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Longitudinal Clinical and MRI Changes Suggestive of Subclinical Disease Progression in Egyptian Patients with Relapsing-Remitting Multiple Sclerosis: A Prospective Observational Study

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Abstract

Background

Progression independent of relapse activity (PIRA) is increasingly recognized as a major contributor to disability accumulation in relapsing-remitting multiple sclerosis (RRMS), reflecting ongoing neurodegeneration despite apparent control of inflammatory disease activity. However, longitudinal data integrating comprehensive clinical assessment with quantitative MRI biomarkers remain limited, particularly in North African populations.

Methods

This prospective observational cohort study included 50 patients with RRMS. Assessments at baseline, 6, and 12 months included the Expanded Disability Status Scale (EDSS), Symbol Digit Modalities Test (SDMT), Nine-Hole Peg Test (9-HPT), Timed 25-Foot Walk Test (T25-FWT), and Arabic Modified Fatigue Impact Scale (A-MFIS). Quantitative brain MRI, including regional volumetric analysis, cortical thickness measurements, and white matter lesion assessment, was performed at baseline and after one year.

Results

During the one-year follow-up, significant deterioration was observed in disability, cognitive performance, upper-limb function, and fatigue, whereas walking performance remained relatively stable. Clinically meaningful cognitive decline (≥ 4-point reduction in SDMT score) occurred in 24% of patients after 6 months and in 44% after one year. EDSS worsening was observed in eight patients at 6 months and seven patients at one year, including progression in 10.3% of patients without documented relapse during the second follow-up period. Quantitative MRI demonstrated significant longitudinal changes in multiple cortical and subcortical brain regions despite stable white matter lesion burden, and clinical deterioration was associated with regional brain volumetric alterations involving the thalamus, cortical and total gray matter, cerebellum, and temporal structures. Older age, longer disease duration, greater relapse burden, and delayed initiation of disease-modifying therapy (DMT) were associated with less favorable clinical outcomes and greater brain atrophy, whereas higher educational attainment and monosymptomatic disease onset were associated with better longitudinal cognitive performance.

Conclusion

One-year longitudinal follow-up demonstrated measurable changes across multiple clinical domains and regional brain structures consistent with early subclinical disease progression in RRMS despite limited inflammatory activity. Quantitative MRI combined with sensitive cognitive and functional assessments

detected changes beyond those captured by conventional disability measures, supporting their complementary role in monitoring early neurodegenerative progression.

Background

Multiple sclerosis (MS) is a chronic immune-mediated disorder of the central nervous system characterized by inflammation, demyelination, axonal injury, and progressive neurodegeneration. Although most patients initially present with RRMS, long-term disability is increasingly recognized to result not only from relapse-associated injury but also from gradual progression of neurological dysfunction that may occur independently of overt inflammatory activity. This evolving understanding has challenged the traditional view that disability accumulation in RRMS is primarily relapse driven and has highlighted the need for more sensitive markers of disease progression.[1]

Recent longitudinal studies have demonstrated that disability may accumulate despite the absence of clinical relapses or new inflammatory MRI activity, a phenomenon referred to as PIRA. Growing evidence suggests that PIRA contributes substantially to long-term disability even during the relapsing phase of MS, reflecting underlying neuroaxonal degeneration that is only partially captured by conventional clinical and radiological assessments. Consequently, reliance on relapse frequency or focal inflammatory lesions alone may underestimate ongoing disease progression.[2]

The Expanded Disability Status Scale remains the most widely used measure of neurological disability in MS; however, it has important limitations, particularly in detecting subtle cognitive impairment, upper-limb dysfunction, fatigue, and early functional decline. Similarly, conventional MRI measures, including T2 lesion burden and gadolinium-enhancing lesions, primarily reflect focal inflammatory activity and correlate only modestly with long-term disability. These limitations have prompted increasing interest in integrating more sensitive clinical and imaging biomarkers into routine disease monitoring. [3]

Advanced quantitative MRI techniques provide valuable insight into the neurodegenerative component of MS. Brain volumetric analysis and cortical thickness measurements enable the assessment of global and regional gray and white matter changes that may precede clinically detectable disability. Progressive cortical thinning, deep gray matter atrophy, and ventricular enlargement have consistently been associated with cognitive decline, physical disability, and unfavorable long-term outcomes. These imaging biomarkers therefore offer the potential to identify ongoing structural damage even in patients who appear clinically stable. [4]

Sensitive clinical outcome measures may further improve the detection of early disease progression. The SDMT is considered the most sensitive screening tool for cognitive impairment in MS, while the 9-HPT and T25-FWT objectively assess upper-limb dexterity and ambulatory function, respectively. Fatigue, one of the most disabling symptoms experienced by people with MS, is commonly evaluated using validated patient-reported outcome measures such as the A-MFIS). When combined with conventional

disability assessment, these measures provide a more comprehensive evaluation of neurological function than EDSS alone. [5]

Although quantitative MRI biomarkers may detect early neurodegenerative changes in multiple sclerosis, longitudinal studies integrating MRI with comprehensive clinical assessment remain limited, particularly in Middle Eastern and North African populations. The relationship between regional brain volume loss and subtle clinical deterioration in Egyptian patients with RRMS is also poorly characterized.

Methods

Therefore, this prospective longitudinal study evaluated clinical and radiological changes suggestive of subclinical disease progression over one year using standardized clinical assessments and quantitative MRI volumetric analysis, aiming to identify early markers of progression beyond conventional measures of inflammatory disease activity.

Study Design and Participants

This prospective longitudinal observational study was conducted at the Multiple Sclerosis Unit, Ain Shams University Hospitals, Cairo, Egypt. The study was conducted between January 2023 and July 2025, with the last follow-up completed in July 2025. Consecutive adult patients with RRMS attending the outpatient MS clinic were screened for eligibility. Of the 55 patients initially enrolled, five were excluded because of pregnancy or loss to follow-up, leaving a final analytical cohort of 50 patients.

Patients aged 18–60 years with a diagnosis of RRMS according to the 2017 McDonald criteria, an EDSS score of ≤ 4 consistent with the Lublin definition for non-progressive disease, and receiving DMT for at least six months before enrollment were eligible for inclusion. Patients with secondary progressive or primary progressive MS, clinical relapse or corticosteroid treatment within 30 days before assessment, other neurological or psychiatric disorders affecting cognitive or motor performance, severe visual impairment interfering with cognitive testing, major systemic illness, pregnancy, or contraindications to MRI were excluded.

Clinical Assessment

Participants underwent standardized neurological evaluations at baseline, 6 months, and 12 months. Demographic data, including age, sex, smoking status, educational level, and family history of multiple sclerosis or other autoimmune diseases, were collected. Disease-related characteristics were also recorded, including age at disease onset, disease duration, clinical presentation of the first attack, relapse history before and during the follow-up period, current DMT, and the interval between diagnosis and initiation of DMT.

Neurological disability was assessed at each visit by certified neurologists using the EDSS[6]. PIRA was defined according to established criteria as confirmed disability worsening in the absence of a clinical relapse, based on sustained EDSS progression relative to baseline that was confirmed after at least 3 months and persisted for 6 months.

Cognitive processing speed was evaluated using the Symbol Digit Modalities Test (SDMT) [7], with a decline of ≥ 4 points considered clinically meaningful cognitive deterioration. Upper-limb dexterity was assessed using the Nine-Hole Peg Test (9-HPT) [8], ambulatory function using the Timed 25-Foot Walk Test (T25-FWT)[9], and fatigue using the validated Arabic version of the Modified Fatigue Impact Scale (A-MFIS)[10]. A deterioration of ≥ 20% in the 9-HPT, T25-FWT, and A-MFIS scores was considered clinically significant worsening of upper-limb function, ambulatory performance, and fatigue, respectively.

MRI Acquisition and Image Processing

Brain MRI examinations were performed at baseline and after one year using a 1.5-T MRI scanner following the standardized institutional MS protocol. Conventional sequences included axial and sagittal fluid-attenuated inversion recovery (FLAIR), T2-weighted, T1-weighted, diffusion-weighted imaging, susceptibility-weighted imaging, and post-contrast T1-weighted imaging when clinically indicated.

Three-dimensional T1-weighted images were processed using FreeSurfer software for automated cortical reconstruction and volumetric segmentation. Whole-brain, cortical, subcortical, ventricular, cerebellar, gray matter, and white matter volumes, as well as cortical thickness measurements, were obtained according to the standard FreeSurfer processing pipeline. White matter lesion burden was assessed on FLAIR images. All image processing was performed using identical acquisition parameters and standardized post-processing procedures.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 25. Continuous variables were assessed for normality using the Shapiro–Wilk test. Normally distributed variables are presented as mean ± standard deviation (SD), whereas non-normally distributed variables are presented as median and interquartile range (IQR). Categorical variables are expressed as frequencies and percentages.

Longitudinal changes in continuous variables were evaluated using repeated-measures analysis or the corresponding non-parametric tests when appropriate. Pairwise comparisons between follow-up visits were adjusted for multiple comparisons. Associations between clinical and MRI variables were examined using Pearson or Spearman correlation coefficients according to data distribution. Univariable and multivariable regression analyses were performed to identify factors associated with longitudinal clinical deterioration and imaging changes. Statistical significance was defined as a two-sided p-value < 0.05.

Results

Participant Characteristics

Fifty patients with RRMS completed the study and were followed prospectively for one year. The mean age was 32.9 ± 8.1 years, and females comprised 88% of the study population. Baseline demographic and disease characteristics are summarized in Tables 1 and 2.

Longitudinal Clinical Outcomes

Longitudinal assessment demonstrated distinct trajectories across the evaluated clinical domains over the one-year follow-up period (Tables 3 and 4). Disability, assessed using the Expanded Disability Status Scale (EDSS), increased significantly during the first six months, with the median score rising from 1.25 to 1.5 ($p = 0.007$), and subsequently remained stable through the 12-month assessment.

Cognitive performance, measured by the SDMT, declined progressively throughout the study, with a highly significant reduction observed over the one-year follow-up ($p < 0.001$). By 12 months, 22 patients (44%) had experienced a clinically meaningful cognitive decline, defined as a reduction of at least four points from baseline.

Upper-limb dexterity demonstrated differential changes between the dominant and non-dominant hands. Performance on the dominant (right) 9-HPT deteriorated significantly at both the 6-month and 12-month assessments ($p < 0.001$), whereas no significant longitudinal change was observed in the non-dominant hand.

Ambulatory function, assessed using the T25-FWT, remained stable throughout the study, with no statistically significant change in walking speed over the one-year follow-up ($p = 0.056$).

Fatigue severity, measured by the A-MFIS, increased significantly during the first six months, with the median score rising from 39 to 42 ($p < 0.001$). At the 12-month assessment, fatigue scores decreased slightly to a median of 38.5, suggesting partial symptomatic recovery following appropriate symptomatic treatment, with no further deterioration observed during the second half of the follow-up period.

Disability Progression According to Relapse Status: RAW versus PIRA

During the one-year follow-up, 39 patients (78%) remained relapse-free, whereas 11 (22%) experienced at least one clinical relapse. At 6 months, EDSS progression was observed in eight patients and was significantly associated with relapse occurrence (54.5% [6/11] vs. 5.1% [2/39], $p < 0.001$). By 12 months, seven patients showed EDSS progression, with no significant difference between patients with and without relapses (27.3% [3/11] vs. 10.3% [4/39]). Notably, four of the seven patients (57.1%) with

disability progression at one year had remained relapse-free throughout follow-up. These findings suggest that relapse-associated worsening predominated early, whereas disability progression without documented relapse became more evident over time. (Table 5)

Longitudinal MRI Findings

Quantitative MRI demonstrated significant longitudinal structural changes involving several cortical and subcortical brain regions. Significant reductions were observed in regional gray matter structures, including the anterior cingulate cortex, caudate nuclei, insula, cerebellum, hippocampus, total white matter and third ventricular measurements, whereas white matter lesion burden remained relatively stable during follow-up. These findings indicate that structural brain changes occurred despite limited changes in conventional inflammatory MRI markers. (Table 6)

Clinical–Radiological Associations

Higher disability (EDSS) was significantly associated with lower total brain volume ($r = -0.300$, $p = 0.039$) and thalamus volume, with the strongest inverse association observed for thalamic volume. Higher EDSS scores were also associated with reduced total, cortical, and subcortical gray matter volumes, as well as frontal and temporal lobe volumes. Conversely, EDSS was positively correlated with hippocampal volume.

Better cognitive performance (SDMT) correlated with greater total brain ($r = 0.371$, $p = 0.008$) and total white matter volumes ($r = 0.368$, $p = 0.009$) and frontal lobe volume, whereas poorer SDMT performance was associated with larger hippocampal volume and greater deep white matter lesion burden.

Worse upper-limb dexterity and slower gait performance were associated with reduced total brain, gray matter, cerebellar, frontal, temporal, thalamic, and ventricular volumes. Higher fatigue scores were associated with lower cortical gray matter and frontal lobe volumes (Tables 8 and 9).

Influence of Demographic and Disease Characteristics

Older age and longer disease duration were associated with greater disability, poorer cognitive performance, slower walking speed, impaired upper-limb function, and increased fatigue. Longer disease duration also correlated with reduced total brain, cortical gray matter, cerebellar gray matter, left thalamic, and posterior cingulate volumes, together with greater infratentorial lesion burden.

Patients with higher educational attainment demonstrated significantly better cognitive performance and motor function at baseline and one-year follow-up, with higher SDMT scores, faster T25-FWT, better right- and left-hand 9-HPT performance, and lower EDSS scores (*all* $p < 0.05$). Education was not associated with fatigue severity.

Patients with monosymptomatic disease onset (56%) had more favorable clinical outcomes than those with polysymptomatic onset, including lower EDSS scores, higher SDMT scores, faster T25-FWT, shorter 9-HPT completion times, and lower A-MFIS scores at one year (*all* $p < 0.05$).

Greater relapse burden and delayed initiation of disease-modifying therapy were associated with higher EDSS scores, poorer cognitive and motor performance, greater fatigue, and more extensive regional brain atrophy, particularly involving the frontal lobes and cerebellum volumes.

Discussion

In this prospective longitudinal study, we investigated clinical and radiological changes in Egyptian patients with RRMS over one year using standardized clinical assessments and quantitative MRI volumetric analysis. Our findings demonstrate progressive deterioration in several functional domains despite relatively stable conventional MRI lesion burden. Regional brain volumetric changes were significantly associated with disability, cognitive impairment, and motor dysfunction, while several demographic and disease-related factors influenced the extent of clinical and radiological progression. Collectively, these findings suggest that subtle clinical deterioration may occur alongside structural brain changes during the relapsing phase of MS and support the complementary role of quantitative MRI and multidomain functional assessment in detecting early disease progression.

Our findings suggest that subtle disability accumulation may occur independently of overt inflammatory activity during the relapsing phase of MS. Although disability progression during the first six months was strongly associated with clinical relapses, this relationship was no longer significant at the 12-month assessment, and more than half of the patients with disability progression had remained relapse-free throughout follow-up. In parallel, conventional white matter lesion burden remained largely stable despite significant deterioration in disability, cognition, and upper-limb function. These observations are consistent with the growing recognition that progression in RRMS may occur through mechanisms extending beyond focal inflammatory lesions.

A particularly important finding was the close relationship between clinical deterioration and regional brain volumetric measures. Higher disability scores were associated with lower total brain, gray matter, frontal and temporal lobe, cerebellar, and thalamic volumes, with the strongest associations with thalamic volume. These findings agree with previous studies demonstrating that thalamic and cortical atrophy are among the earliest MRI markers of neurodegeneration in MS and correlate more closely with long-term disability than conventional lesion measures. Our results therefore support the complementary role of quantitative volumetric MRI in detecting structural changes that may not be reflected by lesion burden alone. [11], [12], [13], [14], [15]

The longitudinal clinical assessments demonstrated distinct patterns across functional domains. Cognitive processing speed declined progressively throughout follow-up, with 44% of patients experiencing clinically meaningful deterioration after one year, whereas walking performance remained relatively stable. Similarly, dominant-hand dexterity worsened despite minimal change in ambulatory performance. These findings highlight the limitations of relying solely on EDSS or walking-based assessments during the early stages of RRMS and emphasize the value of incorporating sensitive multidomain outcome measures such as the SDMT and 9-HPT into routine clinical monitoring. [16]

The observed decline in cognitive performance was accompanied by volumetric reductions total brain and frontal lobe volumes, as well as an increased deep white matter lesion burden 10, whereas deterioration in upper-limb function correlated with reduced cerebellar, cortical gray matter while greater fatigue was associated with cortical gray matter and frontal lobe atrophy. These findings further support the relationship between regional structural damage and functional impairment. [17], [18], [19]

An interesting finding was the apparent increase in global gray matter and frontal lobe volumes despite localized atrophy in several cortical and subcortical regions. Similar observations have been reported in early RRMS and have been attributed to transient inflammatory edema, reactive gliosis, or adaptive neuroplastic responses rather than true tissue growth. This apparent paradox highlights the limitations of global volumetric measures and emphasizes the importance of regional brain analysis, which may detect localized neurodegenerative changes that are obscured when only whole-brain or global gray matter volumes are considered. [11], [20], [21]

Several demographic and disease-related characteristics influenced longitudinal outcomes. Older age, longer disease duration, greater relapse burden, and delayed initiation of DMT were consistently associated with poorer clinical performance and more pronounced structural brain changes, whereas higher educational attainment and monosymptomatic disease onset were associated with more favorable functional outcomes. These findings support the concept of cognitive reserve and reinforce the importance of early diagnosis and prompt initiation of effective therapy to limit irreversible neurological damage. [22], [23], [24], [25]

The strengths of this study include its prospective longitudinal design, comprehensive multidomain clinical assessment, and integration of quantitative MRI volumetric analysis with standardized functional outcome measures. Nevertheless, several limitations should be acknowledged. The study was conducted at a single center with a relatively small sample size and one-year follow-up, which may have limited the ability to detect slower rates of progression. In addition, MRI acquisition was performed using a 1.5-T scanner, which may have reduced sensitivity for detecting subtle structural changes compared with higher-field imaging. Future multicenter studies with larger cohorts and longer follow-up are needed to validate these findings and further clarify the role of quantitative MRI biomarkers in monitoring disease progression.

In conclusion, this prospective study demonstrated that patients with RRMS experienced measurable clinical deterioration and significant regional brain volumetric changes over one year despite relatively stable conventional MRI lesion burden. The observed associations between quantitative MRI measures and multidomain clinical outcomes suggest that integrating brain volumetry with cognitive and functional assessments may facilitate earlier detection of disease progression beyond conventional clinical and radiological measures.

Abbreviations

9-HPT
Nine-Hole Peg Test
A-MFIS
Arabic Modified Fatigue Impact Scale
CNS
Central Nervous System
DMT
Disease-Modifying Therapy
EDSS
Expanded Disability Status Scale
FLAIR
Fluid-Attenuated Inversion Recovery
FMASU
Faculty of Medicine, Ain Shams University
IQR
Interquartile Range
MRI
Magnetic Resonance Imaging
MS
Multiple Sclerosis
PIRA
Progression Independent of Relapse Activity
PPMS
Primary Progressive Multiple Sclerosis
RRMS
Relapsing-Remitting Multiple Sclerosis
SD
Standard Deviation
SDMT
Symbol Digit Modalities Test
SPMS
Secondary Progressive Multiple Sclerosis
SPSS
Statistical Package for the Social Sciences
T1
T1-Weighted Imaging
T2
T2-Weighted Imaging
T25-FWT
Timed 25-Foot Walk Test

Declarations

Ethics approval and consent to participate

This study was submitted to and approved by the Ethical Review Committee, Faculty of Medicine, Ain Shams University (institutional IRB), under reference number (FMASU MD 92/2023). All experiments and procedures were performed in accordance with relevant guidelines and regulations, including the Declaration of Helsinki. Before the study was inaugurated, written informed consent was obtained from all study participants after adequately explaining the study aims and outcomes. The anonymity of the subjects was ensured, no identifying information was collected, and the results were stored in a secure location accessible only to the main author of the study.

Consent for publication: Not applicable

Availability of data and material

The dataset created and analyzed during the current study will be available from the corresponding author on the editor's request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

All authors had made a substantial contribution to the design of work, data collection and interpretation, writing the manuscript, revising it, and approving the final version.

Somaia Hamdy Zidan contributed to patient recruitment and/or data collection and made a major contribution to the drafting of the manuscript. Azza Abd El-Nasser Abd El-Aziz and Lobna Mohamed El-Nabil made a critical revision of the manuscript, Mohamed Aly Abd El-Hafeez, Aya Mohamed Shukry, and Mahmoud Saad Swelam contributed mainly to analysis, and interpretation of the findings. All authors reviewed and approved the final manuscript.

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Tables

Tables 1 to 8 are available in the Supplementary Files section.

Supplementary Files

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