progression, and we found that delay in DMT leads to higher BVL and increased disability. With the advent of easily accessible neuroimaging software, brain atrophy assessment should be translated into daily clinical practice to monitor disease course and responses to DMTs. Volumetric assessment should be implemented into routine MRI protocol for patients with MS. In addition, plenty of new, more promising DMTs are already being tested in progressive MS types, and the assessment of BVL itself should be considered a sufficient marker for treatment escalation. Further studies are required to confirm these promising results.

Conflicts of interest: *None.*
Funding: *None.*
Acknowledgements: *We would like to thank the team at the MRI Centre at Dr. Magnet Ltd, Bratislava.*

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