

## Gray Matter Damage Predicts the Accumulation of Disability and Cognitive Impairment 13 Years Later in Patients With Multiple Sclerosis

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**Introduction.** In multiple sclerosis (MS), the relationship between conventional MRI findings and the clinical evolution of the disease is weak. Magnetization transfer (MT) MRI can provide markers reflecting the most disabling features of MS pathology.

**Objective.** To assess the value of conventional and MT MRI quantities of normal-appearing white matter (NAWM) and gray matter (GM) damage and their 12-month changes in predicting the long-term accumulation of disability and cognitive impairment in MS.

**Methods.** Conventional and MT MRI scans of the brain were obtained at baseline and after 12 months in 73 patients, who were followed prospectively with clinical visits for a median period of 13 years (range 12-17 years). At 13-year follow up, a neuropsychological assessment (Rao's Brief Repeatable Battery) was also performed whenever possible. At baseline and at 12 months, T2-hyperintense and T1-hypointense lesion volume, GM fraction, WM fraction, thalamic fraction, average lesion MT ratio (MTR), average GM MTR, average NAWM MTR and thalamic MTR were measured. A multivariate analysis, adjusted for follow-up duration, was performed to establish which variables were significant and independent predictors of long-term neurological deterioration and cognitive impairment.

**Results.** At 13-year follow-up, EDSS rating was performed in 67 patients. In 31 of them a neuropsychological evaluation was also performed. Forty-two patients (63%) showed a significant disability worsening (death=7 patients) and 30% were cognitively impaired. The multivariate model included baseline GM MTR ( $p=0.01$ , OR=0.97), GM MTR percentage change after 12 months ( $p=0.005$ , OR=1.22), and percentage reduction of GMF after 12 months ( $p=0.1$ , OR=0.91) as independent predictors of disability worsening at 13 years ( $r^2=0.22$ , C-index=77%). Baseline GM MTR ( $p=0.06$ , OR=0.83) and disease duration ( $p=0.04$ , OR=1.97) were the only variables associated to cognitive impairment ( $p=0.06$ , OR=0.83,  $r^2=0.86$ , C-index=99%).

**Conclusions.** GM damage is one of the key factors associated with long-term accumulation of disability and cognitive impairment in MS.

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