Clinical disability predictors over the disease course in multiple sclerosis

V. Penati 1, E. Portaccio 1, R. Bonacchi 2, E. Fainardi 3, A. Caporali 1, I. Addazio 1, M. Betti 1, F. Chiappetta 1, E. De Meo 1, 4, M.P. Amato 1, 5

1 University of Florence, Department of NEUROFARBA, Florence, Italy, 2 Neuroradiology Department Vita-Salute San Raffaele University, Milan, Italy, 3 Neuroradiology Department, Careggi, Florence, Italy, 4 Institute of Neurology, Neuroinflammation department, University College of London, United Kingdom, 5 IRCCS Don Carlo Gnocchi Foundation, Florence, Italy

INTRODUCTION

Emerging evidence suggests that the pathological substrates underlying Multiple Sclerosis (MS) may vary over time, including focal demyelination, neurodegeneration, and compartmentalized chronic inflammation, such as leptomeningeal B-cell follicles.

Over recent decades, several Magnetic Resonance Imaging (MRI) derived biomarkers have been identified as correlates of clinical disability, providing prompts for better understanding how this dynamic and multifactorial pathological process impact on clinical ouctomes of MS patients.

AIM

To identify and compare the relevance of main predictors of clinical disability in MS using MRI-derived biomarkers, stratified by disease stage.

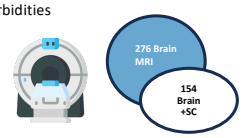
METHOD

Subjects and inclusion criteria

- 276 MS patients; 3 Tesla (3T) Brain MRI and clinical assessments using the EDSS throughout the follow-up period
- For a subset of patients (n = 154), availability of cervical spinal cord (cSC) MRI
- Absence of any neurological comorbidities

Three disease epochs

- 0-5 AA - EARLY STAGE
- 5-10 AA - MID STAGE
- >10 AA - LATE STAGE



MRI biomarkers

- Brain: Normalized Cortical Gray Matter Volume, Normalized Deep Gray Matter Volume, Normalized White Matter Volume, FLAIR White Matter Hyperintensities, T1-weighted White Matter Hypointensities, Normalized Cerebellar Volume, Normalized Brainstem Volume (T1-weighted) , Mean T1/T2 Ratio in White Matter , Mean T1/T2 Ratio in Cortex, Mean T1/T2 Ratio in Deep Gray Matter, Mean T1/T2 Ratio in White Matter Hyperintensities
- SC: Number of lesions (manually segmented using 3D Slicer), Cross-sectional area (analysed using SpinalCord Toolbox (SCT) and FSLeyes)

Analysis

Bayesian linear mixed-effects models within each epoch

- Brms package in R environment.
- EDSS as dependent variable

Scaled measures derived from brain MRI predictors

- Global and regional brain volumes
- T2 and T1 lesion volumes
- T1/T2 intensity ratios in the same areas

Image 1. Spinal Cord segmentation (Spinal Cord Toolbox)

RESULTS

	Brain (n= 276)	Brain + SC (n=154)	P value
Men/Women	91/185	52/102	<0.001
Mean age (SD) [years]	46.5 (13.8)	47.0 (14.7)	0.693
Median EDSS (IQR)	1.5 (0.0-2.0)	1.5 (1.0-2.0)	0.040
Median follow-up [years]	15.7 (8.0-19.0)	12.5 (7.0-15.8)	0.001
Annualized EDSS change (IQR)	0.200 (0.0769-0.400)	0.300 (0.138-0.451)	0.011
HET/MET/Switch	91/144/41	62/68/24	0.231
Total brain volume (SD)	0.725 (0.028)	0.720 (0.030)	0.174
Grey matter volume (SD)	0.398 (0.018)	0.395 (0.020)	0.620
White matter volume (SD)	0.312 (0.021)	0.310 (0.022)	0.268

Table 1. Demographic and clinical characteristics of the cohort

Associations between MRI variables and disability in the early, mid, and late stages

In the early phase, deep gray matter volume emerged as the main group indicator of clinical worsening.

During the intermediate phase, disability was associated with lesion-related metrics—T1-hypointense and T2-hyperintense lesion volumes—as well as with lower cortical gray matter, white matter, and brainstem volumes.

In the late stage, disability was linked to widespread brain and spinal atrophy with a more pronounced impact of white matter loss observed in the Brain+cSC group.

Phase	Parameter	Brain (β)	95% CI	Brain+SC (β)	95% CI
EARLY STAGE (<5 AA)	Normalized Deep Gray Matter Volume	-0.15	[-0.22 – -0.07]	-0.14	[-0.21 – -0.07]

Table 2. Associations between MRI variables and disability in the early stage of the disease

Phase	Parameter	Brain (β)	95% CI	Brain+SC (β)	95% CI
MID STAGE (5-10 AA)	White Matter Hypointensity Volume (T1-weighted)	2.60	[2.18 – 3.01]	2.64	[2.12 – 3.15]
	Normalized Cortical Gray Matter Volume	-1.15	[-1.41 – -0.87]	-1.00	[-1.31 – -0.70]
	Normalized White Matter Volume	-0.65	[-0.78 – -0.51]	-0.48	[-0.64 – -0.32]
	White Matter Hyperintensity Volume (FLAIR)	0.29	[0.16 – 0.41]	0.23	[0.06 – 0.39]
	Mean T1/T2 Cerebral Cortex	0.24	[0.18 – 0.29]	—	—
	Normalized Brainstem Volume (T1-weighted)	-0.52	[-0.61 – -0.43]	-0.51	[-0.61 – -0.42]
	Mean T1/T2 Deep Gray Matter	0.25	[0.16 – 0.35]	0.26	[0.17 – 0.36]

Table 3. Associations between MRI variables and disability in the mid stage of the disease

Phase	Parameter	Brain (β)	95% CI	Brain+SC (β)	95% CI
LATE STAGE (>10 AA)	Normalized Deep Gray Matter Volume	-0.46	[-0.85 – -0.07]	-0.64	[-1.00 – -0.27]
	Normalized Brainstem Volume (T1-weighted)	-0.39	[-0.58 – -0.20]	-0.30	[-0.49 – -0.11]
	Mean T1/T2 Cerebral Cortex	-0.38	[-0.71 – -0.05]	—	—
	Normalized Cortical Gray Matter Volume	-0.28	[-0.45 – -0.11]	-0.20	[-0.37 – -0.03]
	Normalized White Matter Volume	—	—	-0.79	[-1.08 – -0.49]

Table 4. Associations between MRI variables and disability in the late stage of the disease

CONCLUSIONS

This study demonstrates that MRI biomarkers associated with clinical disability in MS vary across disease stage, reflecting the evolving and multifaceted nature of its underlying pathology.

This dynamic approach may improve our ability to monitor and predict disease evolution, thereby supporting more targeted and personalized therapeutic strategies.

REFERENCES

- Calabrese M. et al. "Determinants and Biomarkers of Progression Independent of Relapses in Multiple Sclerosis." *Annals of neurology* (2024)
- De Meo E. et al. "An MRI assessment of mechanisms underlying lesion growth and shrinkage in multiple sclerosis." Annals of clinical and translational neurology (2025)
- Lublin F.et al. "How patients with multiple sclerosis acquire disability." Brain : a journal of neurology (2022)