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ABSTRACT

BACKGROUND AND PURPOSE: Synthetic MRI (SyMRI) is a short-time acquisition sequence that generates different contrast-weighted images based on the measurement of tissue properties and provides quantitative volumetric, relaxation, and myelin maps. It has been used as an alternative to conventional MRI sequences in relapsing-remitting MS for detecting focal lesions and volumetric analysis. This study aimed to find an SyMRI variable associated with an Expanded Disability Status Scale (EDSS) $\geq$ 6 in progressive patients.

MATERIALS AND METHODS: Twenty-four patients with progressive MS underwent SyMRI with a 2D axial QRAPMASTER pulse sequence. We analyzed volumetric parameters, global myelin fraction (MyCF), and quantitative values derived from maps of proton density, R1, R2, and myelin for the masks: normal-appearing white and gray matter, lesion, and corpus callosum. A *t* test compared SyMRI variables between groups, followed by univariate binary logistic regression for significant ($P < .05$) or trending results ($P < .09$).

RESULTS: Patients were categorized into 2 groups (EDSS $<$ 6 versus $\geq$ 6). Variables with significant differences between groups were: brain parenchymal fraction ($P = .05$), white matter fraction ($P = .05$), MyCF ($P = .04$), and corpus callosum volume ($P = .04$). In the binary logistic regression analysis, the best predictor of the EDSS category was MyCF, with a *P* value of .08, and an OR of 0.59.

CONCLUSIONS: Our results confirm differences in volumetric parameters by EDSS by using a single MRI acquisition. Additionally, higher MyCF values were associated with lower disability, highlighting SyMRI and myelin quantification as potential tools for clinical practice.

ABBREVIATIONS: BPF = brain parenchymal fraction; EDSS = Expanded Disability Status Scale; FDR = false discovery rate; GMF = gray matter fraction; MyCF = global myelin fraction; NAGM = normal-appearing gray matter; PD = proton density; SyMRI = synthetic MRI; WMF = white matter fraction; NAWM = normal-appearing white matter

Synthetic MRI (SyMRI; SyntheticMR AB) is a short-time acquisition sequence that provides quantitative T1, R1, T2, R2, and proton density (PD) maps and creates synthetic images with different contrast weights by using a single acquisition. It also provides brain tissue segmentation, including global myelin fraction (MyCF)[1] without additional scan time. Previous studies have reported its use for detecting MS brain lesions on T2-FLAIR, with good reliability, though tending for more imaging artifacts[2,3] and for global and regional volumetric analysis as a proxy of brain atrophy.[4] In a cohort of relapsing-remitting MS, with a mean Expanded Disability Status Scale (EDSS) score of 3.0, brain parenchymal fraction (BPF), white matter fraction (WMF), gray matter fraction (GMF), and MyCF were diminished compared with healthy controls, while GMF and BPF were negatively associated with EDSS.[5] However, there is limited information regarding SyMRI parameters in progressive MS with greater disability.

Progressive MS is essentially characterized by a sustained and confirmed progression in disability throughout 3–6 months, which can manifest with or without disease activity.[6] Evidence suggests that progression can occur independently of relapse activity from the onset of the disease.[7] However, identifying patients with progressive MS in clinical practice poses a significant challenge due to fluctuating symptoms, limited consultation time, and interexaminer variations in established scales such as the EDSS. In this context, a cutoff of an EDSS of 6 is crucial as it represents an important milestone in a patient's progression, indicating that the patient requires a walking aid to walk approximately 100 m. Imaging biomarkers have emerged as potential tools for aiding in the detection of progression, with findings including gray and white matter damage, brain atrophy, spinal

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SUMMARY

PREVIOUS LITERATURE: SyMRI is a rapid imaging technique that generates quantitative maps (T1, T2, R1, R2, and proton density) and synthetic images from a single scan, enabling brain tissue segmentation and myelin quantification. It is valuable for detecting MS lesions and assessing brain atrophy. In relapsing-remitting MS, SyMRI reveals reduced brain parenchymal, white matter, and gray matter fractions, correlating with disability. Progressive MS, characterized by sustained disability progression, lacks easily applicable biomarkers. SyMRI shows potential as a tool for evaluating patients with greater disability.

KEY FINDINGS: In this study of 24 patients with progressive MS, MyCF was the only SyMRI-derived parameter associated with disability (EDSS $\geq$ 6). Logistic regression showed MyCF as the sole predictor of EDSS $<$ 6 versus $\geq$ 6, with an OR of 0.59, showing a trend toward significance ($P = .08$).

KNOWLEDGE ADVANCEMENT: Our study shows that SyMRI can differentiate volumetric parameters based on EDSS in patients with progressive MS with a single scan. Higher MyCF values were associated with lower disability, suggesting SyMRI and myelin quantification could be valuable tools for assessing and managing progressive MS in clinical practice.

cord damage, slowly expanding lesions, and thalamic damage.[8,9] Nevertheless, none of these biomarkers are readily identifiable and feasible in clinical practice, with good specificity and sensitivity for detecting progressive MS, and their assessment can be time consuming.[8] The MyCF demonstrated an association with the mean upper cervical area and appears to be a promising SyMRI parameter for distinguishing between relapsing and progressive MS.[10] Therefore, SyMRI presents itself as a promising and efficient tool for evaluating patients with progressive MS.

We aimed to analyze which of selected SyMRI parameters, R1, R2, PD, and myelin maps from normal-appearing white matter (NAWM), normal-appearing gray matter (NAGM), focal lesions, and corpus callosum, besides volumetric measures (BPF, GMF, WMF, and MyCF), would be associated with an EDSS $\geq$ 6 in progressive MS.

MATERIALS AND METHODS

Study Population

This is a convenience sample of patients diagnosed with progressive MS, according to the 2017 McDonald criteria for MS,[11] recruited in a single center between February and July 2021. Clinical data were retrospectively collected through medical reports.

Participants were required to meet specific inclusion and exclusion criteria. For inclusion, participants needed a diagnosis of progressive MS according to the 2017 McDonald criteria,[11] to be older than 18 years, and have available clinical data, including disease duration and neurologic disability assessments, collected retrospectively from medical reports. Additionally, they had to be able to undergo SyMRI acquisition. Exclusion criteria included other relevant neurologic conditions that might confound MRI interpretations, pregnancy or breastfeeding due to safety concerns with MRI scanning, and the inability to provide informed consent or comply with study procedures.

Disease duration was defined by the time of the first symptom until SyMRI acquisition.

Neurologic disability was assessed by using the EDSS during the visit closest to the MRI, scheduled within a month of proposing the SyMRI scan for study participation.

All patients gave written informed consent. The local ethics committee approved this study.

MRI Acquisition

Images were acquired on a 3T MRI scanner (Magnetom Trio, Siemens) by using a 20-channel head and neck coil and a 2D axial QRAPMASTER pulse sequence (multisection, multiecho, multisaturation delay saturation-recovery turbo spin-echo acquisition method in which images were collected for different combinations of TEs and saturation delay times)[1] with the following parameters: TR, 4800 ms; TI, 25 ms; TE, 23 ms/102 ms; flip angle, 150°; resolution, 0.898 mm $\times$ 0,898 mm $\times$ 4.0 mm; FOV, 186 mm $\times$ 230 mm; distance factor, 10%; acquisition time, 2 minutes: 34 seg.

The intracranial mask in SyMRI was obtained by including WM, GM, and CSF, followed by a region-growing algorithm to ensure a contiguous mask. The edge of the mask was defined at PD = 50, based on the assumption that the intracranial edge is halfway CSF (with PD = 100) and skull bone (PD = 0). Finally, the intracranial mask was reduced 0.5 mm smaller to remove the dura mater.

The tissue definitions of WM, GM, and CSF were defined by using analysis of R1, R2 and PD, as quantified by SyMRI (2019 User Manual, version 0.45.17).

The presence of myelin was obtained from a model that uses multiparametric quantitative MRI to estimate the presence of myelin and edema in the brain. The model relates the simultaneous measurement of R1 and R2 relaxation rates and PD to 4 partial volume compartments, consisting of myelin partial volume, cellular partial volume, free water partial volume, and excess parenchymal water partial volume.[12]

The corpus callosum was segmented by using FreeSurfer (http://surfer.nmr.mgh.harvard.edu),[13] and lesions by using the lesion segmentation toolbox.[14] As a quality control, we reviewed the above toolbox masks and made manual corrections when necessary. WM and GM maps were created with SyMRI. To obtain NAWM and NAGM, lesions were excluded from the respective original regions.

We selected automatic segmentation maps for brain parenchymal volume, white matter volume, gray matter volume, and global myelin volume (Fig 1), each divided by intracranial volume providing a respective fraction (BPF, WMF, GMF, MyCF). Also, quantitative values were derived from PD, R1, R2, and myelin maps for the following masks: NAWM, NAGM, focal lesions, and corpus callosum, as illustrated in Fig 1.

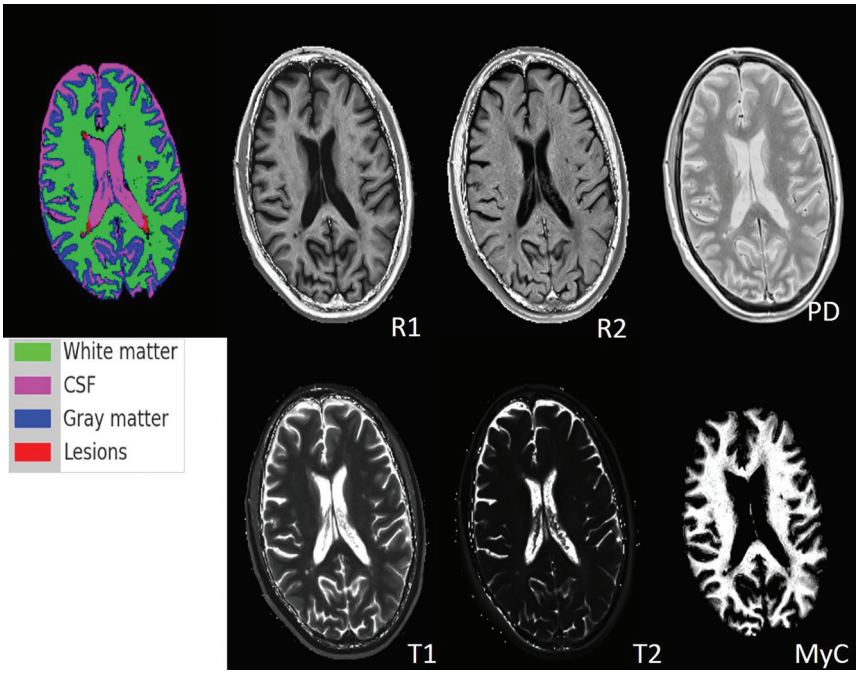

FIG 1. Segmentation maps and global myelin volume (MyC) derived from SyMRI, in a patient with EDSS < 6. Segmentation maps are depicted with different colors: *pink* for CSF, *blue* for gray matter, *green* for white matter, and *red* for lesions.

Table 1: Demographic information of the sample analyzed

	EDSS < 6 (*n*=13)	EDSS ≥ 6 (*n*=11)	*P* Value
Age[a]	48 (6.5)	47 (9)	.35
Woman, *n* (%)	5 (38.5%)	6 (54.5%)	.23
Disease duration[a]	16 (9)	21 (6)	.05
EDSS	5.0 (0.5)	6.5 (0.5)	<.01

Note:—All values are mean (standard deviation [SD]) unless specified.
[a] In years.

Statistical Analysis

Patients were categorized into 2 groups according to their EDSS (< 6 versus ≥ 6). The selection of an EDSS cutoff at 6 was based on its clinical significance as a marker of greater disability in MS. This cutoff was chosen to enhance the sensitivity of detecting meaningful differences in advanced disease stages and ensure comparability in dividing our sample into 2 groups.

For each variable, the SyMRI software provides mean, standard deviation, and asymmetry, and we focused on the mean values for analysis.

First, the normal distribution of the variables was assessed by using the Shapiro-Wilk test, while variance homogeneity was evaluated with the Levene test. Depending on the distribution, either a 1-tailed or 2-tailed independent samples *t* test, or a Mann-Whitney *U* test when appropriate, was conducted to compare SyMRI variables between groups. Both uncorrected *P* values and *P* values adjusted by using the false discovery rate (FDR) correction were reported. The uncorrected ones that were significantly different ($P \leq .05$) or showed a trend ($P > .05$ and < 0.09) were selected and analyzed through a univariate binary logistic regression, and 95% CIs were defined to further explore the relationship between these variables and EDSS. All statistical analysis was performed with SPSS statistics v22.0 (IBM).

RESULTS

A total of 24 patients were included, 4 of whom were defined as having primary-progressive MS, all included in the group EDSS < 6 (n=13). Table 1 shows the demographic and clinical characteristics of the cohort divided by EDSS group. All variables showed a normal distribution except the lesion volume (data not shown). The group with EDSS ≥ 6 presented a significant reduction compared with the group with EDSS < 6, in the following variables: BPF (−4.76%, P = .05), WMF (−8.46%, P = .05), MyCF (−9.74%, P = .04), corpus callosum volume (−25%, P = .04), corpus callosum myelin (−16.32%, P = .08), and focal lesion myelin (−16,33%, P = .08). Tables 2 and 3 summarize these findings, with absolute values for each variable.

As an example, Fig 1, created with SyMRI, illustrates a case with EDSS < 6, while Fig 2 depicts a case with EDSS ≥ 6.

In the binary logistic regression analysis, the only predictor of EDSS < 6 versus ≥ 6 with a trend relevance was MyCF, with an OR of 0.59 (95% CI: 0.327–1.072; P = .08).

DISCUSSION

In this study, we have obtained parameters derived from SyMRI in a cohort of 24 patients with progressive MS, to find a predictor of disability (EDSS ≥ 6). As expected, the group with higher EDSS presented lower BPF, WMF, and corpus callosum volume, as well as lower MyCF. In the binary logistic regression analysis incorporating the aforementioned variables, MyCF emerged as the sole predictor of EDSS < 6 versus ≥ 6, with an OR of 0.59 (95% CI: 0.327–1.072; P = .08), indicating a trend toward significance.

Admittedly, due to the exploratory nature of our study and the small sample size, the statistical power was limited, and most comparisons lost significance after applying the FDR correction. Despite this, we used the MyCF variable in the logistic regression, as it was the closest to achieving statistical significance.

The main advantages of SyMRI are the obtention of objective quantitative maps for relaxation rates, and PD without additional scan time, as well as myelin concentration quantification. It has been validated for use in diagnosing other neurologic pathologies, potentially requiring a conventional T2-FLAIR in cases of severe artifacts,[3] and it offers several possibilities for clinical applications, including Sturge-Weber syndrome, idiopathic normal pressure hydrocephalus, brain metastases detection, and MS.[15]

Table 2: Mean values of selected masks and *t* test of independent samples

		EDSS < 6	EDSS ≥ 6	*P* Value	*P* Value (2-Tailed)	FDR-*P*
Corpus callosum	Volume	2.51 (0.87)	1.88 (0.76)	.04[a]	.074	.370
	Myelin	21.87 (5.06)	18.30 (7.20)	.08[b]	.169	.374
	PD	68.02 (4.05)	70.24 (5.88)	.14	.289	.374
	R2	12.04 (1.42)	11.58 (2.04)	.26	.525	.525
	R1	1.08 (0.13)	1.01 (0.19)	.15	.299	.374
Lesion	Volume	12.73 (11.50)	18.28 (14.70)	.15[c]	.331	.414
	Myelin	9.43 (2.09)	7.90 (2.96)	.08[b]	.151	.380
	PD	81.28 (2,48)	83.11 (4.10)	.10	.193	.380
	R2	9.61 (0.75)	9.62 (0.96)	.12	.976	.976
	R1	0.85 (0.58)	0.82 (0.82)	.49	.228	.380
NAWM	Myelin	30.37 (1.34)	29.76 (1.18)	.13	.255	.393
	PD	65.65 (0.86)	66.03 (0.77)	.14	.277	.393
	R2	15.85 (0.24)	15.80 (0.54)	.36	.744	.744
	R1	1.35 (0.25)	1.34 (0.03)	.14	.295	.393
NAGM	Myelin	2.39 (0.17)	2.44 (0.29)	.29	.592	.789
	PD	84.97 (0.43)	84.85 (0.82)	.66	.661	.661
	R2	12.31 (0.15)	12.27 (0.25)	.58	.567	1
	R1	0.71 (0.01)	0.71 (0.02)	.31	.313	1

[a] $P < .05$.
[b] $P > .05$ and $< .09$, defined as trend. Values are displayed in mean (SD).
[c] Mann-Whitney *U* test values for volume are in mL; PD, and myelin in specific proportion units, R1 and R2 in s^{-1}.

Table 3: Volumetric values and *t* test of independent samples

	EDSS < 6	EDSS ≥ 6	*P* Value	*P* Value (2-Tailed)	FDR-*P*
BPF (%)	79.78 (5.34)	76.16 (5.24)	.05[a]	.093	.296
WMF (%)	38.15 (4.75)	34.93 (4.61)	.05[a]	.106	.296
GMF (%)	38.06 (2.35)	37.57 (2.46)	.31	.624	.624
MyCF (%)	12.212 (1.61)	11.053 (1.46)	.04[a]	.074	.296

[a] $P \leq .05$.

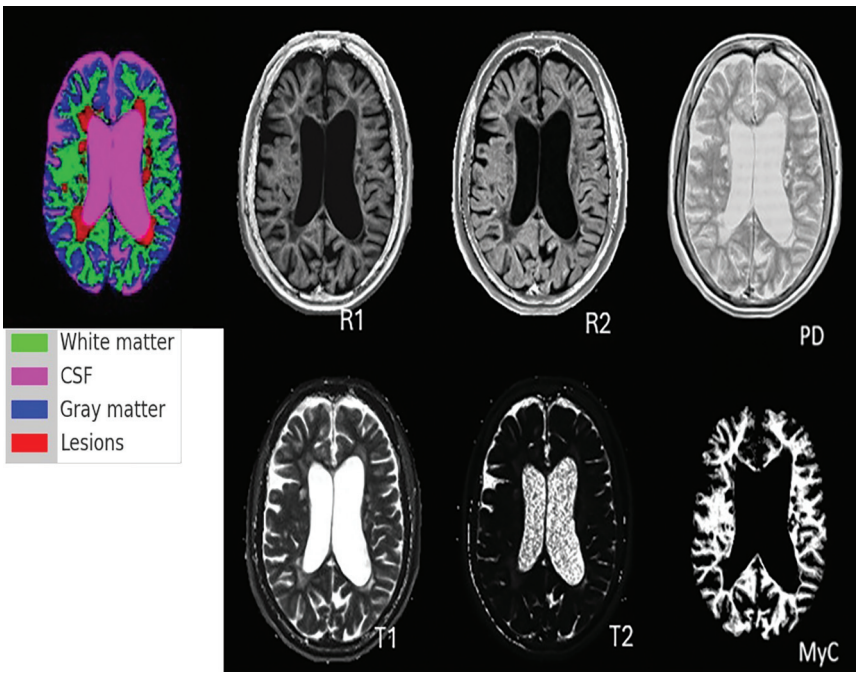

FIG 2. Segmentation maps and global myelin volume (MyC) derived from SyMRI, in a patient with EDSS ≥ 6. Segmentation maps are depicted with different colors: *pink* for CSF, *blue* for gray matter, *green* for white matter, and *red* for lesions.

In MS image analysis, it provides reliable global and regional volumetric measurements[4] and focal lesion identification,[2] although differences in the contrast of lesions and dirty-appearing WM caused discrepancies in lesion count and volume.[2]

A fast methodology for myelin quantification through MRI has the potential to be a valuable tool for analyzing progression and disability in MS, because demyelination is a cornerstone of MS pathophysiology and a significant driver of disability progression.[16] Thus, various mechanisms for promoting remyelination are currently being studied.[17]

The SyMRI validity of myelin quantification has been confirmed in other demyelinating diseases such as methylenetetrahydrofolate reductase deficiency, where it was compared with the established diffusion tensor imaging technique.[18]

Although atrophy has long been associated with disability,[19–21] and is measured quantitatively, it has several limitations: it is susceptible to individual dynamic biologic factors such as hydration, sex, age, and time of day, it requires a re-baseline MRI to account for pseudoatrophy, and is influenced by variations in scanners and software, which restrict its clinical implementation.

Global intracranial myelin volume measured by SyMRI has been described as a good predictor of spinal cord volume loss and brain atrophy,[10] associated with disease progression and disability.[22,23] These findings align with our study, wherein we found MyCF to a trend of association with an EDSS score ≥ 6.

This study is not without limitations, notably a small sample size that subsequently leads to limited statistical power. Furthermore, it is important to acknowledge that convenience sampling introduces acceptance and selection biases, potentially limiting the generalizability of the findings. Despite these limitations, we have chosen to describe the MyCF as a potential predictor. Further studies could analyze it in larger samples and with a prospective design to evaluate its potential as a predictor of disability.

CONCLUSIONS

Our study demonstrates that SyMRI can effectively differentiate volumetric parameters according to EDSS in patients with progressive MS by using a single MRI acquisition. Specifically, we found that higher MyCF values are associated with a trend toward lower disability. These findings highlight the potential of

SyMRI and myelin quantification as valuable tools in clinical practice, aiding in the assessment and management of progressive MS.

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Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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