RESEARCH ASSOCIATION

ABSTRACT BOOK

2026

Multiple Sclerosis Study Group Research Abstracts

123 abstracts · 12 thematic sections

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Cognitive Function and Cognitive Reserve

18 ABSTRACTS

001

Are We Misdiagnosing Memory Impairment in Multiple Sclerosis? The Role of Information Processing Speed in Visuospatial Learning

İrem Kara, Gözde Deniz Ünal, Ela Zengin, Serkan Ozakbas

BACKGROUND Visuospatial learning deficits are common in multiple sclerosis (MS). However, poor performance on learning tasks may reflect impaired information processing speed (IPS) rather than a primary memory deficit, potentially leading to clinical misinterpretation.

OBJECTIVES To determine whether reduced visuospatial learning performance in MS patients with IPS impairment reflects true memory dysfunction or a secondary effect of slowed processing speed.

METHODS This cross-sectional study included 397 MS patients. IPS was assessed using the Symbol Digit Modalities Test (SDMT); impairment was defined as $z \leq -1.5$. Participants were classified as IPS-impaired or IPS-preserved. Visuospatial learning was evaluated with the Brief Visuospatial Memory Test-Revised (BVMT-R), including Trial 1, Trial 2, Trial 3, and a learning index (Trial 3 − Trial 1). Group differences were analyzed, and multivariable regression models adjusted for age, education, EDSS, and disease duration. Sensitivity analyses additionally controlled for depression and fatigue.

RESULTS Among 397 patients, 27 were IPS-impaired and 370 IPS-preserved. IPS-impaired patients showed significantly lower BVMT-R scores on Trial 1 (3.52 ± 2.10 vs 7.13 ± 2.64), Trial 2 (5.11 ± 2.87 vs 10.05 ± 2.23), Trial 3 (6.00 ± 3.51 vs 10.85 ± 1.82), and the learning index (2.48 ± 2.69 vs 3.72 ± 2.13; all $p \leq 0.027$). They were also older and had higher EDSS scores and longer disease duration (all $p < 0.001$). In multivariable analyses, IPS impairment independently predicted lower performance on Trial 1 ($B = -2.07$, $p = 0.0005$), Trial 2 ($B = -3.20$, $p < 0.001$), Trial 3 ($B = -3.52$, $p < 0.001$), and the learning index ($B = -1.45$, $p = 0.004$). Findings remained stable after additional adjustment for depression and fatigue.

CONCLUSION Reduced BVMT-R performance in MS patients with IPS impairment should not automatically be interpreted as a primary memory deficit. Slowed processing speed substantially influences visuospatial learning performance and may lead to overestimation of true memory dysfunction. Integrating IPS into BVMT-R interpretation may improve the clinical accuracy of cognitive assessment in MS.

002

Information Processing Speed Shapes All Phases of Visuospatial Learning in Multiple Sclerosis

İrem Kara, Gözde Deniz Ünal, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Cognitive impairment in multiple sclerosis (MS) commonly affects information processing speed (IPS) and visuospatial learning. However, whether IPS impairment mainly influences initial encoding or also affects later learning stages remains unclear.

OBJECTIVES To examine the independent effect of IPS impairment on different phases of visuospatial learning, including initial encoding, later encoding, and overall learning gain.

METHODS This cross-sectional study included 397 MS patients. IPS was assessed using the Symbol Digit Modalities Test (SDMT), and impairment was defined as $z \leq -1.5$. Visuospatial learning was evaluated with the Brief Visuospatial Memory Test-Revised (BVMT-R). Trial 1 represented initial encoding, Trials 2-3 reflected later encoding, and a learning index (Trial 3 − Trial 1) measured overall learning gain. Hierarchical linear regression analyses were performed separately for each BVMT-R outcome, adjusting sequentially for age, education, EDSS, disease duration, depression, and fatigue.

RESULTS In fully adjusted models, IPS impairment was independently associated with poorer performance across all visuospatial learning components. IPS impairment predicted lower Trial 1 scores ($\beta = -0.169$, 95% CI −0.272 to −0.066, $p = 0.001$), indicating impaired initial encoding. The magnitude of association increased in later learning stages, including Trial 2 ($\beta = -0.305$, 95% CI −0.398 to −0.212, $p < 0.001$) and Trial 3 ($\beta = -0.390$, 95% CI −0.482 to −0.297, $p < 0.001$). IPS impairment was also independently associated with a lower learning index ($\beta = -0.200$, 95% CI −0.313 to −0.088, $p = 0.001$), reflecting reduced overall learning gain. Associations remained significant after adjustment for depression and fatigue.

CONCLUSION IPS impairment in MS affects not only initial encoding but also repeated encoding and cumulative learning gain. The progressively stronger associations across learning trials suggest that slowed processing speed increasingly disrupts learning efficiency over repeated exposures. These findings support IPS as a central determinant of visuospatial learning performance in MS and emphasize its broader role in cognitive dysfunction.

003

Information Processing Speed as a Primary Determinant of Visuospatial Learning in Multiple Sclerosis: Depression and Fatigue Do Not Explain the Effect

İrem Kara, Gözde Deniz Ünal, Ela Zengin, Serkan Ozakbas

BACKGROUND Depression and fatigue are common in multiple sclerosis (MS) and may negatively affect cognitive performance. It remains unclear whether the association between information processing speed (IPS) and visuospatial learning reflects a primary cognitive deficit or a secondary effect of symptom burden.

OBJECTIVES To determine whether IPS impairment independently contributes to visuospatial learning performance after controlling for depression and fatigue in MS patients.

METHODS A total of 397 MS patients were included. IPS was assessed using the Symbol Digit Modalities Test (SDMT), and impairment was defined as $z \leq -1.5$. Visuospatial learning was evaluated with the Brief Visuospatial Memory Test Revised (BVMT-R), including Trial 1, Trial 2, Trial 3, and a learning index (Trial 3 − Trial 1). Hierarchical linear regression analyses were performed for each BVMT-R outcome. Models were sequentially adjusted for age, education, EDSS, disease duration, depression, fatigue, and IPS impairment.

RESULTS A total of 397 MS patients were included. IPS was assessed using the Symbol Digit Modalities Test (SDMT), and impairment was defined as $z \leq -1.5$. Visuospatial learning was evaluated with the Brief Visuospatial Memory Test Revised (BVMT-R), including Trial 1, Trial 2, Trial 3, and a learning index (Trial 3 − Trial 1). Hierarchical linear regression analyses were performed for each BVMT-R outcome. Models were sequentially adjusted for age, education, EDSS, disease duration, depression, fatigue, and IPS impairment.

CONCLUSION The relationship between IPS and visuospatial learning in MS persists independently of depression and fatigue, supporting slowed processing speed as a primary cognitive deficit rather than a secondary effect of symptom burden. IPS impairment affects both early encoding and cumulative learning processes, highlighting its central role in cognitive dysfunction and the importance of considering IPS when interpreting visuospatial memory performance in MS.

004

Baseline Multidomain Cognitive Impairment Predicts Physical but Not Cognitive Trajectories Over 3 Years in Multiple Sclerosis

İrem Kara, Gözde Deniz Ünal, Ela Zengin, Serkan Ozakbas

BACKGROUND Cognitive impairment is a core feature of multiple sclerosis (MS), affecting information processing speed, verbal learning, and visuospatial memory. Although cross-sectional associations with disability are established, the prognostic value of multidomain cognitive impairment for long-term disease progression remains unclear.

OBJECTIVES To determine whether the severity of baseline multidomain cognitive impairment predicts 3-year changes in cognitive and physical outcomes in MS.

METHODS A total of 423 MS patients with baseline and 3-year follow-up assessments were included. Cognitive performance was assessed using the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test-II (CVLT-II), and Brief Visuospatial Memory Test-Revised (BVMT-R). Cognitive impairment was defined using normative cut-offs from healthy controls. Patients were stratified according to the number of impaired cognitive tests at baseline (0-3), representing increasing cognitive burden. Longitudinal changes in cognitive outcomes (SDMT, CVLT-II, BVMT-R) and physical outcomes (Timed 25-Foot Walk [T25FW], Nine-Hole Peg Test [9HPT]) were analyzed.

RESULTS All baseline cognitive groups showed modest improvements in cognitive test scores over 3 years (SDMT: +2.5 to +4.9; CVLT-II: +5.4 to +7.8; BVMT-R: +1.8 to +4.0), with no significant between-group differences in cognitive trajectories (all $p > 0.05$). In contrast, physical outcomes demonstrated progressively greater worsening with increasing baseline cognitive burden. T25FW increased by +7.83 in severely impaired patients versus +2.13 in cognitively preserved individuals. Similarly, 9HPT worsening ranged from +0.14 in cognitively preserved patients to +3.37 in those with very severe impairment ($p < 0.05$).

CONCLUSION Greater baseline multidomain cognitive impairment is associated with worse physical progression over time, despite similar cognitive trajectories across groups. The lack of differential cognitive decline may reflect practice effects and limited sensitivity of short-term follow-up. These findings suggest that cumulative cognitive burden is a marker of overall disease severity and may help identify MS patients at higher risk of future physical deterioration.

005

Baseline Cognitive Impairment Predicts Five-Year Physical and Cognitive Progression in Multiple Sclerosis

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BACKGROUND Cognitive impairment is common in multiple sclerosis (MS) and is associated with greater disease burden. Although cross-sectional associations between cognition and disability are well established, the prognostic value of baseline cognitive impairment for future progression remains unclear.

OBJECTIVES To determine whether baseline cognitive impairment predicts subsequent physical and cognitive progression over five years in patients with MS.

METHODS This study included 268 MS patients assessed using the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), including the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test-II (CVLT-II), and Brief Visuospatial Memory Test-Revised (BVMT-R). Patients were classified as cognitively impaired or cognitively preserved using established cut-offs. Baseline demographic and clinical variables, including EDSS, Timed 25-Foot Walk (T25FW), and 9-Hole Peg Test (9HPT), were recorded. Five-year progression was evaluated using longitudinal worsening in physical and cognitive measures.

RESULTS Of 268 patients, 48 (17.9%) were cognitively impaired at baseline and 220 (82.1%) cognitively preserved. Cognitively impaired patients were older (42.9 ± 11.4 vs 33.2 ± 10.0 years, $p < 0.001$), had longer disease duration (9.9 ± 9.1 vs 5.9 ± 9.9 years, $p = 0.007$), higher EDSS scores (2.09 ± 2.01 vs 1.31 ± 1.39, $p = 0.012$), and worse dominant-hand 9HPT performance (28.2 ± 22.5 vs 21.2 ± 10.3 seconds, $p = 0.040$). Baseline cognitive scores were lower across all BICAMS measures (all $p < 0.001$). During follow-up, cognitively impaired patients showed greater worsening in T25FW (31.3% vs 16.4%, $p = 0.029$), dominant-hand 9HPT (20.8% vs 8.6%, $p = 0.027$), SDMT (20.8% vs 7.7%, $p = 0.014$), and BVMT-R (27.1% vs 10.5%, $p = 0.005$). Longitudinal CVLT-II change did not differ between groups ($p = 0.952$).

CONCLUSION Baseline cognitive impairment in MS is associated with increased risk of subsequent physical and cognitive progression over five years. Greater worsening in walking speed, upper extremity motor performance, processing speed, and visuospatial memory suggests that cognitive impairment may represent an early marker of future disease progression and supports routine cognitive assessment in longitudinal MS monitoring.

006

Baseline Neurological Disability Predicts Five-Year Cognitive Worsening Beyond Baseline Cognition in Multiple Sclerosis

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BACKGROUND Identifying people with multiple sclerosis (MS) at risk of long-term cognitive decline remains challenging. Whether baseline neurological disability predicts future cognitive worsening independently of baseline cognition is unclear.

OBJECTIVES To determine whether baseline disability predicts five-year cognitive worsening beyond baseline cognition and to compare its association with physical deterioration.

METHODS People with MS completing baseline and five-year assessments were included. Disability was assessed using the Expanded Disability Status Scale (EDSS). Cognition was evaluated with the Symbol Digit Modalities Test, California Verbal Learning Test, and Brief Visuospatial Memory Test-Revised; physical performance with the Timed 25-Foot Walk and Nine-Hole Peg Test. Cognitive worsening was defined as a ≥20% decline in at least one cognitive test, and physical worsening as a ≥20% increase in completion time on either physical test. Multivariable logistic regression examined baseline EDSS as a predictor of cognitive worsening, adjusted for age, sex, disease duration, education, and a baseline cognitive composite. A separate model assessed physical worsening after adjustment for baseline physical performance.

RESULTS Among 322 participants, 74 (23.0%) showed cognitive worsening. Its frequency increased from 15.5% in those with baseline EDSS 0-1.5 to approximately 50% in those with EDSS ≥5. Each one-point increase in baseline EDSS independently increased the odds of cognitive worsening by 24% (OR=1.24, 95% CI 1.04- 1.48; p=0.016). Lower baseline cognition (OR=1.39 per 1-SD decrease, 95% CI 1.08-1.79; p=0.011) and older age (OR=1.03 per year, 95% CI 1.00-1.06; p=0.034) were also independent predictors. Sex, disease duration, and education were not significant. Physical worsening occurred in 75 participants (23.3%), and baseline EDSS independently predicted this outcome (OR=1.20 per point, 95% CI 1.01-1.44; p=0.042). Estimates in the highest EDSS categories should be interpreted cautiously because of small subgroup sizes.

CONCLUSION Baseline EDSS predicted five-year cognitive worsening independently of baseline cognition and was also associated with physical deterioration. Combining disability and cognitive assessments may improve long-term risk stratification and identify people requiring closer monitoring.

007

Differential Contributions of EDSS Functional Systems to Cognitive Decline in Multiple Sclerosis: A 5-Year Longitudinal Analysis

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BACKGROUND Cognitive impairment is a major feature of multiple sclerosis (MS), yet its relationship with neurological disability remains incompletely understood. The Expanded Disability Status Scale (EDSS) total score may mask the distinct contributions of individual functional systems to cognition.

OBJECTIVES To determine which EDSS functional system scores are associated with baseline cognitive performance and 5-year cognitive decline, and to evaluate motor-cognitive progression phenotypes.

METHODS This longitudinal study included 120 individuals with MS with baseline EDSS functional system scores and cognitive assessments, with follow-up closest to 5 years (4-6 years). Functional systems included pyramidal, cerebellar, brainstem, sensory, bowel/bladder, visual, and mental scores. Cognition was assessed using the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test-II (CVLT-II), and Brief Visuospatial Memory Test (BVMT). Cognitive decline was defined as ≥20% worsening in at least one cognitive test, while motor progression was defined as ≥1-point worsening in at least one EDSS functional system. Regression analyses adjusted for age and disease duration were performed.

RESULTS Participants had a mean age of 38.3±10.6 years, disease duration of 9.2±12.4 years, and EDSS score of 2.03±1.88. At baseline, pyramidal dysfunction showed the strongest association with cognition, particularly SDMT (rho=−0.36, $p<0.001$) and BVMT (rho=−0.24, $p=0.009$). Cerebellar dysfunction correlated with SDMT, CVLT-II, and BVMT (all $p<0.05$), while sensory dysfunction was associated with SDMT (rho=−0.34, $p<0.001$). During follow-up, 16 participants (13.3%) exhibited cognitive decline and 38 (31.7%) showed motor progression. Phenotypes were distributed as stable (63.3%), motor-driven (23.3%), combined (8.3%), and cognition-driven (5.0%). Baseline pyramidal dysfunction independently predicted cognitive decline (OR=2.63, $p=0.005$), whereas sensory worsening was associated with longitudinal cognitive decline (OR=5.16, $p=0.008$).

CONCLUSION EDSS functional systems demonstrate differential associations with cognitive performance and longitudinal decline in MS. Pyramidal dysfunction showed the most consistent relationship with cognition, while sensory and cerebellar systems contributed to domain-specific outcomes. Motor and cognitive progression were partially dissociated, supporting a more granular interpretation of EDSS beyond the total score.

008

Baseline Cognitive Reserve Selectively Predicts Early Cognitive but Not Physical Decline in Multiple Sclerosis: A 3-Year Longitudinal Study

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BACKGROUND Cognitive reserve (CR) is thought to confer resilience against cognitive decline in multiple sclerosis (MS), yet its influence on the temporal sequence of disability progression across cognitive and physical domains remains unclear.

OBJECTIVES To determine whether baseline cognitive reserve predicts the domain of earliest clinical deterioration - cognitive versus physical - over a 3-year follow-up in MS.

METHODS In this longitudinal cohort study, 124 patients with MS underwent baseline assessment of cognitive reserve using a composite BRIA-based measure. Participants were followed annually for 3 years with the Brief International Cognitive Assessment for MS (BICAMS), Timed 25-Foot Walk (T25FW), and 9-Hole Peg Test (9HPT). Clinically meaningful worsening was defined using established reliable change indices. Patients were classified into three groups based on the first domain of deterioration: cognitive-first (BICAMS), physical-first (T25FW and/or 9HPT), or stable (no significant decline). Between-group differences in baseline CR were assessed using ANOVA, and multinomial logistic regression was performed adjusting for demographic and disease-related covariates.

RESULTS During follow-up, 38 patients (30.6%) exhibited cognitive-first deterioration, 34 (27.4%) physical-first deterioration, and 52 (41.9%) remained stable. Baseline cognitive reserve differed significantly across groups ($F=9.12$, $p<0.001$), being lowest in the cognitive-first group (92.4±11.8), intermediate in the physical-first group (98.7±10.5), and highest in the stable group (104.3±9.6). Post-hoc analyses confirmed significantly lower CR in the cognitive-first group compared to the stable group ($p<0.001$), whereas differences between the physical-first and stable groups were not statistically significant ($p=0.08$). In adjusted multinomial logistic regression, lower baseline CR independently predicted cognitive-first deterioration (OR=1.08 per unit decrease, 95% CI: 1.03-1.14, $p=0.002$), but was not associated with physical-first deterioration (OR=1.02, $p=0.41$). Higher baseline EDSS ($p=0.01$) and progressive MS phenotype ($p=0.03$) were the main predictors of physical-first decline.

CONCLUSION Baseline cognitive reserve selectively predicts earlier cognitive decline but not physical disability progression in multiple sclerosis. These findings support a domain-specific protective effect of cognitive reserve, suggesting it primarily buffers against cognitive vulnerability rather than motor system deterioration.

009

Dynamic Cognitive Reserve Is Associated With Long-Term Cognitive Trajectories in Multiple Sclerosis

Serkan Ozakbas, İrem Kara, Gözde Deniz Ünal, Ulvi Samadzade

BACKGROUND Cognitive reserve may protect against cognitive impairment in multiple sclerosis (MS), but whether longitudinal changes in reserve-related activities are associated with long-term cognitive trajectories remains unclear.

OBJECTIVES To investigate whether changes in cognitive reserve over eight years are associated with changes in cognitive performance in people with MS.

METHODS Fifty-eight people with MS completed the Brief International Cognitive Assessment for MS cognitive reserve questionnaire (BRIA) and the Brief International Cognitive Assessment for MS (BICAMS) at baseline and after 8.1±0.6 years. BICAMS included the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test-II (CVLT-II), and Brief Visuospatial Memory Test-Revised (BVMT-R). Demographically adjusted z-scores and a global BICAMS composite were calculated. Change scores represented follow-up minus baseline values. Associations between BRIA and cognitive changes were examined using Pearson correlations and hierarchical linear regression adjusted for age, sex, disease duration, baseline cognition, baseline Expanded Disability Status Scale (EDSS), and EDSS change.

RESULTS Mean age was 38.6±8.2 years, 70.7% were women, and median baseline EDSS was 2.0 (IQR 1.5-3.0). BRIA scores increased by a mean of 1.8±7.4 points, with substantial interindividual variability. Greater BRIA increases were associated with more favourable changes in global BICAMS performance (r=0.34, p=0.009), SDMT (r=0.38, p=0.003), and BVMT-R (r=0.27, p=0.041), but not CVLT-II (r=0.16, p=0.229). After adjustment, BRIA change remained independently associated with global BICAMS change (standardised β=0.29, p=0.018), explaining an additional 7.2% of variance beyond baseline cognition and clinical covariates. BRIA change also independently predicted SDMT change (β=0.33, p=0.009), whereas associations with BVMT-R and CVLT-II were no longer significant.

CONCLUSION Maintenance or improvement of cognitive reserve-related activities was independently associated with more favourable eight-year cognitive trajectories, particularly in information processing speed. Cognitive reserve may therefore represent a dynamic and potentially modifiable factor, although interventional studies are needed to determine whether enhancing reserve-related activities improves long-term cognition in MS.

010

Physical Activity Enhances the Cognitive Benefits of Cognitive Reserve in Multiple Sclerosis

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BACKGROUND Cognitive reserve (CR) contributes to resilience against cognitive decline in multiple sclerosis (MS), but its protective effect varies across individuals. Physical activity may influence how effectively CR translates into preserved cognitive functioning.

OBJECTIVES To investigate whether physical activity moderates the relationship between cognitive reserve and cognitive performance in MS.

METHODS This cross-sectional study included MS patients with measures of cognitive reserve, physical activity, and neuropsychological performance. Cognitive reserve was assessed using the BRIA score, and physical activity with the Godin Leisure-Time Exercise Questionnaire. Cognitive outcomes included information processing speed (SDMT), verbal learning (CVLT), visuospatial learning (BVMT-R total score), and a global cognitive composite z-score. Multiple linear regression analyses adjusted for age, sex, disease duration, and EDSS. Moderation effects were examined using a BRIA × physical activity interaction term.

RESULTS Higher cognitive reserve was associated with better global cognition ($p = .023$), faster information processing speed (SDMT, $p = .021$), and better visuospatial learning (BVMT-R, $p = .020$), whereas the association with verbal learning did not reach significance ($p = .075$). Physical activity alone was not significantly associated with cognitive outcomes (all $p > .50$). A significant interaction between cognitive reserve and physical activity was observed for visuospatial learning (BVMT-R total score; $\beta = 1.34$, $p = .028$), indicating that the cognitive benefit of reserve depended on activity level. No interaction effects were found for global cognition, SDMT, or CVLT (all $p > .16$). Simple slope analyses showed that cognitive reserve was unrelated to visuospatial performance at low physical activity levels ($p = .751$), became significant at moderate activity ($p = .020$), and was strongest at high activity levels ($p < .001$).

CONCLUSION The protective effect of cognitive reserve in MS is not uniformly expressed across individuals. Physical activity significantly moderates the relationship between cognitive reserve and visuospatial learning, with little observable benefit of reserve among physically inactive patients. These findings suggest that physical activity may enhance or enable the cognitive benefits of reserve and represent a modifiable pathway for improving cognitive outcomes in MS.

011

Intensity of Physical Activity Differentially Relates to Cognitive and Physical Performance in Multiple Sclerosis

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BACKGROUND Regular physical activity has been associated with better cognitive and physical outcomes in multiple sclerosis (MS). However, it remains unclear whether all activity intensities contribute equally to these associations or whether moderate-to-vigorous activity is more strongly related to neurological function than mild activity.

OBJECTIVES To examine the independent associations of different physical activity intensities with cognitive and physical performance in patients with MS.

METHODS A total of 567 patients with MS were included. Leisure-time physical activity was assessed using the Godin Leisure-Time Exercise Questionnaire (GLTEQ), generating separate mild, moderate, and strenuous activity scores. A moderate-to-vigorous physical activity (MVPA) score was calculated by combining the moderate and strenuous components. Cognitive performance was evaluated using the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), including the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test-II (CVLT-II), and Brief Visuospatial Memory Test-Revised (BVMT-R). Physical performance was assessed using the Timed 25-Foot Walk (T25FW) and 9-Hole Peg Test (9HPT). Associations between physical activity intensity and functional outcomes were examined .

RESULTS Higher total GLTEQ scores were independently associated with better cognitive performance and better physical function. However, these associations were primarily driven by moderate-to-vigorous activity rather than mild activity. MVPA was independently associated with all cognitive and physical outcomes, with the strongest relationships observed for information processing speed (SDMT: $\beta=0.28$, $p<0.001$) and walking performance (T25FW: $\beta=-0.26$, $p<0.001$). ignificant independent associations were also observed for CVLT-II ($\beta=0.19$, $p=0.004$), BVMT-R ($\beta=0.17$, $p=0.009$), and 9HPT ($\beta=-0.18$, $p=0.006$). In contrast, after multivariable adjustment, mild activity was not independently associated with any cognitive or physical outcome (all $p>0.05$).

CONCLUSION The relationship between leisure-time physical activity and neurological function in MS appears to depend more on activity intensity than total activity volume. These findings suggest that physical activity intensity may be a more informative marker of preserved neurological function than total leisure-time activity in MS. Prospective studies are warranted to determine whether increasing moderate-intensity physical activity leads to improved long-term cognitive and physical outcomes.

012

Cognitive Reserve Is Independently Associated With Dual-Task Cognitive Performance Beyond Processing Speed in Multiple Sclerosis

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BACKGROUND Dual-task walking requires simultaneous cognitive and motor resource allocation and is frequently impaired in multiple sclerosis (MS). Although information processing speed is an important determinant of dual-task performance, individuals with similar processing speed often show different cognitive performance during walking. Cognitive reserve may explain this additional variability.

OBJECTIVES To determine whether cognitive reserve independently explains cognitive performance during dual-task walking beyond processing speed, neurological disability, and walking performance.

METHODS This cross-sectional study included people with MS who completed standardized single- and dual-task walking assessments. During dual-task walking, participants performed a concurrent verbal task, and cognitive performance was quantified by the number of correct responses. Cognitive reserve was assessed using the Cognitive Reserve Index Questionnaire (CRIq), information processing speed with the Symbol Digit Modalities Test (SDMT), neurological disability with the Expanded Disability Status Scale (EDSS), and walking performance with the mean Timed 25-Foot Walk (T25FW). Spearman correlations examined associations between CRIq and dual-task cognitive performance. Hierarchical linear regression entered age, sex, EDSS, T25FW, and SDMT in the first step, followed by CRIq. Robust standard errors were applied.

RESULTS Complete data were available for 60 participants (mean age 39.6±8.8 years; median EDSS 2.0 [IQR 1.5- 2.5]). Higher cognitive reserve was associated with better dual-task cognitive performance (ρ=0.468, $p<0.001$). Education, occupational activity, and leisure domains were each significantly associated with the number of correct responses (all $p\leq0.006$). Age, sex, EDSS, walking performance, and SDMT explained 43.0% of the variance in dual-task cognitive performance. Adding cognitive reserve explained an additional 5.5% ($\Delta R2=0.055$; $p=0.021$). In the final model, cognitive reserve ($\beta=0.282$, $p=0.022$) and SDMT ($\beta=0.599$, $p<0.001$) remained independent predictors, explaining 48.5% of the variance.

CONCLUSION Cognitive reserve was independently associated with cognitive performance during dual-task walking beyond processing speed, disability, and walking performance. These findings suggest that cognitive reserve captures aspects of cognitive-motor integration not reflected by conventional processing-speed measures alone.

013

Clinical and Cognitive Correlates of STROOP Test Performance in Multiple Sclerosis

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BACKGROUND Cognitive impairment is common in multiple sclerosis (MS), affecting information processing speed, memory, attention, and executive functions. The STROOP test assesses inhibitory control, selective attention, and cognitive flexibility, but its clinical and cognitive correlates in MS remain incompletely characterized.

OBJECTIVES To investigate the clinical and cognitive correlates of STROOP test performance in people with MS.

METHODS This cross-sectional study included 55 people with MS who underwent standardized clinical and cognitive assessments. Cognitive performance was evaluated using the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test (CVLT), Brief Visuospatial Memory Test-Revised (BVMT-R), and the STROOP test, in which higher scores indicate poorer performance. Clinical variables included age, disease duration, Expanded Disability Status Scale (EDSS), Patient Determined Disease Steps (PDDS), relapse history, MS phenotype, and disease-modifying treatment (DMT) category. Group comparisons were performed using the Mann-Whitney U test, associations were examined using Spearman correlation analysis, and a multivariable linear regression model including SDMT, CVLT, and BVMT-R scores was used to identify cognitive measures independently associated with STROOP performance.

RESULTS Fifty-five participants were included (67.3% women; mean age 40.9±10.7 years; mean disease duration 12.1±6.8 years). STROOP scores were significantly higher in participants with secondary progressive MS than in those with relapsing-remitting MS (49.84±13.03 vs 35.00±16.32; p=0.018), whereas no differences were observed according to sex (p=0.484) or DMT category (p=0.424). Poorer STROOP performance correlated with older age (ρ=0.434, p=0.001), longer disease duration (ρ=0.282, p=0.037), higher EDSS scores (ρ=0.352, p=0.008), lower SDMT scores (ρ=-0.614, p<0.001), lower CVLT scores (ρ=-0.348, p=0.009), and lower BVMT-R scores (ρ=-0.399, p=0.003). In the multivariable model, only SDMT remained independently associated with STROOP performance (standardized β=-0.542, p=0.003), explaining approximately 25% of the variance in STROOP scores (R2=0.248; adjusted R2=0.204; p=0.002)

CONCLUSION Poorer STROOP performance was associated with greater disease burden and lower cognitive performance in people with MS. SDMT was the only independent predictor, suggesting that STROOP mainly reflects information processing speed in this cohort. Findings should be interpreted cautiously due to the modest sample size and limited number of participants with secondary progressive MS.

014

Error-Based Cognitive Measures Identify Cognitive Vulnerability Beyond Conventional Test Scores in Multiple Sclerosis

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BACKGROUND Cognitive assessment in multiple sclerosis (MS) mainly relies on correct-response scores. Error-based measures may capture response accuracy, monitoring, and cognitive efficiency.

OBJECTIVES To determine whether error-based measures reflect cognitive impairment extent and signal longitudinal worsening in MS.

METHODS This longitudinal study included 267 people with MS assessed at baseline, 6 months, 1 year, and 2 years. Cognition was evaluated using the SDMT, CVLT-II, and BVMT-R. Impairment extent was the number of impaired tests (0-3); worsening was an increase at follow-up. SDMT error rate, CVLT-II intrusion and repetition rates, and dual-task cognitive accuracy were examined using Spearman correlations and Mann- Whitney U tests.

RESULTS Classification was available for 266 participants: 15 worsened, 222 remained stable, and 29 improved. Higher SDMT error rates were associated with more impaired domains at baseline (r_s=0.195, p=0.001) and follow-up (r_s=0.155, p=0.011). Participants who worsened had higher baseline SDMT error rates than those stable or improved (median 3.0% vs 0%; p=0.020). Higher CVLT-II intrusion rates were associated with greater impairment at baseline (r_s=0.162, p=0.034) and follow-up (r_s=0.128, p=0.038); increases in intrusion rate paralleled increases in impaired domains (r_s=0.174, p=0.023). Lower dual-task cognitive accuracy was associated with greater impairment at baseline (r_s=−0.172, p=0.005) and follow-up (r_s=−0.209, p<0.001). CVLT-II repetition rate was not significant.

CONCLUSION Error-based measures provide information beyond correct-response scores. Baseline SDMT errors signalled subsequent worsening, CVLT-II intrusions tracked multidomain progression, and dual-task accuracy reflected the functional expression of cognitive impairment. These metrics may strengthen cognitive monitoring in MS.

015

Symbol Digit Modalities Test Errors Reveal Long-Term Cross-Domain Cognitive Vulnerability in Multiple Sclerosis

Ela Zengin, Gözde Deniz Ünal, Can Caliskan, İrem Kara, Ebru Isgandarli, Serkan Ozakbas

BACKGROUND Cognitive assessment in multiple sclerosis (MS) relies mainly on correct-response scores, which may miss differences in accuracy and error monitoring. Symbol Digit Modalities Test (SDMT) errors may reflect inefficiency and predict decline in other domains.

OBJECTIVES To test whether baseline SDMT errors predict visuospatial memory decline beyond conventional scores.

METHODS Among 267 people with MS, 52 completed about five-year follow-up. After excluding missing, zero-coded, or clinically implausible endpoint values, 49 had paired SDMT and Brief Visuospatial Memory Test-Revised (BVMT-R) data. Median follow-up was 4.87 years (IQR: 4.49-5.26). Error rate was the proportion of incorrect responses among all attempts; participants were classified by at least one baseline error. Change was follow up minus baseline score; at least 20% BVMT-R decline was substantial. Wilcoxon, Spearman, Mann-Whitney U, and Fisher exact tests were used.

RESULTS Over five years, SDMT correct responses improved (median: 53 vs 58; p=0.002) and error rate decreased (p=0.023). BVMT-R showed no significant group-level decline (median: 27 vs 31; p=0.081). Higher baseline SDMT error rate correlated with greater BVMT-R decline (r(cid:0)=-0.330, p=0.021). Participants with at least one baseline error had a median BVMT-R change of -1.5 points (IQR: -9.5 to 3.0), versus 4.0 points (IQR: 0.5-6.0) without errors (p=0.032). Substantial decline occurred in 38.9% (7/18) versus 6.5% (2/31), corresponding to approximately nine-fold greater odds (odds ratio=9.23; Fisher exact p=0.008). Baseline SDMT error rate was unrelated to subsequent SDMT correct-response change (r(cid:0)=−0.026, p=0.859).

CONCLUSION SDMT errors provide clinically relevant information beyond the conventional correct-response score in people with MS. Even a single baseline SDMT error identified individuals at substantially increased risk of five-year visuospatial memory decline despite stable or improving group-level processing-speed performance. These findings suggest that systematic assessment of SDMT error patterns may enhance the early identification of long-term cognitive vulnerability that is not captured by conventional SDMT scoring. Given the relatively small and younger longitudinal sample, these hypothesis-generating findings should be confirmed in larger prospective cohorts

016

Domain-Specific Association Between Disease Severity Scores and Cognitive Worsening in Multiple Sclerosis

Ulvi Samadzade, Tuncay Basaran, Can Caliskan, Yasemin Şimşek Aras, Serkan Ozakbas

BACKGROUND Cognitive impairment is a common and disabling manifestation of multiple sclerosis (MS), affecting processing speed, memory, and visuospatial functions. Disease severity indices such as the Multiple Sclerosis Severity Score (MSSS) and Age-Related MSSS (ARMSSS) are widely used to estimate long-term disability; however, their association with longitudinal cognitive decline remains insufficiently characterized.

OBJECTIVES To investigate the association between baseline MSSS and ARMSSS scores and domain-specific cognitive worsening over a 3-year follow-up period in a real-world MS cohort.

METHODS We retrospectively analyzed 409 patients with MS who underwent cognitive assessments at baseline and after at least 3 years. Cognitive function was evaluated using the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test (CVLT), and Brief Visuospatial Memory Test (BVMT). MSSS and ARMSSS scores were recorded at baseline. Group comparisons between patients with and without cognitive worsening were performed using the Mann-Whitney U test.

RESULTS The cohort included 409 patients (69.9% female), with a mean baseline EDSS of 1.71 ± 1.87. The majority had relapsing-remitting MS (88.8%), followed by secondary progressive (8.1%) and primary progressive MS (3.2%). Mean MSSS and ARMSSS scores were 2.30 ± 2.42 and 2.50 ± 2.60, respectively. Cognitive worsening was observed in 12 patients (2.9%) for SDMT, 25 (6.1%) for CVLT, and 36 (8.8%) for BVMT. SDMT worsening was associated with higher ARMSSS scores ($Z = -2.201$, $p = 0.028$), while MSSS showed a non-significant trend ($p = 0.177$). No association was observed between CVLT worsening and disease severity scores. In contrast, BVMT worsening was significantly associated with both higher ARMSSS ($Z = -2.415$, $p = 0.016$) and MSSS ($Z = -3.469$, $p < 0.001$).

CONCLUSION Higher MSSS and ARMSSS scores are associated with an increased risk of domain-specific cognitive worsening, particularly in visuospatial memory. These findings suggest that disease severity indices may capture aspects of vulnerability to specific cognitive domains rather than global cognitive decline in MS.

017

Identification of Dissociable Cognitive Phenotypes in Multiple Sclerosis Based on Information Processing Speed and Visuospatial Learning

Serkan Ozakbas, İrem Kara, Gözde Deniz Ünal, Ulvi Samadzade

BACKGROUND Cognitive impairment in multiple sclerosis (MS) is heterogeneous, commonly affecting information processing speed (IPS) and visuospatial learning. Whether these domains form clinically meaningful and distinct cognitive phenotypes remains insufficiently characterized.

OBJECTIVES To identify and clinically characterize distinct cognitive phenotypes in MS based on IPS and visuospatial learning performance.

METHODS In this cross-sectional study, patients with MS fulfilling McDonald criteria underwent cognitive assessment including the Symbol Digit Modalities Test (SDMT) and Brief Visuospatial Memory Test-Revised (BVMT-R). BVMT-R components were selected to capture different stages of visuospatial learning. All cognitive variables were standardized as z-scores. Unsupervised k-means clustering was performed using SDMT and BVMT-R variables to represent complementary domains of processing speed and visuospatial learning. The optimal number of clusters was determined using elbow and silhouette methods, and cluster robustness was assessed with internal validation metrics. Phenotypes were compared across demographic and clinical variables including age, education, disability (EDSS), disease duration, depression, and fatigue.

RESULTS A total of 397 individuals with MS were included. Three distinct cognitive phenotypes were identified: a learning-dominant phenotype (34.3%), an IPS-dominant phenotype (41.1%), and a globally impaired phenotype (24.7%). Mean SDMT z-scores differed significantly across groups (0.21 ± 0.62 vs −1.42 ± 0.48 vs −1.76 ± 0.71, $p < 0.001$), confirming distinct processing speed profiles. The globally impaired phenotype demonstrated significantly higher disability (EDSS: 3.01 ± 1.98 vs 1.84 ± 1.42 vs 1.47 ± 1.31, $p < 0.001$) and longer disease duration (14.9 ± 8.8 vs 10.3 ± 7.6 vs 8.6 ± 6.9 years, $p = 0.002$). Depression and fatigue scores were also higher in this group, whereas education level did not differ significantly between phenotypes ($p = 0.18$).

CONCLUSION Cognitive impairment in MS can be stratified into distinct and clinically meaningful phenotypes reflecting dissociable underlying mechanisms. Phenotype-based cognitive profiling may improve individualized patient monitoring and has potential implications for targeted interventions and clinical trial design.

018

Early Cognitive Decline as an Independent Axis of Multiple Sclerosis Progression

Serkan Ozakbas, Gözde Deniz Ünal, Can Caliskan, Ebru Isgandarli, Ulvi Samadzade

BACKGROUND Cognitive impairment is increasingly recognized as a core feature of multiple sclerosis (MS) and may emerge early in the disease course. However, disease monitoring remains largely focused on physical disability measures such as the Expanded Disability Status Scale (EDSS). Whether early cognitive decline independently predicts long-term progression remains unclear.

OBJECTIVES To determine whether early cognitive decline predicts long-term disability progression and conversion to secondary progressive MS (SPMS), and to compare its prognostic value with motor performance measures.

METHODS This longitudinal study included individuals with MS followed in a large registry with baseline and follow-up assessments. Cognitive performance was evaluated using the Brief International Cognitive Assessment for MS (BICAMS), including the Symbol Digit Modalities Test, California Verbal Learning Test, and Brief Visuospatial Memory Test. Early cognitive decline was defined as ≥20% worsening in at least two cognitive tests during early follow-up. Early motor decline was defined as ≥20% worsening in at least two motor measures, including the Timed 25-Foot Walk Test and Nine Hole Peg Test. Outcomes included EDSS worsening and conversion to SPMS. Multivariate logistic regression models adjusted for age, sex, baseline EDSS, and disease duration were performed.

RESULTS A total of 376 individuals with MS were included. Mean age was 38.3 ± 10.6 years, mean disease duration was 9.2 ± 12.4 years, 68% were female, and mean baseline EDSS was 2.03 ± 1.88. Early cognitive decline was significantly associated with long-term disability progression and SPMS conversion (both $p < 0.001$). Individuals with early cognitive decline had a higher risk of EDSS worsening independent of baseline characteristics. The predictive value of cognitive decline was comparable to established motor measures and exceeded motor-based prediction in some models. Early cognitive decline remained an independent predictor after adjustment for motor performance measures. Combined models showed that individuals with both cognitive and motor decline had the highest risk of progression, while isolated cognitive decline alone also conferred increased risk.

CONCLUSION Early cognitive decline is a strong and independent predictor of long-term disability progression and SPMS conversion. These findings support cognitive dysfunction as an early and clinically meaningful axis of MS progression and highlight the importance of incorporating cognitive assessment into routine clinical evaluation.

SECTION II

Motor Function, Mobility and Motor-Cognitive Phenotypes

26 ABSTRACTS

019

Upper Extremity Fatigability in Multiple Sclerosis Defines Distinct Phenotypes Linked to Processing Speed

Gözde Deniz Ünal, Can Caliskan, Said Alizada, İrem Kara, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Multiple sclerosis (MS) is characterized by both motor and cognitive dysfunction. Upper extremity function is commonly assessed using single point strength measures, but these do not capture changes during repeated effort, which may be more relevant to daily function. Fatigability, defined as performance decline or variability over time, may therefore represent a sensitive marker of motor impairment. However, its phenotypic variability and relationship with cognitive domains remain insufficiently understood.

OBJECTIVES To identify upper extremity fatigability phenotypes based on repeated grip performance and examine their associations with cognition and clinical disability in individuals with MS.

METHODS Upper extremity performance was assessed with a Jamar dynamometer using a 15 repetition maximal grip protocol, with grip strength recorded at each repetition. Fatigability was calculated from early to late repetition changes and intra task variability. Participants were classified as stable, decline, or fluctuating phenotypes. Cognition was assessed using SDMT, CVLT, and BVMT. Associations with EDSS and disease duration were evaluated using Spearman correlation, and phenotype differences were tested with nonparametric analyses. Significance was set at $p < 0.05$.

RESULTS A total of 121 individuals with MS were included. Mean age was 37.99 ± 11.04 years, disease duration was 11.20 ± 8.16 years, and EDSS was 1.33 ± 1.72. Time dependent grip analysis identified distinct fatigability phenotypes, with the decline pattern being the largest subgroup, followed by fluctuating and stable patterns. Greater fatigability was associated with higher EDSS and longer disease duration (both $p < 0.001$), indicating a clinically meaningful relationship with disease burden. Fatigability was also selectively associated with processing speed, as higher fatigability correlated with lower SDMT performance ($p < 0.001$). No significant associations were observed with CVLT or BVMT ($p > 0.05$). Phenotype comparisons supported this finding, with the decline phenotype showing lower SDMT performance than the stable phenotype, while memory scores did not differ significantly.

CONCLUSION Upper extremity fatigability in MS reflects distinct temporal performance phenotypes rather than a uniform construct. These phenotypes are associated with disability and disease duration and show a domain specific relationship with cognition, particularly processing speed. Time dependent grip assessment may provide clinically relevant information beyond single point strength testing.

020

Four Motor Phenotypes Define Functional Heterogeneity in Multiple Sclerosis

Gözde Deniz Ünal, Can Caliskan, Ebru Isgandarli, İrem Kara, Ela Zengin, Serkan Ozakbas

BACKGROUND Motor impairment in multiple sclerosis (MS) is commonly assessed using isolated performance tests or global disability scales such as EDSS. However, motor dysfunction may involve distinct domains, including walking speed, endurance, functional mobility, agility, and upper extremity dexterity. Identifying data driven motor phenotypes may therefore better capture functional heterogeneity beyond global disability measures.

OBJECTIVES To identify latent motor phenotypes in individuals with MS using a data driven approach and to evaluate their clinical relevance beyond EDSS.

METHODS This cross sectional study included individuals with MS who underwent same visit motor assessment. Motor performance was evaluated using T25FW, 2MWT, 6MWT, TUG, SSST, and bilateral mean 9HPT.All measures were converted into age adjusted z scores, with higher scores indicating better performance. Latent profile analysis was performed using robust maximum likelihood estimation, testing one to five class models. Model selection was based on BIC, sample adjusted BIC, entropy, likelihood ratio tests, and clinical interpretability. Clinical validity was assessed by comparing phenotypes for EDSS, disease duration, fatigue, and depressive symptoms. Sensitivity analyses using alternative clustering methods tested model robustness.

RESULTS A total of 1,842 individuals with MS were included. Mean age was 38.9 ± 11.7 years, mean disease duration was 9.8 ± 8.5 years, and median EDSS was 2.5. A four class model showed optimal fit (entropy = 0.83), identifying four motor phenotypes: preserved motor function (34%), mobility predominant impairment with relatively preserved dexterity (29%), dexterity predominant impairment with preserved ambulation (21%), and global motor impairment (16%). EDSS, disease duration, fatigue, and depressive symptoms increased progressively across phenotypes ($p < 0.001$ for all). Despite this gradation, EDSS overlapped substantially between groups, indicating that similar EDSS scores may reflect different motor profiles. Sensitivity analyses confirmed the stability of the four class structure.

CONCLUSION Motor impairment in MS includes distinct data driven phenotypes reflecting differential involvement of mobility and dexterity domains. These phenotypes reveal functional heterogeneity not captured by EDSS. A phenotype based framework may improve clinical stratification and support multidimensional motor assessment in MS.

021

Endurance-Based Walking Performance Provides a Superior Measure of Disability in Multiple Sclerosis Compared to Short-Duration Testing

Gözde Deniz Ünal, Can Caliskan, Ebru Isgandarli, İrem Kara, Ergi Kaya, Serkan Ozakbas

BACKGROUND Walking impairment is a major feature of multiple sclerosis and is commonly evaluated with EDSS. While the 6 Minute Walk Test is widely used to assess walking endurance, the 2 Minute Walk Test may be more feasible in clinical practice. However, whether shorter walking tests adequately reflect MS related motor disability across different disease severity levels remains unclear. Walking performance may also reflect endurance capacity, fatigue, and functional reserve, rather than motor speed alone.

OBJECTIVES To compare the ability of 2MWT and 6MWT to reflect disability in MS as measured by EDSS, and to determine whether short-duration walking tests adequately capture clinically meaningful motor impairment across different disability levels.

METHODS This cross sectional study included 950 individuals with multiple sclerosis who completed both the 2 Minute Walk Test and 6 Minute Walk Test within the same clinical evaluation period (±90 days). Walking performance was defined as total distance covered. Clinical variables included age, sex, disease duration, and EDSS. Associations between walking tests and EDSS were evaluated using Spearman correlation analysis. Separate multivariable linear regression models were built with EDSS as the dependent variable and either 2MWT or 6MWT as the main predictor. Model performance was compared using explained variance. Subgroup and interaction analyses were performed to assess whether these associations differed across EDSS severity strata.

RESULTS A total of 950 individuals with MS were included. Mean age was 37.99 ± 11.04 years, mean disease duration was 11.20 ± 8.16 years, and mean EDSS was 1.33 ± 1.72. Both 2MWT and 6MWT were significantly associated with EDSS ($p < 0.001$), but 6MWT showed a stronger relationship and explained more variance in EDSS. Subgroup analyses indicated that both tests performed similarly at lower disability levels, whereas 6MWT remained more sensitive at higher EDSS strata. Interaction analysis confirmed that disability level modified the association between walking performance and EDSS, with a stronger effect for 6MWT in more disabled patients.

CONCLUSION Both 2MWT and 6MWT were significantly associated with disability in MS, but 6MWT better reflected EDSS, especially at higher disability levels. These findings suggest that 2MWT mainly captures immediate motor performance, whereas 6MWT also reflects endurance capacity and fatigue related functional reserve. Walking disability in MS is therefore better characterized by endurance based assessment than by short duration walking speed alone

022

Inhibitory Control Is Associated With Walking, Mobility and Upper Extremity Function in Multiple Sclerosis

Sudenur İnan, Can Caliskan, Ela Zengin, Gözde Deniz Ünal, Tuncay Basaran, Serkan Ozakbas

BACKGROUND Executive dysfunction, particularly impaired inhibitory control, has been increasingly recognized as an important contributor to disability in multiple sclerosis (MS). However, its relationship with routinely used clinical measures of physical function remains insufficiently characterized.

OBJECTIVES To investigate the association between inhibitory control, assessed by the Stroop Test, and walking, mobility, and upper extremity function in people with MS.

METHODS In this cross-sectional study, Stroop performance was assessed alongside the Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9HPT), Timed Up and Go (TUG), 2-Minute Walk Test (2MWT), and Six Spot Step Test (SSST). Associations were examined using Spearman correlation and multiple linear regression analyses.

RESULTS Fifty-five participants were included (37 women, 67.3%). Poorer inhibitory control was associated with slower walking (T25FW: rho=0.325, p=0.017), poorer upper extremity function (9HPT: rho=0.387, p=0.004), and impaired functional mobility (TUG: rho=0.357, p=0.012). No significant associations were observed with the 2MWT or SSST. In the multivariable regression model, physical performance measures explained 31.1% of the variance in Stroop performance (R2=0.311, p=0.039). Among these measures, the 9HPT remained independently associated with inhibitory control (β=0.428, p=0.033).

CONCLUSION Poorer inhibitory control was associated with slower walking, impaired functional mobility, and reduced upper extremity function in people with MS. The independent association between manual dexterity and inhibitory control suggests that upper extremity performance may provide a clinically meaningful indicator of executive dysfunction. Integrating cognitive and physical assessments may therefore improve the characterization of functional impairment in MS.

023

Respiratory Muscle Function Provides Additional Information Beyond Neurological Disability for Upper-Extremity Performance in Multiple Sclerosis

Gözde Deniz Ünal, Said Alizada, Ebru Isgandarli, İrem Kara, Can Caliskan, Ela Zengin, Serkan Ozakbas

BACKGROUND Upper-extremity dysfunction is a major contributor to disability and loss of independence in multiple sclerosis (MS). Although neurological disability is a principal determinant of manual dexterity, respiratory muscles also contribute to trunk stability, postural control, and coordinated upper-limb movement. Whether respiratory muscle function provides additional information about upper-extremity performance beyond conventional disability measures remains unclear.

OBJECTIVES To determine whether respiratory muscle function explains upper-extremity performance beyond neurological disability and demographic characteristics in people with MS. Material &

METHODS This cross-sectional study included 136 people with MS. Manual dexterity (9HPT) and respiratory muscle function (MIP, MEP, chest expansion, and inspiratory/expiratory chest circumferences) were assessed, alongside mid-upper arm and forearm circumferences as markers of peripheral muscle mass. Correlations between respiratory variables and 9HPT performance were examined, followed by hierarchical multivariable regression: Model 1 (age, sex, disease duration, EDSS), Model 2 (+MIP, MEP), and Model 3 (+chest expansion and anthropometric measures), to test whether respiratory function added explanatory value beyond conventional clinical characteristics

RESULTS A total of 136 participants were included (mean age 41.8±10.6 years; 71% women; median EDSS 2.0 [IQR 1.0-3.0]). Mean 9HPT completion time was 19.4±4.8 seconds. Poorer manual dexterity was associated with lower inspiratory muscle strength (MIP), lower expiratory muscle strength (MEP), reduced chest expansion, and smaller upper-arm and forearm circumferences (all $p \leq 0.018$). Conventional demographic and clinical variables explained 35% of the variance in 9HPT performance. Addition of respiratory muscle strength increased the explained variance to 41% ($\Delta R2=0.06$), and inclusion of chest expansion further increased it to 45% ($\Delta R2=0.04$). In the fully adjusted model, MIP and chest expansion remained independently associated with manual dexterity, whereas MEP and peripheral anthropometric measurements were no longer independently associated. EDSS remained the strongest overall predictor of upper-extremity performance.

CONCLUSION In people with MS, inspiratory muscle strength and chest expansion independently predict manual dexterity beyond age, sex, disease duration, and EDSS, suggesting that respiratory muscle assessment captures motor impairment not reflected by disability scales alone and may complement upper-extremity evaluation in MS rehabilitation

024

Temporal Dissociation of Physical and Cognitive Fatigability Reveals Distinct Network Dynamics in Multiple Sclerosis

Gözde Deniz Ünal, İrem Kara, Ebru Isgandarli, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Fatigability in multiple sclerosis (MS) reflects a time-dependent decline in functional performance across motor and cognitive domains. Although frequently considered a single symptom, increasing evidence suggests that physical and cognitive fatigability may arise from distinct neural mechanisms. However, the temporal relationship between these domains remains poorly understood.

OBJECTIVES To investigate and compare the temporal dynamics of physical and cognitive fatigability and their association with disability in individuals with MS.

METHODS A total of 269 individuals with MS were included. Physical fatigability was assessed using the 6-Minute Walk Test (6MWT), with walking distance recorded at each minute. Cognitive fatigability was evaluated using a time-resolved Symbol Digit Modalities Test (SDMT), with performance measured at 30-second intervals. Temporal changes were analyzed using Friedman's Two-Way ANOVA by ranks and Wilcoxon signed-rank tests. Associations with disability were examined using Spearman correlation analyses with Expanded Disability Status Scale (EDSS) scores. Statistical significance was set at p<.001.

RESULTS A total of 269 individuals with MS were included. Physical fatigability was assessed using the 6-Minute Walk Test (6MWT), with walking distance recorded at each minute. Cognitive fatigability was evaluated using a time-resolved Symbol Digit Modalities Test (SDMT), with performance measured at 30-second intervals. Temporal changes were analyzed using Friedman's Two-Way ANOVA by ranks and Wilcoxon signed-rank tests. Associations with disability were examined using Spearman correlation analyses with Expanded Disability Status Scale (EDSS) scores. Statistical significance was set at p<.001.

CONCLUSION A total of 269 individuals with MS were included. Physical fatigability was assessed using the 6-Minute Walk Test (6MWT), with walking distance recorded at each minute. Cognitive fatigability was evaluated using a time-resolved Symbol Digit Modalities Test (SDMT), with performance measured at 30-second intervals. Temporal changes were analyzed using Friedman's Two-Way ANOVA by ranks and Wilcoxon signed-rank tests. Associations with disability were examined using Spearman correlation analyses with Expanded Disability Status Scale (EDSS) scores. Statistical significance was set at p<.001.

025

Dual-Task Performance in Multiple Sclerosis Reflects Cognitive-Motor Integration Rather Than Processing Speed

Gözde Deniz Ünal, İrem Kara, Can Caliskan, Ela Zengin, Tuncay Basaran, Said Alizada, Serkan Ozakbas

BACKGROUND Dual-task paradigms are increasingly used to assess cognitive-motor interaction in multiple sclerosis (MS). Although dual-task impairment is often attributed to reduced processing speed, dual-task performance also requires attention, executive control, and motor coordination, suggesting a broader neurofunctional basis.

OBJECTIVES To investigate whether dual-task cost reflects processing speed alone or a multidimensional cognitive-motor integration process in MS.

METHODS This cross-sectional study included 269 individuals with MS who underwent motor and cognitive assessments. Dual-task performance was assessed using the Six Spot Step Test (SSST) under single-task and dual-task conditions. Dual-task cost (DTC) was calculated as the relative percentage change between conditions. Processing speed was evaluated using the Symbol Digit Modalities Test (SDMT). Correlation and multivariate regression analyses were performed to identify predictors of DTC.

RESULTS Participants had a mean age of 37.99±11.04 years, disease duration of 11.20±8.16 years, and EDSS score of 1.33±1.72. Dual-task cost showed no significant correlation with SDMT performance ($p>0.05$), indicating that processing speed alone did not explain variability in dual-task performance. In contrast, DTC was significantly associated with clinical disability and disease duration, with higher DTC values observed in individuals with higher EDSS ($p<0.01$) and longer disease duration ($p<0.05$). When participants were stratified according to DTC, the high-DTC group demonstrated significantly higher EDSS and longer disease duration compared to the low-DTC group (both $p<0.01$), whereas SDMT performance did not differ between groups. In multivariate regression analyses, SDMT was not an independent predictor of DTC, while EDSS remained significantly associated ($p<0.01$).

CONCLUSION Dual-task performance in MS is not driven by processing speed alone. The absence of association between DTC and SDMT, together with its strong relationship with disability, suggests that dual-task performance reflects a broader cognitive-motor integration process rather than a single cognitive domain. These findings support the interpretation of dual-task performance as a marker of distributed network dysfunction in MS.

026

Frailty in Multiple Sclerosis Reflects a Progressive Divergence Between Objective Disability and Patient-Reported Experience

Gözde Deniz Ünal, Can Caliskan, İrem Kara, Ela Zengin, Serkan Ozakbas

BACKGROUND Frailty in multiple sclerosis (MS) is commonly viewed as a consequence of neurological disability. However, this approach may not fully capture the discrepancy between objective performance and patient-reported experience.

OBJECTIVES To evaluate frailty as a multidimensional construct in MS and to quantify the divergence between objective clinical performance and patient-reported outcomes.

METHODS A total of 469 individuals with MS were included. Objective motor, cognitive, and patient-reported outcomes were standardized using z-scores and combined into domain-specific composite scores. Frailty was defined as the mean of objective, cognitive, and patient-reported composites. A mismatch score was calculated as the difference between patient-reported and objective performance domains. Associations with age, disease duration, and EDSS were analyzed using correlation and multivariate regression models.

RESULTS Frailty showed strong associations with neurological disability and motor performance measures, including EDSS (rho=0.75), T25FWT (rho=0.79), TUG (rho=0.72), and 6MWT (rho=-0.86) (all $p<0.001$). Cognitive processing speed measured by SDMT demonstrated stronger associations with frailty than memory-based measures. Patient-reported outcomes showed the strongest relationships with frailty, particularly balance confidence and fatigue-related measures. Mismatch analysis revealed substantial inter-individual variability between objective performance and patient-reported outcomes. Importantly, mismatch magnitude increased significantly with both age and disease duration ($p<0.001$), indicating a progressive divergence between objective disability and subjective disease burden over time. In multivariate analyses, EDSS remained the strongest predictor of frailty, whereas mismatch was independently associated with patient-reported outcomes. Age remained an independent predictor of both frailty and mismatch.

CONCLUSION Frailty in MS reflects not only neurological disability but also a progressive divergence between objective clinical performance and patient-reported experience. This dissociation increases with age and disease duration, suggesting that perceived disease burden progressively diverges from measurable impairment over time. These findings challenge purely disability-based models of MS and support integration of patient-reported outcomes into multidimensional disease assessment frameworks.

027

Motor Asymmetry as a Clinical Marker of Cognitive Dysfunction and Disease Burden in Multiple Sclerosis

Gözde Deniz Ünal, Said Alizada, İrem Kara, Ela Zengin, Tuncay Basaran, Serkan Ozakbas

BACKGROUND Multiple sclerosis (MS) is characterized by heterogeneous motor and cognitive involvement. While upper extremity performance is routinely assessed, interlimb motor asymmetry is less frequently explored as a marker of broader neurological dysfunction.

OBJECTIVES To evaluate the association between motor asymmetry, cognitive performance, disability, and disease duration in individuals with MS.

METHODS To evaluate the association between motor asymmetry, cognitive performance, disability, and disease duration in individuals with MS.

RESULTS Participants had a mean age of 37.99±11.04 years, disease duration of 11.20±8.16 years, and EDSS score of 1.33±1.72. Motor asymmetry was significantly associated with reduced processing speed (SDMT, rho=−0.285, $p<0.001$), whereas no significant associations were observed with visuospatial memory or verbal learning in univariate analyses. In multivariate analyses, EDSS emerged as the strongest independent predictor of SDMT performance, while motor asymmetry did not retain independent significance for processing speed after adjustment. In contrast, motor asymmetry demonstrated an independent association with verbal learning performance (CVLT-II, $p=0.013$), suggesting a domain-specific cognitive relationship. Additionally, motor asymmetry was independently associated with higher EDSS scores and longer disease duration, supporting its relationship with cumulative disease burden.

CONCLUSION Interlimb motor asymmetry is associated with both cognitive performance and clinical disease burden in MS. Although its relationship with processing speed appears largely mediated by global disability, its independent association with verbal learning suggests a domain-specific cognitive correlate. These findings support motor asymmetry as a clinically relevant marker of distributed neurological involvement in MS.

028

Motor Asymmetry Is Independently Associated With Cognitive Processing Speed in Multiple Sclerosis

Serkan Ozakbas, Gözde Deniz Ünal, Tuncay Basaran, Ulvi Samadzade

BACKGROUND Upper extremity impairment in multiple sclerosis (MS) frequently presents asymmetrically, yet side-specific motor dysfunction is rarely quantified beyond descriptive comparisons. Such asymmetry may reflect disrupted large-scale network integration, potentially linking motor dysfunction with cognitive impairment. However, whether side-specific motor deficits are independently associated with cognitive performance remains unclear.

OBJECTIVES To quantify upper extremity motor asymmetry in MS and determine its independent association with cognitive processing speed.

METHODS This retrospective study included 932 patients with MS. Upper extremity performance was assessed bilaterally using a Nine-Hole Peg Test-equivalent measure (DDPT). The clinically affected side was recorded, and an asymmetry index was calculated as the normalized difference between affected and non-affected sides. Cognitive processing speed was evaluated using the Symbol Digit Modalities Test (SDMT). Group comparisons between affected and non-affected sides were performed using paired t-tests. Associations between motor performance and SDMT were initially explored using Pearson correlation. A multivariable linear regression model was constructed with SDMT score as the dependent variable and asymmetry index as the main predictor, adjusting for age, sex, disease duration, and disability level (EDSS).

RESULTS Motor performance differed modestly but significantly between sides, with the affected side showing worse performance compared to the non-affected side (24.17 ± 8.12 vs 26.41 ± 9.03 seconds, $p = 0.021$). Affected side performance correlated with SDMT scores ($r = -0.25$, $p < 0.001$). In multivariable analysis, greater motor asymmetry remained independently associated with lower SDMT scores after adjustment for age, sex, disease duration, and EDSS ($\beta = -0.21$, $p < 0.001$).

CONCLUSION Upper extremity motor asymmetry in MS is modest but clinically relevant and independently associated with cognitive processing speed. These findings suggest that lateralized motor dysfunction may reflect broader network-level impairment rather than isolated motor pathway damage. Quantifying motor asymmetry may provide a simple and scalable marker for identifying patients at risk of cognitive dysfunction.

029

Dissociation Between Upper and Lower Extremity Motor Performance in Multiple Sclerosis Across EDSS Levels

Gözde Deniz Ünal, İrem Kara, Ebru Isgandarli, Said Alizada, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Motor disability in multiple sclerosis (MS) is commonly summarized using the Expanded Disability Status Scale (EDSS), which primarily reflects ambulatory function. However, EDSS may underestimate impairment in non-ambulatory domains, particularly upper extremity function.

OBJECTIVES To evaluate the concordance between upper and lower extremity motor performance across EDSS-defined disability levels and identify domain-specific motor phenotypes in MS.

METHODS This cross-sectional study included 1,842 individuals with MS who underwent concurrent upper and lower extremity assessments. Upper extremity function was evaluated using the Nine Hole Peg Test (9HPT). Lower extremity performance was assessed using the Timed 25-Foot Walk Test, Timed Up and Go, 2-/6-Minute Walk Test, and Six Spot Step Test. All outcomes were transformed into age-adjusted z-scores and combined into domain-specific composite scores. Participants were stratified into low (≤2.5), moderate (3.0-5.5), and high (≥6.0) EDSS groups. Dissociation between domains was defined according to relative differences between composite scores. Correlation and multivariate regression analyses adjusted for EDSS, age, and disease duration were performed.

RESULTS Participants had a mean age of 38.9±11.7 years, disease duration of 9.8±8.5 years, and median EDSS of 2.5. Upper and lower extremity performances demonstrated only moderate correlation (rho=0.46, $p<0.001$), indicating partial dissociation between domains. Upper extremity function showed greater variability than lower extremity measures, particularly in individuals with low disability. Motor phenotype analysis revealed that 27.4% of participants exhibited upper-dominant impairment, 38.9% lower-dominant impairment, 18.6% combined impairment, and 15.1% preserved function. Notably, 22.8% of individuals with low EDSS demonstrated isolated upper extremity impairment despite preserved ambulatory performance. These patterns remained significant after adjustment for EDSS, age, and disease duration (all $p<0.001$).

CONCLUSION Upper and lower extremity motor functions in MS demonstrate significant dissociation across EDSS-defined disability levels. EDSS-based assessment masks substantial within-level heterogeneity and underrepresents upper extremity dysfunction, particularly in early disease stages. These findings support a multidimensional approach to motor evaluation beyond ambulatory-based disability measures.

030

Functional Instability as an Early Marker of Network Dysfunction in Multiple Sclerosis

Gözde Deniz Ünal, Ulvi Samadzade, Can Caliskan, İrem Kara, Serkan Ozakbas

BACKGROUND Conventional clinical measures in multiple sclerosis (MS) primarily focus on mean performance decline. However, intra-task performance variability may better reflect early network-level dysfunction before overt disability becomes apparent.

OBJECTIVES To investigate whether intra-task performance variability across cognitive, motor endurance, and upper extremity domains represents an independent marker of disability and subclinical dysfunction in MS.

METHODS This cross-sectional study included 121 individuals with MS. Cognitive variability was derived from three 30-second blocks of the Symbol Digit Modalities Test (SDMT). Walking variability was calculated from minute-by-minute performance during the 6-Minute Walk Test (6MWT), and upper extremity variability was assessed using repeated Jamar grip strength measurements. Variability was quantified using coefficient of variation values, and a Global Variability Index was created by combining domain-specific measures. Associations with EDSS, disease duration, SDMT, 6MWT, and 2MWT were analyzed using correlation and multivariate regression analyses. A subgroup analysis was performed in participants with low disability (EDSS≤2.0).

RESULTS Participants had a mean age of 39.76±10.98 years, disease duration of 9.83±7.25 years, and EDSS score of 1.06±1.35. Cognitive variability was associated with lower SDMT performance (rho=-0.278, p=0.002), while walking variability correlated with reduced 6MWT distance (rho=-0.361, p<0.001). Grip variability was associated with higher EDSS (rho=0.264, p=0.003) and lower 6MWT and 2MWT performance (both p<0.05). The Global Variability Index showed significant associations with EDSS (rho=0.184, p=0.043), SDMT (rho=-0.239, p=0.008), 6MWT (rho=-0.420, p<0.001), and 2MWT (rho=-0.303, p=0.001). Higher variability tertiles demonstrated lower cognitive and walking performance. Importantly, variability differences were detectable even in individuals with low disability, indicating subclinical dysfunction. In multivariate analyses, the Global Variability Index independently predicted both EDSS (β=0.795, p<0.001) and SDMT performance (β=-3.93, p=0.034).

CONCLUSION Performance variability across cognitive and motor domains represents a marker of functional instability in MS. Increased variability appears to reflect distributed network dysfunction and may identify subclinical impairment before overt disability or mean performance decline becomes evident.

031

Forward Reach as a Marker of Multidimensional Functional Instability and Fall Risk in Wheelchair-Dependent Multiple Sclerosis

Gözde Deniz Ünal, Zuhal Abasiyanik, Can Caliskan, İrem Kara, Serkan Ozakbas

BACKGROUND In advanced multiple sclerosis (MS), seated balance is a key determinant of independence and quality of life. Forward reach is commonly used to assess sitting balance, but it may also reflect broader neurological and functional instability.

OBJECTIVES To evaluate forward reach as a multidimensional marker of disability, fall risk, and patient-reported burden in wheelchair-dependent individuals with MS.

METHODS This cross-sectional study included 57 wheelchair-dependent individuals with MS (mean age 55.6±10.7 years; disease duration 23.5±12.4 years; EDSS 6.49±0.65). Forward and lateral reach were assessed as the mean of three trials. Clinical outcomes included disability, disease duration, and fall frequency. Patient-reported outcomes included fatigue, depressive symptoms, activities of daily living, perceived health, and quality of life. Correlation, ROC, and multivariate regression analyses were performed. Directional discordance was defined as mismatch between forward and lateral reach performance.

RESULTS This cross-sectional study included 57 wheelchair-dependent individuals with MS (mean age 55.6±10.7 years; disease duration 23.5±12.4 years; EDSS 6.49±0.65). Forward and lateral reach were assessed as the mean of three trials. Clinical outcomes included disability, disease duration, and fall frequency. Patient-reported outcomes included fatigue, depressive symptoms, activities of daily living, perceived health, and quality of life. Correlation, ROC, and multivariate regression analyses were performed. Directional discordance was defined as mismatch between forward and lateral reach performance.

CONCLUSION Forward reach represents a multidimensional marker of functional instability in wheelchair-dependent individuals with MS, integrating disability, fall risk, and psychosocial burden. Directional discordance findings suggest asymmetric postural control dysfunction, supporting the use of forward reach as a practical clinical tool for risk stratification in advanced MS.

032

Dissociation Between Walking Speed and Endurance Reveals Hidden Heterogeneity in Multiple Sclerosis

Gözde Deniz Ünal, Ebru Isgandarli, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Walking impairment in multiple sclerosis (MS) is commonly assessed using short-distance walking speed tests such as the Timed 25-Foot Walk (T25FW). However, walking is a multidimensional function involving both speed and endurance, which may rely on partially distinct neural and physiological mechanisms. Short-duration walking assessments may therefore fail to capture real-world mobility limitations.

OBJECTIVES To investigate whether walking speed and walking endurance represent unified or dissociable domains of ambulatory performance in MS and to identify clinically relevant discordant walking phenotypes.

METHODS This cross-sectional study included 269 individuals with MS who completed the T25FW and at least one endurance-based walking test (2MWT and/or 6MWT). Outcomes were standardized into age-adjusted z-scores. Associations between domains were analyzed using Spearman correlation and Bland-Altman analyses. Multivariate regression models adjusted for EDSS, age, and disease duration were performed. Participants were categorized into ambulatory phenotypes based on preserved or impaired speed and endurance performance.

RESULTS Participants had a mean age of 37.99±11.04 years, disease duration of 11.20±8.16 years, and EDSS score of 1.33±1.72. Walking speed and endurance demonstrated statistically significant but only moderate correlations ($p<0.001$), indicating partial overlap rather than equivalence. Bland-Altman analysis revealed wide limits of agreement and clinically unacceptable percent error between short- and long-duration walking measures. In multivariate regression, T25FW significantly predicted endurance outcomes; however, substantial variance in 6MWT performance remained unexplained after adjustment. EDSS and disease duration independently contributed to endurance performance. Importantly, approximately 20-25% of participants demonstrated discordant ambulatory profiles characterized by preserved walking speed but impaired endurance. This subgroup was not fully explained by EDSS, indicating clinically silent ambulatory dysfunction not captured by standard disability measures.

CONCLUSION Walking speed and endurance in MS represent related but functionally dissociable domains of ambulation. Short-distance walking tests may overestimate functional mobility in a clinically meaningful subgroup of patients with impaired endurance despite preserved walking speed. These findings support a multidimensional model of ambulation in MS rather than a single unified construct.

033

Motor and Cognitive Phenotyping in Multiple Sclerosis: Same Score, Different Clinical Meaning

Gözde Deniz Ünal, Can Caliskan, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Motor and cognitive tests in multiple sclerosis (MS) are typically interpreted independently, although individuals with similar scores may represent different clinical states.

OBJECTIVES To identify motor and motor-cognitive phenotypes in MS and determine whether identical performance scores carry different clinical meaning depending on phenotype membership.

METHODS This cross-sectional study included 551 individuals with MS who underwent concurrent motor and cognitive assessments. Motor performance was evaluated using the Timed 25-Foot Walk, 2- and 6-Minute Walk Tests, Timed Up and Go, Six Spot Step Test, and 9-Hole Peg Test. Cognitive performance was assessed using the Symbol Digit Modalities Test (SDMT) and Brief Visuospatial Memory Test-Revised (BVMT-R). All outcomes were standardized into age-adjusted z-scores. Latent profile analysis was used to derive motor and motor-cognitive phenotypes. Phenotypes were externally validated using disability, disease duration, fatigue, and depression measures. Participants were stratified into predefined motor and cognitive score bands to evaluate whether phenotype membership explained clinical variability beyond isolated test scores.

RESULTS Participants had a mean age of 35.93±10.90 years, disease duration of 8.09±11.12 years, and EDSS score of 1.74±2.07. Latent profile analysis identified distinct motor and motor-cognitive phenotypes characterized by different patterns of gait, mobility, upper extremity function, and cognition. Phenotypes differed significantly in disability, fatigue, and depression despite being derived solely from performance measures. Importantly, individuals within identical motor performance bands demonstrated substantially different clinical profiles according to phenotype membership, including differences in EDSS, TUG, 6SST, 9HPT, and BVMT-R performance. Similarly, participants with comparable SDMT scores differed significantly in motor impairment and disability burden. In multivariable analyses, phenotype membership independently predicted clinical outcomes beyond individual motor and cognitive scores ($p<0.05$).

CONCLUSION Motor and motor-cognitive phenotyping identifies clinically meaningful heterogeneity in MS not captured by isolated test scores. Individuals with similar performance scores may represent fundamentally different clinical states depending on phenotype membership, supporting phenotype-based approaches for clinical assessment and stratification in MS.

034

Same Disability, Different Mobility: Functional Mobility Is Not Captured by Walking Speed in Multiple Sclerosis

Gözde Deniz Ünal, İrem Kara, Said Alizada, Ela Zengin, Can Caliskan, Serkan Ozakbas

BACKGROUND Walking disability in multiple sclerosis (MS) is commonly assessed using walking speed and endurance measures such as the Timed 25-Foot Walk (25FW), 2-Minute Walk Test (2MWT), and 6-Minute Walk Test (6MWT). However, real-world mobility also requires turning, coordination, and transitional movements, which may represent distinct motor processes.

OBJECTIVES To determine whether functional mobility reflects a motor domain not fully explained by walking speed, endurance, or disability level in MS.

METHODS This cross-sectional study included individuals with MS who completed functional mobility tests, including the Timed Up and Go (TUG) and Six Spot Step Test (6SST), together with conventional walking assessments. Clinical variables included age, disease duration, Expanded Disability Status Scale (EDSS), fatigue, and depression scores. Correlation and hierarchical multivariable regression analyses were performed to determine whether TUG and 6SST performance could be explained by walking speed, endurance, disability, and clinical variables.

RESULTS A total of 623 participants were included in the TUG analysis and 217 in the 6SST analysis. The cohort had a mean EDSS score of 1.10±1.66. TUG demonstrated significant correlations with 25FW, 2MWT, 6MWT, and EDSS (all $p<0.001$). However, EDSS lost significance after inclusion of walking variables in multivariable models. The final TUG model retained 25FW, 2MWT, and depression as independent predictors, explaining 23.5% of variance. Similarly, 6SST was significantly associated with 25FW, 2MWT, and 6MWT (all $p<0.001$). In regression analyses, 25FW and 2MWT remained independent predictors; however, substantial unexplained variability persisted despite the final model explaining 61.5% of total variance. Importantly, individuals with similar EDSS levels and walking performance demonstrated marked differences in functional mobility.

CONCLUSION Functional mobility represents a distinct motor domain in MS that is not fully captured by walking speed, endurance, or EDSS. Individuals with similar disability levels may exhibit substantially different functional mobility profiles, supporting the inclusion of functional mobility assessments in multidimensional motor evaluation frameworks for MS.

035

Dual-Task Four Square Step Test Captures Cognitive-Motor Function Beyond Information Processing Speed in Multiple Sclerosis

Gözde Deniz Ünal, Can Caliskan, İrem Kara, Ela Zengin, Serkan Ozakbas

BACKGROUND Dual-task assessments evaluate cognitive-motor integration in multiple sclerosis (MS). Although impaired dual-task performance is often attributed to slowed information processing, the Four Square Step Test (FSST) also requires dynamic balance, multidirectional stepping, motor planning, attention, and executive control. Whether dual-task FSST reflects processes beyond information processing speed remains unclear.

OBJECTIVES To determine whether dual-task FSST provides information beyond processing speed and identify clinical factors associated with cognitive-motor stepping performance in MS.

METHODS This cross-sectional study included people with MS who completed the FSST under single- and cognitive dual-task conditions together with the Symbol Digit Modalities Test (SDMT). Age, disease duration, and Expanded Disability Status Scale (EDSS) were recorded. Associations between dual-task FSST and SDMT, age, disease duration, and EDSS were examined using Spearman correlations. Participants were classified according to dual-task interference and compared using non-parametric tests. Multivariable regression evaluated independent associations with dual-task FSST performance. EDSS-adjusted and low-disability sensitivity analyses were also performed.

RESULTS A total of 143 people with MS were included (mean age 38.0±11.0 years; disease duration 11.2±8.2 years; EDSS 1.33±1.72). Dual-task FSST performance was not associated with SDMT ($p>0.05$), indicating that information processing speed did not explain variability in cognitive-motor stepping. In contrast, poorer performance was associated with higher EDSS and longer disease duration. Participants with greater dual-task interference had significantly higher EDSS scores and longer disease duration, whereas SDMT scores did not differ between groups. In multivariable regression, EDSS remained independently associated with dual-task FSST performance, whereas SDMT showed no independent contribution. Results were unchanged in sensitivity analyses.

CONCLUSION Dual-task FSST was not explained by information processing speed alone but was more closely related to neurological disability. These findings suggest that dual-task FSST captures broader cognitive-motor integration than conventional processing-speed testing and may improve detection of subtle functional impairment, including in people with low disability.

036

Operationalizing Motor Reserve in Multiple Sclerosis: A Residual-Based Framework for Quantifying Motor Resilience

Gözde Deniz Ünal, İrem Kara, Can Caliskan, Ebru Isgandarli, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND People with multiple sclerosis (MS) with similar disability often exhibit markedly different motor performance, suggesting that conventional clinical measures explain only part of motor function variability. While cognitive reserve has been operationalised using residual-based approaches, an equivalent framework for motor reserve is lacking

OBJECTIVES To develop and evaluate a residual-based operational framework for motor reserve in MS and examine its associations with multidimensional motor phenotypes, cognitive performance and clinical characteristics

METHODS This cross-sectional study analysed data from a prospectively maintained MS registry. Participants with complete baseline assessments of age, sex, disease duration, Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk (T25FW), Timed Up and Go (TUG), Two-Minute Walk Test (2MWT), Six-Step Square Test (6SST), and Dynamic Balance/Performance Test (DBPT) were included. A multidimensional motor composite was generated from standardized motor test z-scores. Expected motor performance was estimated using multivariable regression including age, sex, disease duration, and EDSS. Motor reserve was defined as the standardized residual (observed minus predicted performance) and analysed as both tertiles and a continuous variable. Associations with cognitive performance (SDMT, CVLT-II, BVMT-R) and motor phenotypes were evaluated using adjusted regression models

RESULTS Among 2,444 registry participants, 780 met the inclusion criteria. Age, sex, disease duration, and EDSS explained 35.1% of the variance in motor performance ($R2=0.351$, $p<0.001$). Participants with high motor reserve demonstrated better performance across all motor tests than those with expected or low reserve (all $p<0.001$). The preserved motor phenotype increased from 61.5% in the low reserve group to 91.5% and 95.0% in the expected and high reserve groups, whereas the widespread multidomain impairment phenotype decreased from 25.0% to 2.3% and 0.8%, respectively. Higher continuous motor reserve was independently associated with better SDMT, CVLT-II, and BVMT-R performance and lower odds of impaired motor phenotypes after adjustment for age, sex, disease duration and EDSS (all $p<0.001$)

CONCLUSION Motor reserve can be quantified using a residual-based framework that captures motor performance beyond expected disability. This construct is associated with preserved cognition and favourable motor phenotypes and provides a practical quantitative framework for future longitudinal studies of disability progression and rehabilitation response

037

Motor-Cognitive Phenotypes Reveal Hidden Clinical Heterogeneity in Multiple Sclerosis

Serkan Ozakbas, Gözde Deniz Ünal, Said Alizada, Ebru Isgandarli, Can Caliskan, İrem Kara, Ulvi Samadzade

BACKGROUND Motor and cognitive impairments in multiple sclerosis (MS) may evolve independently. Their combined assessment may reveal clinically meaningful phenotypes not captured by conventional disability measures.

OBJECTIVES To identify motor-cognitive phenotypes in people with MS using latent profile analysis and characterise their clinical features.

METHODS Baseline data from 2,251 people with MS were screened. Participants with complete Timed 25-Foot Walk (T25FW), Nine-Hole Peg Test (9HPT), Timed Up and Go (TUG), Symbol Digit Modalities Test (SDMT), California Verbal Learning Test-II (CVLT-II), and Brief Visuospatial Memory Test-Revised (BVMT-R) data were included. Clinically implausible values were excluded. Scores were age-adjusted, standardised, and aligned so that higher values indicated better performance. Gaussian finite-mixture models with one to six profiles were compared using BIC, entropy, posterior probabilities, class size, interpretability, and bootstrap stability. Profiles were externally validated using EDSS, disease duration, fatigue, MSWS-12, MSNQ, and MS course.

RESULTS A total of 1,652 participants were analysed. A three-profile solution showed the best balance of fit and interpretability (BIC=18,402.9; entropy=0.731; mean posterior probability=0.882; bootstrap agreement=93.7%). Profile 1 (n=1,146; 69.4%) showed preserved motor and cognitive performance. Profile 2 (n=419; 25.4%) demonstrated cognitive and manual-dexterity impairment despite preserved ambulation: T25FW z=−0.02, TUG z=−0.05, 9HPT z=−0.57, SDMT z=−0.75, CVLT-II z=−0.37, and BVMT-R z=−0.53. Profile 3 (n=87; 5.3%) showed widespread motor impairment with moderate cognitive dysfunction. Mean EDSS increased across profiles (0.98±1.09, 2.27±2.04, and 4.91±2.01; p<0.001), alongside longer disease duration, higher MSWS-12 scores, and greater progressive MS prevalence (2.7%, 10.5%, and 57.4%).

CONCLUSION Three distinct motor-cognitive phenotypes were identified. One-quarter of participants had prominent cognitive and upper-extremity impairment despite preserved walking, indicating that mobility-weighted disability measures may underestimate their disease burden. Combined motor and cognitive assessment may provide a more comprehensive characterisation of MS disability.

038

Integrated Motor-Cognitive Phenotypes in Multiple Sclerosis: A Latent Profile Analysis of Functional Disability Patterns

Gözde Deniz Ünal, Said Alizada, İrem Kara, Ebru Isgandarli, Can Caliskan, Ela Zengin, Serkan Ozakbas

BACKGROUND Multiple sclerosis (MS) is a heterogeneous disease with variable motor and cognitive involvement. As these domains may share underlying disease mechanisms, integrated motor-cognitive phenotypes could improve disease stratification beyond conventional disability measures such as the Expanded Disability Status Scale (EDSS).

OBJECTIVES To identify data-driven motor-cognitive phenotypes in MS using latent profile analysis (LPA) and examine their associations with disability, disease duration, and patient-reported outcomes.

METHODS This multicenter cross-sectional study included 1,398 people with MS. Motor function (T25FW, TUG, 9HPT) and cognitive performance (SDMT, CVLT-II, BVMT-R) were standardized and entered into LPA. Model selection was based on BIC, entropy, interpretability, and bootstrap stability. Clinical and patient-reported outcomes were compared across profiles.

RESULTS Participants were 70.6% female (mean age 37.3±11.4 years; disease duration 7.9±7.7 years; EDSS 1.48±1.64). LPA identified four stable profiles: Preserved Function (n=555; EDSS 0.74), Mild Impairment (n=556; EDSS 1.18), Moderate Impairment (n=220; EDSS 2.98), and Severe Impairment (n=67; EDSS 5.25). Although disease duration increased across profiles, substantial overlap suggested phenotype membership was not solely explained by disease duration. Fatigue, walking perception, balance confidence, and quality of life differed significantly between profiles (all $p<0.001$).

CONCLUSION Distinct motor-cognitive phenotypes can be identified in MS using multimodal performance measures. These profiles capture clinically meaningful functional differences beyond EDSS and disease duration, supporting their potential utility for individualized disease stratification and rehabilitation. Longitudinal studies are needed to determine whether they represent stable biological subtypes or stages of disease progression.

039

Age-Related Redistribution of Multidimensional Motor Phenotypes in Multiple Sclerosis: Evidence From a Large Real-World Cohort

Gözde Deniz Ünal, Can Caliskan, Said Alizada, Ebru Isgandarli, Serkan Ozakbas

BACKGROUND Motor impairment is a major contributor to disability in multiple sclerosis (MS). Although physical performance generally declines with age, it remains unclear whether ageing is associated with uniform deterioration across motor functions or redistribution of multidimensional motor phenotypes. Understanding these age-related patterns may improve rehabilitation strategies.

OBJECTIVES To examine the distribution of multidimensional motor phenotypes across the adult lifespan in MS and determine whether age is independently associated with motor phenotype after accounting for disease-related factors.

METHODS Data were obtained from a prospectively maintained MS registry. Motor performance was assessed using the Timed 25-Foot Walk (T25FW), Timed Up and Go (TUG), Nine-Hole Peg Test (9HPT), Two-Minute Walk Test (2MWT), Six-Step Square Test (6SST), and Dynamic Balance/Performance Test. Participants had previously been classified into motor phenotypes using latent profile analysis. Individuals were grouped into five age categories (18-30, 31-40, 41-50, 51-60, and ≥60 years). Phenotype distributions were compared using the $\chi 2$ test for trend, and multinomial logistic regression adjusted for sex, disease duration, and Expanded Disability Status Scale (EDSS) examined the independent association between age and motor phenotype.

RESULTS Among 2,445 registry participants, 893 with complete motor assessments were included. Motor phenotype distribution differed significantly across age groups ($p<0.001$). The proportion with a preserved motor phenotype progressively declined with age (55.7%, 39.9%, 16.7%, 9.9%, and 0%), while the multidomain motor impairment phenotype increased (9.6%, 20.6%, 43.3%, 63.7%, and 100%). The largest shift occurred between the fifth and sixth decades of life, when preserved motor function became uncommon and multidomain impairment predominated. After adjustment for sex, disease duration, and EDSS, older age remained independently associated with membership in progressively more impaired motor phenotypes (adjusted effect estimate and 95% CI to be inserted; $p<0.001$).

CONCLUSION Older age was independently associated with redistribution toward more impaired multidimensional motor phenotypes. These findings suggest that multidimensional phenotypes capture age-related motor changes more effectively than isolated motor tests and may provide a more informative framework for monitoring disease progression and guiding rehabilitation in MS.

040

Beyond Walking: A Multidimensional Framework for Identifying Invisible Disability in Multiple Sclerosis

Gözde Deniz Ünal, Ebru Isgandarli, Can Caliskan, Said Alizada, İrem Kara, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Disability assessment in multiple sclerosis (MS) remains largely centred on objective motor performance, despite increasing recognition that cognitive impairment, fatigue, and patient-reported limitations contribute substantially to disease burden. Consequently, individuals with preserved walking ability may experience clinically meaningful disability that remains unrecognised by conventional mobility-based assessments. A practical multidimensional framework for identifying this "invisible disability" has not been established.

OBJECTIVES To develop and evaluate a multidimensional framework for identifying invisible disability among people with MS who demonstrate preserved objective mobility.

METHODS This cross-sectional study included 896 people with MS with preserved mobility (T25FW ≤5.5 s; TUG ≤8.0 s). Invisible disability was defined as preserved mobility with clinically meaningful impairment in non-motor domains. Group differences were examined, and multivariable logistic regression adjusted for age, sex, disease duration, and EDSS identified factors independently associated with invisible disability.

RESULTS Nearly one-third of participants (30.7%) with preserved mobility met criteria for multidimensional invisible disability. Despite similar mobility performance, they had significantly worse cognition, fatigue, subjective cognitive complaints, balance confidence, perceived walking limitations, and health-related quality of life (all $p<0.001$). Fatigue, cognitive impairment, and reduced quality of life remained independently associated with invisible disability after adjustment, highlighting the limitations of conventional mobility measures alone.

CONCLUSION Nearly one-third of people with MS who demonstrated preserved objective walking performance exhibited clinically meaningful multidimensional disability that was not detected by conventional mobility assessments. These findings highlight the limitations of relying solely on motor performance to evaluate disability and support a multidimensional framework incorporating cognition, fatigue, and patient-reported outcomes to identify otherwise unrecognised disease burden in MS.

041

Motor System Heterogeneity in Multiple Sclerosis: A Multidimensional Phenotype Architecture

Gözde Deniz Ünal, Ebru Isgandarli, Can Caliskan, Said Alizada, İrem Kara, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Motor dysfunction in multiple sclerosis (MS) is traditionally characterized using global disability measures such as the Expanded Disability Status Scale (EDSS). However, motor performance is multidimensional, including walking speed, endurance, upper extremity dexterity, and functional mobility. These domains rely on partly distinct neural systems and may be differentially affected in MS. This suggests motor impairment is not uniform but reflects structured patterns of subsystem dysfunction. A phenotype-based approach may therefore better represent motor system organization.

OBJECTIVES To identify motor phenotypes in MS using a multidimensional performance framework and characterize their clinical profiles in terms of disability, disease duration, fatigue, and depression.

METHODS This cross-sectional study included 269 individuals with MS (mean age 37.99 ± 11.04; disease duration 11.20 ± 8.16; EDSS 1.33 ± 1.72). Motor performance was assessed across domains: walking speed (Timed 25-Foot Walk), endurance (2- and 6-Minute Walk Tests), functional mobility (Timed Up and Go, Six Spot Step Test), and upper extremity function (Nine-Hole Peg Test). Measures were standardized (z-scores) and aligned so higher scores indicated better performance. Motor phenotypes were identified using unsupervised clustering, and clinical variables were compared across groups.

RESULTS Five motor phenotypes emerged. A preserved phenotype (26.8%) showed high performance, low disability, and shorter disease duration. A speed-dominant phenotype (17.8%) showed reduced walking speed despite preserved endurance. An endurance-dominant phenotype (20.8%) showed reduced endurance with relatively preserved speed. An upper extremity-dominant phenotype (14.1%) showed disproportionate fine motor impairment. A combined phenotype (20.4%) showed global dysfunction and was associated with highest disability, longest disease duration, and greatest fatigue and depression. Between-group differences in EDSS, disease duration, fatigue, and depression were significant (all $p < 0.01$).

CONCLUSION Motor dysfunction in MS reflects distinct phenotypic architectures rather than a unitary decline. These phenotypes show clinically meaningful differences, supporting a network-level model of motor heterogeneity. This framework may inform personalized assessment and rehabilitation strategies.

042

Motor Decline in Multiple Sclerosis Is Domain-Specific and Age-Dependent: A 5-Year Longitudinal Analysis of Upper and Lower Extremity Function

Gözde Deniz Ünal, Ebru Isgandarli, Can Caliskan, Ela Zengin, Serkan Ozakbas

BACKGROUND Motor impairment in MS affects upper and lower extremities, which may not deteriorate in parallel. Although walking performance is a common progression marker, upper extremity function may follow a distinct trajectory. Clarifying domain-specific decline and age effects may improve longitudinal assessment.

OBJECTIVES To compare 5-year changes in upper and lower extremity function, identify meaningful deterioration patterns, and assess the influence of age and disease duration.

METHODS Individuals with MS with baseline and 5-year follow-up assessments were included. Upper and lower extremity function were assessed with 9HPT and T25FWT. Percentage change from baseline was calculated; ≥20% worsening defined meaningful deterioration. Participants were classified as upper-first, lower-first, global decline, or stable. Follow-up was the closest visit to 5 years (range 4-6 years). Age was analyzed continuously and as 18-30, 30-50, and >50 years; disease duration was a covariate. Analyses used McNemar, chi-square, Spearman, Kruskal-Wallis, and logistic regression.

RESULTS Among 478 individuals, mean age was 36.7±11.4 years, disease duration 7.7±7.8 years, and follow-up 4.54±0.87 years. Trajectories were stable (n=363), lower-first (n=75), upper-first (n=23), and global decline (n=17). Isolated lower extremity deterioration was more frequent than isolated upper extremity deterioration (McNemar $p < 0.001$). Trajectory distribution differed by age group ($p < 0.001$): younger individuals were mainly stable, whereas older individuals showed reduced stability with higher global and upper extremity decline. Age correlated with upper extremity deterioration (rho = 0.195, $p < 0.001$) and lower extremity deterioration (rho = 0.139, $p = 0.003$). In multivariate analyses, age predicted upper extremity deterioration (OR 1.08, $p < 0.001$) and lower extremity deterioration (OR 1.05, $p < 0.001$); disease duration was not significant.

CONCLUSION Upper and lower extremity functions in MS exhibit distinct longitudinal trajectories over a 5-year period. Lower extremity decline is more frequent overall; however, motor deterioration follows an age-dependent pattern characterized by increasing involvement of both domains, particularly upper extremity function at older ages. These findings support domain-specific monitoring strategies and emphasize the importance of incorporating upper extremity assessment into routine longitudinal evaluation of MS progression.

043

Motor and Cognitive Phenotypes in Multiple Sclerosis: Stability, Transition, and Clinical Meaning Beyond Individual Performance Scores

Gözde Deniz Ünal, Ela Zengin, İrem Kara, Can Caliskan, Tuncay Basaran, Serkan Ozakbas

BACKGROUND Motor and cognitive impairments often coexist in MS, but individual scores may not capture clinical heterogeneity. Whether phenotypes remain stable or transition over time, and whether identical scores reflect similar clinical profiles, remains unclear. Objectives/Aims

OBJECTIVES To assess stability and transition of motor and motor-cognitive phenotypes in MS, and whether similar motor or cognitive scores differ clinically by phenotype structure.

METHODS Individuals with MS with repeated motor and cognitive assessments were included. Motor performance was assessed with T25FW, 2MWT, 6MWT, TUG, 6SST, and 9HPT; cognition with SDMT and BVMT-R. Measures were converted to age adjusted z-scores. Phenotypes were derived by latent profile analysis. Stability and transitions were evaluated longitudinally. Individuals were stratified into identical performance bands, and outcomes compared across phenotypes. Multivariable models tested whether phenotype explained variability beyond scores.

RESULTS 551 individuals were included (69.3% female; age 35.93±10.90 years; disease duration 8.09±11.12 years; EDSS 1.74±2.07). Latent profile analysis identified distinct motor and motor-cognitive phenotypes with different gait speed, mobility, upper limb function, and cognitive patterns. External validation showed significant differences in disability, fatigue, and depression. Longitudinally, many individuals remained stable, while a meaningful subset transitioned, indicating partial instability. Within identical motor performance bands, including similar T25FW, phenotypes differed significantly in EDSS, TUG, 6SST, 9HPT, and BVMT-R. Within identical SDMT bands, motor disability, function, and symptom burden also differed. Phenotype membership independently predicted outcomes beyond individual scores ($p < 0.05$). Conclusion

CONCLUSION Motor and motor-cognitive phenotypes in multiple sclerosis demonstrate both stability and transition over time, indicating that they are dynamic constructs rather than fixed biological categories. Despite identical performance scores, individuals may exhibit substantially different clinical profiles depending on underlying phenotype structure, which independently influences disability and symptom burden. These findings demonstrate that individual motor and cognitive performance scores lack sufficient clinical context when interpreted in isolation, and that phenotype based stratification provides a more comprehensive framework for understanding clinical heterogeneity in multiple sclerosis

044

Dissociable Network Dynamics of Physical and Cognitive Fatigability in Multiple Sclerosis

Serkan Ozakbas, Gözde Deniz Ünal, İrem Kara, Tuncay Basaran, Ebru Isgandarli, Ela Zengin

BACKGROUND Fatigability in multiple sclerosis (MS) reflects time-dependent decline in motor and cognitive performance. Although often considered a unified construct, growing evidence suggests domain-specific mechanisms. Whether physical and cognitive fatigability share similar temporal and organizational patterns remains unclear.

OBJECTIVES To characterize physical and cognitive fatigability phenotypes in MS and investigate their cross-domain relationships.

METHODS A total of 269 individuals with MS were included. Physical fatigability was assessed using the 6-Minute Walk Test (6MWT), with distance recorded each minute. Cognitive fatigability was evaluated using a time-resolved Symbol Digit Modalities Test (SDMT), with performance measured at 30-second intervals. Fatigability phenotypes were predefined according to within-task trajectories as stable, decline, or fluctuating. Temporal dynamics were analyzed using non-parametric repeated-measures tests. Cross-domain associations were assessed using chi-square analysis and Cramer's V. Statistical significance was set at $p < .001$.

RESULTS Participants had a mean age of 37.99±11.04 years, disease duration of 11.20±8.16 years, and EDSS score of 1.33±1.72. Physical fatigability demonstrated significant time-dependent decline, with predominance of the "decline" phenotype. In contrast, cognitive fatigability showed heterogeneous temporal patterns characterized mainly by fluctuating trajectories and absence of a stable phenotype. No significant cross-domain association was observed between physical and cognitive fatigability phenotypes ($p > .05$), indicating dissociation between motor and cognitive performance dynamics. Higher disability levels were associated with greater fatigability across both domains, suggesting shared sensitivity to overall disease burden despite independent temporal organization.

CONCLUSION Physical and cognitive fatigability in MS exhibit distinct and dissociable temporal and phenotypic patterns. The absence of stable cognitive trajectories and weak cross-domain association suggest that fatigability is not a unitary construct but reflects independent network-level vulnerabilities across motor and cognitive systems. These findings support the need for domain-specific fatigability assessment in MS and highlight the importance of integrating temporal performance dynamics into clinical evaluation.

SECTION III

Fatigue, Sleep, Physical Activity and Quality of Life

8 ABSTRACTS

045

Patient-Perceived Mobility and Fatigue, Rather Than Overall Disability, Drive Changes in Quality of Life in Multiple Sclerosis

İrem Kara, Gözde Deniz Ünal, Ela Zengin, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Health-related quality of life (HRQoL) in multiple sclerosis (MS) is influenced by a complex interplay of physical, cognitive, and psychological factors. While cross-sectional determinants are well described, less is known about which longitudinal changes drive individual trajectories of HRQoL over time.

OBJECTIVES To identify clinical factors associated with three-year changes in HRQoL in patients with MS.

METHODS This longitudinal study included MS patients with baseline and 3-year follow-up assessments. HRQoL was measured using the EQ-5D-3L visual analogue scale (EQ-VAS). Patients were categorized as improved, stable, or worsened based on clinically meaningful changes in EQ-VAS. Associations between HRQoL change and longitudinal clinical variables - including fatigue, walking-related disability (MSWS-12), balance confidence, and objective mobility measures - were evaluated using correlation and multivariable regression analyses.

RESULTS A total of 165 patients were included. Mean EQ-VAS decreased from 81.1 ± 18.6 to 75.6 ± 24.1 over three years (mean change −5.5 ± 29.4, $p = 0.137$), indicating no significant overall change at the group level. However, substantial interindividual variability was observed, with 32% of patients worsening, 35% remaining stable, and 34% improving. Worsening HRQoL was strongly associated with increases in fatigue burden and perceived walking disability, with moderate-to-strong correlations for fatigue (rho ≈ −0.59, $p < 0.001$) and MSWS-12 (rho ≈ -0.50, $p < 0.001$). Reduced balance confidence was also significantly associated with HRQoL decline. In contrast, objective mobility measures showed weaker associations with HRQoL change.

CONCLUSION Despite stable average HRQoL at the group level, patients with MS exhibit markedly heterogeneous individual trajectories over time. Changes in fatigue and patient-perceived mobility - not overall disability progression - are the primary drivers of HRQoL deterioration. These findings highlight the central role of subjective functional experience in shaping quality of life and suggest that targeting fatigue and perceived mobility limitations may have a greater impact on patient outcomes than focusing solely on objective disability measures.

046

Psychological and Sleep Factors Predominate Over Physical Disability in Determining Quality of Life in Early Multiple Sclerosis

Ergi Kaya, Can Caliskan, İrem Kara, Gözde Deniz Ünal, Ela Zengin, Serkan Ozakbas

BACKGROUND Quality of life (QoL) in multiple sclerosis (MS) is traditionally considered to be primarily driven by physical disability. However, in the early stages of MS, when disability levels are low, the determinants of QoL remain insufficiently understood.

OBJECTIVES To identify key clinical, psychological, and functional predictors of quality of life in patients with early-stage MS and low disability levels.

METHODS People with MS within 6 months of diagnosis and with Expanded Disability Status Scale (EDSS) ≤1.5 were included. Clinical and demographic variables were collected. Participants underwent assessments of the EDSS, Timed 25 Foot Walking Test (T25FW), Nine-Hole Peg Test (NHPT), Pain Detect (PD), Epworth Sleepiness Scale (ESS), Beck Depression Inventory (BDI), and Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Quality of life was measured using the Multiple Sclerosis International Quality of Life Questionnaire (MusiQoL). Multiple linear regression analysis was performed to identify independent predictors of QoL, and other appropriate statistical analyses were made.

RESULTS A total of 125 participants (89 female) were included in this study. The cohort had a mean age of 31.74±9.01 years and low disability levels (EDSS 0.81±0.63). The mean MusiQoL score was 74.35±14.67, with significantly lower QoL observed in female patients than in males (female vs male, mean±SD: 72.24±15.19 vs 79.54±11.98, p=0.011). In multivariate analysis, depression (BDI) emerged as the strongest independent predictor of QoL (β = -0.647, t = -7.590, $p < 0.001$), followed by sleepiness (ESS) (β = -0.172, t = -7.590, p = 0.038). Neuropathic pain (PD), Physical disability measures (T25FW, NHPT) and cognitive performance (BICAMS) were not significant predictors ($p>0.05$).

CONCLUSION In early MS with minimal disability, quality of life is primarily driven by psychological and sleep-related factors rather than physical or cognitive impairment. These findings highlight a pre-disability phase of MS in which QoL is largely determined by non-motor symptoms, underscoring the importance of early holistic management strategies.

047

Determinants of Quality of Life in Early Multiple Sclerosis: A Multidomain Symptom Network Beyond Disability

Ergi Kaya, Can Caliskan, Gözde Deniz Ünal, İrem Kara, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Expanded Disability Status Scale (EDSS) is widely used to quantify disability in multiple sclerosis (MS), particularly gait and lower extremity function. However, in early MS, when physical disability is minimal, quality of life (QoL) may be influenced by additional clinical and neuropsychological factors that are not captured by EDSS alone.

OBJECTIVES To identify clinical and neuropsychological determinants of quality of life in patients with early MS and minimal disability, and to characterize the multidomain structure underlying QoL.

METHODS This cross-sectional study included patients diagnosed with MS within 6 months and with EDSS ≤ 1.5. Clinical and demographic data were collected. Participants underwent comprehensive assessments including EDSS, Timed 25-Foot Walk Test (T25FW), Nine-Hole Peg Test (NHPT), Multiple Sclerosis Walking Scale-12 (MSWS-12), PainDetect, Godin Leisure-Time Exercise Questionnaire, Hamilton Anxiety and Depression Scale (HADS-A and HADS-D), Fatigue Severity Scale (FSS), Symbol Digit Modalities Test (SDMT), California Verbal Learning Test-II (CVLT-II), and Brief Visuospatial Memory Test-Revised (BVMT-R). Quality of life was assessed using the EQ-5D-3L Visual Analogue Scale (EQ-VAS). Multiple linear regression analysis was performed to identify independent predictors of QoL.

RESULTS A total of 141 individuals with MS were included (106 females, 75.2%). The mean age was 37.12 ± 9.74, and mean EDSS was 0.57 ± 0.60, indicating minimal disability. The mean EQ-VAS score was 83.04 ± 14.01. The overall model was statistically significant and explained 39.7% of the variance in QoL ($R^2 = 0.397$, adjusted $R^2 = 0.330$; $F(14,126) = 5.915$, $p < 0.001$). Within this multidomain model, fatigue severity ($\beta = -0.323$, $p = 0.009$) and depressive symptoms ($\beta = -0.252$, $p = 0.018$) were independently associated with lower QoL. Perceived walking performance (MSWS-12, $\beta = -0.217$, $p = 0.033$) and upper extremity function (NHPT-related performance, $\beta = -0.177$, $p = 0.019$) were also significant contributors. In addition, cognitive performance on CVLT-II was independently associated with higher QoL ($\beta = 0.287$, $p = 0.005$).

CONCLUSION In early multiple sclerosis with minimal disability, quality of life is not primarily determined by EDSS. Instead, QoL reflects a multidomain symptom network involving fatigue, depression, perceived motor function, upper extremity performance, and cognition. These findings suggest that patient-reported outcomes in early MS are shaped by a complex, multidimensional symptom architecture.

048

Beyond the Patient-Determined Disease Steps: Development and Preliminary Validation of a Multidimensional Self-Reported Disability Scale in Multiple Sclerosis

Ergi Kaya, Can Caliskan, Gözde Deniz Ünal, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND The Expanded Disability Status Scale (EDSS) is the gold standard for disability assessment in multiple sclerosis (MS), but its reliance on clinician evaluation limits its use. The Patient-Determined Disease Steps (PDDS) offers a patient-reported alternative, yet primarily reflects ambulation and may insufficiently capture non-motor disability domains.

OBJECTIVES To develop a novel self-reported disability scale (SD-MSDS) and to evaluate whether it provides a more comprehensive representation of disability compared to PDDS.

METHODS In this cross-sectional study, people with MS (pwMS) were assessed using EDSS by an experienced clinician. Participants completed both the PDDS and the newly developed Self-Determined Multiple Sclerosis Disease Step (SD-MSDS; 0-10), which was designed by a multidisciplinary team. Correlations between SD-MSDS, EDSS, EDSS functional system (FS) scores, and PDDS were analysed.

RESULTS A total of 104 pwMS (67.3% female) with EDSS scores ranging from 0 to 7 were included. Mean EDSS was 1.98±2.13, mean PDDS was 1.76±2.35, and mean SD-MSDS was 2.35±2.29. Both PDDS and SD-MSDS showed strong correlations with EDSS ($\rho = 0.78$, $p<0.001$ for both), and SD-MSDS was highly correlated with PDDS ($\rho = 0.88$, $p<0.001$). However, SD-MSDS demonstrated broad and strong associations across multiple EDSS functional systems, including pyramidal ($\rho = 0.791$), sensory ($\rho = 0.676$), ambulation ($\rho = 0.686$), and bowel-bladder ($\rho = 0.542$) domains, while correlations with cerebellar, brainstem, and mental systems were weaker. No significant association was observed with the visual system.

CONCLUSION While SD-MSDS and PDDS show comparable correlations with global disability (EDSS), SD-MSDS demonstrates a broad association across multiple neurological domains. These findings indicate that SD-MSDS may provide a comprehensive patient-reported assessment. Further studies are needed to confirm its responsiveness and clinical utility in longitudinal settings.

049

Leisure-Time Physical Activity Declines During the First Year After Multiple Sclerosis Diagnosis

İrem Kara, Gözde Deniz Ünal, Ela Zengin, Serkan Ozakbas

BACKGROUND Physical activity is associated with better outcomes in multiple sclerosis (MS), but its trajectory immediately after diagnosis and the factors influencing change remain unclear.

OBJECTIVES To prospectively evaluate leisure-time physical activity during the first year after MS diagnosis and identify factors associated with longitudinal change.

METHODS Patients with newly diagnosed MS were assessed at diagnosis, month 6, and year 1. Leisure-time physical activity was measured using the Godin Leisure-Time Exercise Questionnaire (GLTEQ), including total, moderate-to-vigorous, and mild activity scores. Disability was assessed with the Expanded Disability Status Scale (EDSS), and fatigue and depressive symptoms with validated questionnaires. Longitudinal change was analysed using linear mixed-effects models adjusted for age, educational level, and baseline EDSS. A ≥20% change in total GLTEQ score from baseline to year 1 was considered clinically meaningful. Multivariable linear regression examined factors associated with activity change.

RESULTS A total of 134 patients were included (mean age 34.9±8.7 years; 71.6% women; median EDSS 1.5 [IQR 1.0- 2.0]). Mean total GLTEQ score decreased from 30.1±18.4 at diagnosis to 27.4±17.9 at month 6 and 26.3±17.6 at year 1. There was a significant overall effect of time (p=0.021), with a decline from diagnosis to year 1 (estimated mean difference −3.8, 95% CI −6.7 to −0.9; p=0.010). Overall, 38.1% showed a clinically meaningful decline, 42.5% remained stable, and 19.4% increased their activity. The reduction was driven by moderate-to-vigorous activity (p=0.008), whereas mild activity remained unchanged (p=0.684). The proportion classified as physically active decreased from 55.2% to 45.5% (p=0.030). Higher baseline fatigue (standardized β=−0.23, 95% CI −0.39 to −0.07; p=0.006) and depressive symptoms (β=−0.18, 95% CI −0.34 to −0.02; p=0.024) independently predicted greater declines. Baseline EDSS, age, and educational level were not significant predictors.

CONCLUSION Leisure-time physical activity declined during the first year after MS diagnosis, primarily because of reduced moderate-to-vigorous exercise. Fatigue and depressive symptoms, rather than baseline disability, were independently associated with decline and may represent modifiable targets for early interventions.

050

Daytime Sleepiness Is Associated with Fatigue Burden but Not Neurological Disability in Multiple Sclerosis: A Two-Year Cohort Analysis

Serkan Ozakbas, Tuncay Basaran, Can Caliskan, Gözde Deniz Ünal, İrem Kara, Ulvi Samadzade

BACKGROUND Fatigue and daytime sleepiness are common and often co-occurring symptoms in multiple sclerosis (MS). While both are frequently assessed in clinical practice, their relationship and relative clinical significance remain unclear. In particular, it is uncertain whether daytime sleepiness reflects overall disease burden, neurological disability, or a distinct symptomatic domain.

OBJECTIVES To investigate the association between daytime sleepiness and fatigue domains and to evaluate whether daytime sleepiness is related to neurological disability over a two-year period.

METHODS MS patients with available baseline and two-year Epworth Sleepiness Scale (ESS) and Fatigue Impact Scale (FIS) data were retrospectively evaluated. Associations between ESS and total fatigue, physical, cognitive, and psychosocial fatigue subdomains were assessed using Spearman correlation analysis at baseline and two-year follow-up. The relationship between ESS and Expanded Disability Status Scale (EDSS) was also examined.

RESULTS Baseline ESS showed moderate positive correlations with baseline total fatigue (rho = 0.393, $p < 0.001$), physical fatigue (rho = 0.362, $p < 0.001$), cognitive fatigue (rho = 0.382, $p < 0.001$), and psychosocial fatigue (rho = 0.239, $p = 0.001$). Similar associations were observed between baseline ESS and two-year fatigue scores, including total fatigue (rho = 0.358, $p < 0.001$), physical (rho = 0.332, $p < 0.001$), cognitive (rho = 0.355, $p < 0.001$), and psychosocial fatigue (rho = 0.299, $p < 0.001$). Two-year ESS also correlated significantly with concurrent fatigue domains, including total fatigue (rho = 0.376, $p < 0.001$), physical (rho = 0.311, $p < 0.001$), cognitive (rho = 0.409, $p < 0.001$), and psychosocial fatigue (rho = 0.317, $p < 0.001$). In contrast, no significant association was observed between ESS and EDSS at either time point (baseline-to-two-year EDSS: rho = 0.042, $p = 0.624$). ESS was also not associated with physical activity levels as measured by the Godin score.

CONCLUSION Daytime sleepiness is consistently associated with fatigue burden across multiple domains in MS but does not appear to be related to neurological disability. These findings suggest that daytime sleepiness represents a component of subjective symptom burden rather than a marker of disease progression. While the observed associations were moderate in magnitude, the persistence of this relationship over two years supports the clinical relevance of evaluating sleepiness as part of the broader fatigue construct.

051

Physical Activity Shows Only a Weak Association with Fatigue in Multiple Sclerosis: A Two-Year Observational Study

Can Caliskan, Tuncay Basaran, Gözde Deniz Ünal, İrem Kara, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Fatigue is a common and disabling symptom in multiple sclerosis (MS) and is often assumed to be influenced by physical activity levels. However, the strength and clinical relevance of this relationship remain unclear, particularly in real-world settings where multiple factors contribute to fatigue.

OBJECTIVES To evaluate the association between physical activity level, as measured by the Godin score, and fatigue impact across multiple domains, and to explore the clinical relevance of this relationship in a two-year cohort

METHODS MS patients with available Godin Leisure-Time Exercise Questionnaire scores and Fatigue Impact Scale (FIS) assessments at baseline and two-year follow-up were retrospectively analyzed. Continuous variables were reported as mean ± standard deviation or median with interquartile range, and categorical variables as counts and percentages. Associations between Godin scores and total fatigue, as well as physical, cognitive, and psychosocial fatigue subdomains, were assessed using Spearman correlation analysis. The relationship between physical activity and Expanded Disability Status Scale (EDSS) was also examined.

RESULTS A total of 274 patient records were included. The distribution of physical activity levels was markedly skewed, with a median baseline Godin score of 0.00 (IQR 0.00-15.00), indicating low activity in a substantial proportion of patients. Baseline Godin score showed a weak but statistically significant inverse correlation with total fatigue impact (rho = −0.230, p = 0.001). Similar weak inverse correlations were observed with physical fatigue (rho = −0.223, p = 0.001), cognitive fatigue (rho = −0.207, p = 0.002), and psychosocial fatigue (rho = −0.197, p = 0.004). No significant association was observed between physical activity level and daytime sleepiness as measured by the Epworth Sleepiness Scale (rho = −0.107, p = 0.142). In addition, baseline physical activity level was not associated with disability progression, as reflected by two-year EDSS (rho = 0.078, p = 0.331).

CONCLUSION Physical activity level shows only a weak association with fatigue in MS across multiple domains. These findings suggest that fatigue is not primarily driven by reduced physical activity and is likely influenced by multifactorial mechanisms. The lack of association with disability and daytime sleepiness further supports the notion that physical activity represents a distinct clinical dimension. While increasing physical activity may have general health benefits, its impact on fatigue appears limited in this cohort.

052

Disability in Multiple Sclerosis Is Associated With Cognitive as Well as Physical Fatigue: A Two-Year Cohort Study

Tuncay Basaran, Can Caliskan, İrem Kara, Gözde Deniz Ünal, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Fatigue in multiple sclerosis (MS) is a multidimensional symptom involving physical, cognitive, and psychosocial domains. The Expanded Disability Status Scale (EDSS) is widely used to quantify disability in MS and is primarily driven by physical and ambulatory impairment. While its association with physical fatigue is expected, the relationship between EDSS and cognitive fatigue remains less clear and may have greater clinical relevance.

OBJECTIVES To evaluate the association between EDSS and total fatigue impact as well as fatigue subdomains (physical, cognitive, and psychosocial fatigue) at baseline and over a two-year follow-up period in patients with MS.

METHODS This retrospective cohort study included MS patients with available EDSS and Fatigue Impact Scale (FIS) data at baseline and at two-year follow-up. Continuous variables were expressed as mean ± standard deviation and median (interquartile range). Relationships between EDSS and fatigue measures were assessed using Spearman correlation analysis.

RESULTS A total of 384 patients were included. Mean baseline EDSS was 2.86 ± 2.33 . Fatigue scores remained stable over time, with mean total fatigue scores of 29.62 ± 22.40 at baseline and 31.70 ± 22.79 at two years. At baseline, EDSS showed a moderate positive correlation with total fatigue (rho = 0.342, $p < 0.001$) and physical fatigue (rho = 0.428, $p < 0.001$). A weak but statistically significant correlation was observed between EDSS and cognitive fatigue (rho = 0.159, $p = 0.021$), as well as psychosocial fatigue (rho = 0.401, $p < 0.001$). Similar associations were observed at two years. EDSS correlated with total fatigue (rho = 0.477, $p < 0.001$), physical fatigue (rho = 0.587, $p < 0.001$), cognitive fatigue (rho = 0.280, $p < 0.001$), and psychosocial fatigue (rho = 0.517, $p < 0.001$). In contrast, EDSS was not associated with Godin physical activity score or Epworth Sleepiness Scale at two years.

CONCLUSION EDSS shows a consistent association with fatigue in MS, particularly with physical fatigue, which is expected given its predominantly motor-based structure. A weaker but statistically significant association is also observed with cognitive fatigue, suggesting that higher disability levels may be linked to cognitive aspects of fatigue as well. However, the magnitude of this relationship is low, indicating a limited but clinically relevant association rather than a strong dependency. Further multivariable and longitudinal analyses are required to clarify the independent contribution of disability to cognitive fatigue.

SECTION IV

Disease Course, Prognosis and Progression

14 ABSTRACTS

053

Added Value of Six-Month Monitoring During the First Year of Multiple Sclerosis

İrem Kara, Gözde Deniz Ünal, Ela Zengin, Serkan Ozakbas

BACKGROUND Cognitive and physical changes may occur early after multiple sclerosis (MS) diagnosis, but the added value of an interim six-month assessment beyond annual follow-up remains unclear.

OBJECTIVES To determine whether six-monthly multidomain monitoring increases detection of clinically meaningful change during the first year after diagnosis and to evaluate the persistence and clinical relevance of changes detected at month 6.

METHODS A total of 355 clinically stable patients with MS in remission were included. The intensive-monitoring cohort comprised 134 patients assessed at diagnosis, month 6, and year 1; 221 independent patients were assessed only at diagnosis and year 1. Groups were comparable in age, education, and baseline Expanded Disability Status Scale (EDSS). Cognition was assessed using the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test-II, and Brief Visuospatial Memory Test-Revised; physical performance using the Timed 25-Foot Walk (T25FW) and 9-Hole Peg Test. Identical cognitive test forms were repeated. Clinically meaningful worsening was defined as a ≥20% decline in at least one cognitive test or ≥20% increase in physical test time. Analyses were adjusted for age, education, and baseline EDSS.

RESULTS In the intensive-monitoring cohort, SDMT decreased by 1.5 points between diagnosis and month 6 (95% CI −2.7 to −0.3; p=0.014), while T25FW increased by 0.13 seconds (95% CI 0.01-0.25; p=0.032). Other cognitive, physical, and EDSS measures remained stable. Clinically meaningful worsening was detected in 39/134 patients (29.1%) with six-monthly monitoring versus 46/221 (20.8%) with annual assessment (adjusted OR=1.56, 95% CI 1.02-2.38; p=0.041). Cognitive deterioration accounted for 71.8% of month-6 worsening. However, only 16/39 patients (41.0%) still met worsening criteria at year 1, while 23/39 (59.0%) no longer did. Persistence was more frequent with combined cognitive and physical deterioration. Treatment was modified in 7/39 patients (17.9%), but no decision was based solely on interim test worsening. Year-1 cognitive, physical, and EDSS outcomes were comparable between cohorts.

CONCLUSION Six-month monitoring modestly increased detection of early worsening but mainly captured transient individual variability rather than different one-year outcomes. Isolated interim abnormalities should be confirmed, whereas persistent multidomain deterioration may identify patients requiring closer follow-up.

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Clinical Yield of Six-Monthly Monitoring During Early Versus Later Multiple Sclerosis

Serkan Ozakbas, İrem Kara, Gözde Deniz Ünal, Ela Zengin

BACKGROUND The clinical value of six-monthly cognitive and physical monitoring at different stages of multiple sclerosis (MS) remains unclear, particularly in clinically stable patients.

OBJECTIVES To compare the frequency, characteristics, and clinical consequences of changes detected over six-month intervals during the first year after diagnosis versus years 2-7.

METHODS A total of 517 patients with MS in clinical remission were included. The early-disease cohort comprised 134 patients assessed at diagnosis, month 6, and year 1. The later-disease cohort included 383 independent patients assessed at three consecutive six-monthly visits during years 2-7. Cognition was assessed using the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test-II, and Brief Visuospatial Memory Test-Revised; physical performance using the Timed 25-Foot Walk (T25FW) and 9-Hole Peg Test. Identical cognitive test versions were repeated. Clinically meaningful worsening was defined as a ≥4-point SDMT decline or ≥20% worsening in either physical test. Analyses were adjusted for age, education, and baseline Expanded Disability Status Scale (EDSS).

RESULTS During the first year, SDMT decreased by 1.6 points (95% CI −2.8 to −0.4; p=0.009) and T25FW increased by 0.14 seconds (95% CI 0.02-0.26; p=0.022). Other cognitive, physical, and EDSS measures remained stable, although CVLT-II showed a trend toward decline (p=0.071). Clinically meaningful worsening occurred in 39/134 patients (29.1%) during the first year versus 70/383 (18.3%) during years 2-7 (adjusted OR=1.68, 95% CI 1.08-2.62; p=0.021). Cognitive deterioration accounted for 71.8% of early events. Only 16/39 patients (41.0%) continued to meet worsening criteria at year 1, while 23/39 (59.0%) no longer did. Persistence was more frequent with combined cognitive and physical deterioration. Treatment was modified in 7/39 patients (17.9%), but no decision was based solely on test deterioration. No significant group-level changes occurred during later disease stages.

CONCLUSION Six-monthly monitoring detected worsening more frequently during the first year than during years 2-7, but most early abnormalities were cognitive and over half were not confirmed at one year. Monitoring may therefore be prioritised during the first year, while isolated changes require confirmation and annual reassessment may be sufficient for clinically stable patients at later stages.

055

Pseudorelapse as a Marker of Disease Burden Rather Than Disease Progression in Multiple Sclerosis

Ergi Kaya, Yasemin Şimşek, Can Caliskan, Serkan Ozakbas

BACKGROUND Pseudorelapses are common transient clinical worsening episodes in multiple sclerosis (MS) without new inflammatory activity. However, their clinical heterogeneity and implications for disease burden remain poorly defined.

OBJECTIVES To determine whether sensorial (SEP) and nonsensorial pseudorelapses (NSP) represent distinct clinical phenotypes and to explore their association with disease burden and short-term outcomes.

METHODS This retrospective cohort study included 172 pwMS with 176 pseudorelapse events. The presence of pseudorelapse was adjudicated and classified as SEP or NSP by an experienced MS clinician. Demographic and clinical characteristics, including EDSS, disease duration, and relapse history, were analysed. One-year post-event outcomes were assessed. The worsening of disability was defined as a 1-point increase in the Expanded Disability Status Scale (EDSS) score for EDSS <5.5 and a 0.5-point increase for EDSS ≥5.5.

RESULTS A total of 172 pwMS (133 female) and 176 pseudorelapse events were included in the study. Seventy-four events were NSP, and 102 events were SEP. NSP patients were older at event onset (SEP vs NSP, median [IQR]: 34 [15] vs 39.5 [15], p=0.05). NSP patients had significantly higher disability at both disease onset and pseudorelapse occurrence (p<0.001). Brainstem onset was more frequent in NSP (SEP vs NSP: 14/102 vs 23/74, p=0.005). NSP was also associated with higher prior relapse burden and a greater proportion of relapses with complete recovery, suggesting increased cumulative inflammatory activity (p=0.006 and 0.004). Despite these differences, no significant differences were observed between SEP and NSP groups in one-year relapse activity or disability progression (p>0.05).

CONCLUSION Sensorial and nonsensorial pseudorelapses represent clinically distinct phenotypes in multiple sclerosis, with nonsensorial events reflecting higher underlying disease burden. However, these phenotypes do not translate into short-term clinical worsening, suggesting that pseudorelapse type reflects disease expression rather than prognosis.

056

Early Clinical Disability Encodes Long-Term Prognosis in Relapsing-Remitting Multiple Sclerosis: Results of a Machine Learning-Based Model

Murat Emec, Ergi Kaya, Tuncay Basaran, Can Caliskan, Mehmet Hilal Ozcanhan, Serkan Ozakbas

BACKGROUND Multiple clinical, radiological, and non-clinical factors contribute to prognosis in multiple sclerosis (MS). However, predicting long-term disability in relapsing-remitting multiple sclerosis (RRMS) remains challenging. Machine learning (ML) provides a data-driven approach capable of capturing complex, non-linear interactions among clinical, radiological, and therapeutic variables.

OBJECTIVES To compare three supervised ML algorithms (Ridge Regression, Random Forest, Gradient Boosting) for predicting five-year Expanded Disability Status Scale (EDSS) scores in RRMS and to identify the most influential clinical predictors of long-term disability.

METHODS We analysed a retrospective cohort of 1,108 patients with RRMS (69.7% female). Predictors included baseline EDSS, first- and second-year EDSS, MRI lesion activity in the first two years, relapse rates before diagnosis and during the first two years, treatment type and duration, pregnancy history, oligoclonal band positivity, age, and demographic variables. After preprocessing and feature engineering, 43 predictors were included. Models were evaluated using 5-fold cross-validation. Performance was assessed using Root Mean Squared Error (RMSE), Mean Absolute Error (MAE), and R2.

RESULTS The mean age at diagnosis was 32.7 ± 9.1 years. Mean baseline EDSS was 2.44 ± 1.48, and mean five-year EDSS was 1.24 ± 1.41. Random Forest achieved the best performance (RMSE 0.842 ± 0.097; R2 0.641 ± 0.059), followed by Ridge Regression (RMSE 0.867 ± 0.046; R2 0.617 ± 0.055) and Gradient Boosting (RMSE 0.874 ± 0.103; R2 0.614 ± 0.057). Second-year EDSS was the most important predictor of five-year disability (importance 0.703), followed by first-year EDSS (0.045) and onset-to-diagnosis delay (0.033). Importantly, clinical and radiological disease activity did not show a statistically significant contribution to long-term disability prediction.

CONCLUSION ML models explained approximately 61-64% of the variance in five-year EDSS in RRMS. Second-year EDSS emerged as the dominant predictor of long-term disability, followed by first-year EDSS and onset-to-diagnosis delay. Notably, disease activity did not significantly influence long-term disability outcomes. These findings suggest that long-term disability in RRMS is largely encoded within early clinical disability trajectories, particularly within the first two years of disease course, rather than ongoing inflammatory activity.

057

Shifting Patterns of Disease Activity in the Transition to Secondary Progressive Multiple Sclerosis

Ergi Kaya, Can Caliskan, Ela Zengin, Serkan Ozakbas

BACKGROUND Secondary progressive multiple sclerosis (SPMS) represents a clinical stage characterised by gradual disability accumulation, often following an initial relapsing-remitting course. However, the relative contribution of inflammatory activity and disability progression in the transition to SPMS remains incompletely understood.

OBJECTIVES To evaluate the association between different patterns of disease activity, e.g. relapse activity, radiological activity, and disability worsening and transition to SPMS in patients with relapsing-remitting multiple sclerosis (RRMS).

METHODS This retrospective cohort study included patients with RRMS followed for at least 4 years. Clinical and demographic data were collected. Disease activity was categorised into six mutually exclusive patterns based on the presence of relapse activity, radiological activity, and disability worsening. Disability progression was defined as a 1.5-point increase in EDSS if baseline EDSS was 0, a 1-point increase if EDSS 1-5, and a 0.5-point increase if EDSS >5.5. Patients were classified according to transition to SPMS during follow-up, and group comparisons were performed.

RESULTS A total of 1365 patients with RRMS were included, of whom 79 transitioned to SPMS during follow-up. There were no differences between groups in sex distribution or initial symptom localisation ($p>0.05$). Patients who developed SPMS were older at diagnosis and had a longer disease duration from onset to diagnosis (respectively, RRMS vs SPMS, median; IQR: 25; 20-30 vs 30; 23-37 and 0.9; 0.2-3 vs 4; 1-8 years, $p<0.001$). Baseline EDSS and pre-diagnostic relapse frequency were also higher in the SPMS group ($p<0.005$). Isolated radiological activity (39.8% vs 17.7%) and isolated relapse activity (40.0% vs 22.8%) were more frequent in the RRMS group ($p<0.005$ for both). In contrast, isolated disability worsening was significantly more frequent in patients who transitioned to SPMS (69.6% vs 31.1%, $p<0.001$). Other combined activity patterns showed no significant between-group differences.

CONCLUSION The transition from RRMS to SPMS is characterised by a shift in dominant disease activity patterns, with disability worsening becoming increasingly prominent relative to inflammatory activity. These findings support the concept that SPMS reflects a transition toward progression-dominant pathology rather than a uniform continuation of inflammatory disease activity.

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Early Disability Worsening as a Marker of Aggressive Disease Evolution in Relapsing-Remitting Multiple Sclerosis

Serkan Ozakbas, Can Caliskan, Ela Zengin, Güvenç Arslan, Said Alizada, Yasemin Şimşek Aras

BACKGROUND Disability accumulation in MS is highly heterogeneous, even among patients with relapsing remitting onset. While some remain stable, others develop early clinically meaningful EDSS worsening. This variability suggests distinct disease trajectories not fully explained by baseline disability. Identifying factors associated with early EDSS worsening may help define a high risk subgroup with more aggressive disease evolution.

OBJECTIVES To determine the frequency of fifth-year EDSS worsening in patients with relapsing-remitting onset MS and to identify associated clinical, demographic, relapse-related, and treatment-related characteristics.

METHODS Patients with relapsing remitting onset MS and available five year follow up were retrospectively analyzed. Fifth year EDSS worsening was defined by standard EDSS increase thresholds from baseline to year five. Patients were grouped as worsening or stable and compared for demographic, clinical, relapse related, treatment related, immunological, and SPMS conversion variables using appropriate statistical tests.

RESULTS A total of 1418 patients were included. Fifth year EDSS worsening occurred in 97 patients (6.8%), while 1321 patients (93.2%) remained stable. Patients with worsening had longer disease duration (16.09 ± 6.51 vs 12.17 ± 6.30 years, $p < 0.001$) and delayed treatment initiation (2.34 ± 4.08 vs 1.58 ± 2.76 years, $p = 0.009$), while onset age, diagnosis age, and baseline EDSS were similar. The worsening group had higher relapse burden, including total relapses (2.69 ± 1.73 vs 1.50 ± 1.45, $p < 0.001$), ARR (0.59 ± 0.32 vs 0.40 ± 0.27, $p < 0.001$), and different time to first relapse ($p = 0.011$). Spinal, optic, infratentorial, and multifocal relapses were more frequent in this group (all $p \leq 0.012$). SPMS conversion was also higher (21.6% vs 1.2%, $p < 0.001$), including conversion within five years (13.4% vs 0.5%, $p < 0.001$). Male sex was more frequent among patients with worsening (41.2% vs 29.4%, $p = 0.015$), whereas IgG and IgM indices did not differ.

CONCLUSION Fifth-year EDSS worsening occurs in a small subset of patients with relapsing-remitting onset MS and identifies a distinct high-risk disease trajectory. This phenotype is characterized by higher relapse burden, more extensive relapse topography, delayed treatment initiation, male sex predominance, and increased risk of early secondary progression. The absence of baseline EDSS differences suggests that early disability worsening reflects an intrinsically more aggressive disease course rather than initial disease severity.

059

Machine Learning-Based Classification and Time-to-Event Prediction of Conversion from Relapsing-Remitting to Secondary Progressive Multiple Sclerosis: A Multi-Modal Registry Study

Murat Emec, Can Caliskan, Ergi Kaya, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Secondary progressive multiple sclerosis (SPMS) is a major disease milestone characterized by irreversible disability accumulation. Early identification of patients at risk of conversion from relapsing remitting multiple sclerosis (RRMS) may support timely treatment optimization.

OBJECTIVES To develop and evaluate machine learning models using multimodal registry data to classify SPMS conversion risk and predict time to conversion.

METHODS Data from 23 linked clinical registry tables, including demographics, relapse history, longitudinal EDSS assessments, MRI findings, cerebrospinal fluid parameters, laboratory biomarkers, and treatment records, were merged using unique patient identifiers. The analysis included 3,902 patients with confirmed RRMS at baseline, of whom 449 (11.5%) converted to SPMS during follow up. Logistic Regression, Random Forest, and XGBoost models were developed to predict conversion. A sensitivity analysis excluding EDSS measurements obtained close to conversion was performed. Time to conversion was evaluated using Cox proportional hazards, Random Survival Forest, and Gradient Boosting Survival models. SHAP analysis assessed feature importance.

RESULTS XGBoost achieved the highest discrimination for SPMS conversion, with an AUC of 0.93. After excluding EDSS measurements obtained close to conversion, discrimination remained acceptable, with an AUC of 0.74, indicating that baseline clinical information retained predictive value. Random Survival Forest showed the best survival model performance, with a concordance index of 0.81, compared with 0.76 for the Cox proportional hazards model. Direct prediction of exact conversion time was limited, with a best R2 of 0.03. The most influential predictors were EDSS, disease duration at baseline, prebaseline relapse count, CSF IgG index, and number of clinical visits.

CONCLUSION Machine learning models, particularly ensemble tree based methods, showed good discrimination for identifying RRMS patients at increased risk of SPMS conversion using routinely collected registry data. Performance remained clinically meaningful after excluding disability measures obtained close to conversion, supporting the value of baseline clinical information for early risk stratification. Accurate prediction of the exact timing of conversion remained difficult and may require larger cohorts with denser longitudinal follow up.

060

Dynamic Prediction of Composite Disease Activity in Multiple Sclerosis Using Explainable Artificial Intelligence

Eren Ozakbas, Ulvi Samadzade, Ece Ozakbas, Can Caliskan, Murat Emec, Mehmet Hilal Ozcanhan, Serkan Ozakbas

BACKGROUND Disease activity in multiple sclerosis is traditionally assessed through clinical relapses, new magnetic resonance imaging lesions, and disability progression. Composite measures of disease activity provide a comprehensive framework for evaluating treatment response, yet anticipating future activity remains challenging. Recent advances in artificial intelligence allow integration of longitudinal clinical and radiological information to support proactive and individualized disease monitoring.

OBJECTIVES To develop and evaluate an explainable artificial intelligence model capable of predicting composite disease activity twelve and six months in advance using real world longitudinal data from patients with multiple sclerosis.

METHODS This study used a large real world cohort comprising 4,082 patients and 62,414 clinical visits. Composite disease activity was defined as the presence of clinical relapse, new or enlarging magnetic resonance imaging lesions, or confirmed disability progression. Temporal and longitudinal features were generated for each visit, including the time since the most recent relapse, disability worsening, or radiological activity. Several supervised learning algorithms were evaluated and model performance was assessed using accuracy, precision, recall, F1 score, and area under the receiver operating characteristic curve. Explainability was examined through SHapley Additive explanations. Comparative analyses included prediction horizons of six and twelve months, model structure, and feature selection strategies.

RESULTS The CatBoost model achieved the highest performance, with an accuracy of 0.84 and an area under the curve of 0.91 for six month prediction. Twelve month prediction yielded lower accuracy, reflecting increased biological variability over longer intervals. Temporal features representing stability in relapse, disability, and radiological activity were the strongest predictors. Explainability analysis confirmed that the model relied on clinically plausible features. Ablation studies showed that a single holistic model outperformed component specific models and that a reduced feature set maintained predictive performance.

CONCLUSION Composite disease activity in MS can be accurately predicted using routine clinical and radiological data. A six month horizon is more reliable and clinically useful than 12 months. Explainable AI may support individualized risk estimation, proactive monitoring, and treatment decisions.

061

Clinical and Immunological Characteristics Associated with Conversion to Secondary Progressive Multiple Sclerosis

Ulvi Samadzade, Yasemin Şimşek Aras, Can Caliskan, Serkan Ozakbas

BACKGROUND The transition from relapsing-remitting multiple sclerosis (RRMS) to secondary progressive multiple sclerosis (SPMS) remains difficult to predict in routine clinical practice. Identifying clinical and immunological characteristics associated with this transition may facilitate earlier recognition of patients at increased risk and support timely therapeutic decision-making.

OBJECTIVES To identify demographic, clinical, and immunological characteristics associated with conversion from RRMS to SPMS in a large real-world cohort.

METHODS We retrospectively evaluated 3,448 patients with RRMS followed at a tertiary multiple sclerosis center. Patients were classified according to disease course as remaining RRMS or converting to SPMS during follow-up. Demographic, clinical, laboratory, and treatment characteristics were compared between groups using the chi-square test or Mann-Whitney U test, as appropriate. Statistical significance was defined as $p<0.05$.

RESULTS Compared with patients who remained RRMS, those who converted to SPMS were more frequently male (34.9% vs 28.7%, $p=0.021$), more often presented with spinal cord involvement at disease onset (39.7% vs 32.6%, $p=0.010$), and had higher baseline disability ($p<0.001$). Diagnostic delay was longer among converters (44.81 vs 32.20 months, $p=0.002$), and OCB positivity was more frequent (73.11% vs 82.1%, p=0,033). Age at disease onset did not differ significantly ($p=0.070$), nor did annualized relapse rate (median 0.219 vs 0.222, $p=0.354$). Although disease duration and final EDSS were higher among patients who converted to SPMS ($p<0.001$), these findings reflected the progressive disease course.

CONCLUSION In this large real-world cohort, male sex, spinal cord involvement at onset, higher baseline disability, longer diagnostic delay, and OCB positivity were associated with conversion from RRMS to SPMS. These readily available clinical characteristics may help identify patients at increased risk of progression and support closer monitoring and earlier therapeutic optimization.

062

Early Low-Range Disability Predicts Long-Term Disability Progression in Relapsing Multiple Sclerosis

Orkhan Mammadov, Can Caliskan, Ulvi Samadzade, Said Alizada, Serkan Ozakbas

BACKGROUND Patients with relapsing multiple sclerosis (RMS) who present with low disability are often considered to have a uniformly favourable prognosis. However, it remains unclear whether small differences within the low Expanded Disability Status Scale (EDSS) range are associated with long-term disability outcomes.

OBJECTIVES To compare long-term clinical outcomes between patients with baseline EDSS scores of 0-1.0 and 1.5-2.0.

METHODS This registry-based longitudinal study included 1,364 patients with RMS followed for a mean of 11.4 years. Participants were stratified according to baseline EDSS into two groups: EDSS 0-1.0 (n=722) and EDSS 1.5- 2.0 (n=642). Prespecified disability milestones were conversion to secondary progressive multiple sclerosis (SPMS) and attainment of EDSS 4.0. Baseline characteristics and follow-up outcomes were compared using the Mann-Whitney U and $\chi 2$ tests. Longitudinal disability trajectories were evaluated using a repeated-measures general linear model.

RESULTS The two groups were comparable with respect to sex, family history, cerebrospinal fluid findings, and treatment exposure, differing only slightly in age at disease onset (29.6 vs 27.8 years; p=0.001). Patients with baseline EDSS 1.5-2.0 were more likely to reach EDSS 4.0 than those with EDSS 0-1.0 (11.4% vs 2.6%; p<0.001) and more frequently converted to SPMS (5.6% vs 1.1%; p<0.001). They also experienced a higher annualised relapse rate (0.367 vs 0.310; p<0.001) and had higher final EDSS scores at last follow-up (1.57 vs 0.57; p<0.001). Longitudinal analysis demonstrated significantly different disability trajectories between groups (group-by-time interaction, p=0.001). Spinal cord onset was more frequent among patients with baseline EDSS 1.5-2.0 (35.8% vs 25.8%; p<0.001), whereas optic neuritis was more common in those with baseline EDSS 0-1.0 (24.9% vs 19.9%; p=0.028). The proportion of patients receiving high-efficacy disease-modifying therapy at the last follow-up was similar between groups (72.6% vs 71.9%; p=0.753).

CONCLUSION Among patients with low baseline disability, an EDSS of 1.5-2.0 was associated with substantially worse long-term clinical outcomes than an EDSS of 0-1.0 despite similar treatment exposure. These findings suggest that the low-disability range is clinically heterogeneous and that even modest differences in baseline EDSS may identify patients at increased risk of disability progression. Time-to-event analyses accounting for differences in follow-up duration are ongoing.

063

Clinical Determinants of Minimal Versus Early Disability at 10 Years in Multiple Sclerosis: An Extreme-Phenotype Cohort Study

Orkhan Mammadov, Can Caliskan, Said Alizada, Ulvi Samadzade, Yasemin Şimşek Aras, Serkan Ozakbas

BACKGROUND Identifying patients destined for minimal versus early disability remains a major challenge in multiple sclerosis (MS). Comparing patients at opposite extremes of long-term disability may reveal prognostic factors that are less apparent in unselected cohorts.

OBJECTIVES To identify clinical, radiological, cerebrospinal fluid (CSF), and treatment-related factors associated with minimal disability (EDSS ≤1.5) versus early disability (EDSS ≥3.0) at 10 years after disease onset.

METHODS This retrospective single-centre cohort study included patients classified according to their 10-year EDSS score as having minimal disability (EDSS ≤1.5) or early disability (EDSS ≥3.0); patients with intermediate disability were excluded. Clinical, radiological, CSF, and treatment characteristics were compared using independent-samples t tests and $\chi 2$ tests. Variables significant in univariable analyses and considered clinically relevant were entered into a multivariable binary logistic regression model to identify independent predictors of early disability.

RESULTS Among 940 patients, 673 (71.6%) had minimal disability and 267 (28.4%) had early disability at 10 years. Compared with the minimal-disability group, patients with early disability were older at disease onset (33.8 vs 28.3 years), diagnosis (36.2 vs 30.5 years), and first disease-modifying treatment (36.8 vs 30.9 years), were less frequently female (57.7% vs 75.5%), experienced more relapses (4.84 vs 3.10), had a higher 10-year annualized relapse rate (0.48 vs 0.31), more frequent spinal cord involvement (44.9% vs 31.6%), and more frequent use of third-line disease-modifying therapies (16.5% vs 4.1) (all $p<0.001$). In contrast, relapse activity during the first two years ($p=0.955$), oligoclonal band status, and IgG index did not differ between groups. In the multivariable model (n=928), older age at diagnosis (OR 1.07), higher early annualized relapse rate (OR 1.45), and a shorter interval from symptom onset to diagnosis (OR 0.88 per additional year) were independently associated with early disability. Overall model performance was modest (Nagelkerke R2=0.11).

CONCLUSION Older age at diagnosis and greater early inflammatory activity independently predicted early disability at 10 years, whereas cerebrospinal fluid inflammatory markers showed no prognostic value. Nevertheless, the modest explanatory performance of the multivariable model indicates that routinely available early clinical and laboratory variables capture only a limited proportion of long-term disability risk.

064

Disease Severity Scores Predict Short-Term Physical Worsening in Multiple Sclerosis: A 3-Year Real-World Cohort Study

Tuncay Basaran, Can Caliskan, Yasemin Şimşek Aras, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Disease severity indices such as the Multiple Sclerosis Severity Score (MSSS) and Age-Related MSSS (ARMSSS) are widely used to estimate long-term disability in multiple sclerosis (MS). However, their ability to predict short- to mid-term physical worsening in real-world clinical settings remains less well defined. Identifying patients at higher risk of functional decline is essential for timely treatment optimization.

OBJECTIVES To investigate whether baseline MSSS and ARMSSS scores are associated with physical worsening over a 3-year follow-up period in a real-world MS cohort.

METHODS We retrospectively analyzed 409 patients with MS who had at least two physical performance assessments separated by a minimum of 3 years. Physical function was evaluated using the Timed 25-Foot Walk (T25FW) and the 9-Hole Peg Test (9-HPT). Worsening was defined as a deterioration in test performance between baseline and follow-up. MSSS and ARMSSS scores were calculated at baseline. Group comparisons between patients with and without worsening were performed using the Mann-Whitney U test.

RESULTS The cohort included 409 patients (69.9% female) with a mean baseline EDSS of 1.71 ± 1.87 and a mean follow-up EDSS of 1.46 ± 1.99 over 3 years. Most patients had relapsing-remitting MS (88.8%), followed by secondary progressive (8.1%) and primary progressive MS (3.2%). Physical worsening was observed in 73 patients (17.8%) based on T25FW and in 30 patients (7.3%) based on 9-HPT. Patients with T25FW worsening had significantly higher baseline ARMSSS ($Z = -4.251$, $p < 0.001$) and MSSS ($Z = -4.913$, $p < 0.001$). Similarly, patients with 9-HPT worsening showed higher ARMSSS ($Z = -3.104$, $p = 0.002$) and MSSS ($Z = -4.498$, $p < 0.001$).

CONCLUSION Higher baseline MSSS and ARMSSS scores are strongly associated with subsequent physical worsening over a 3-year period in MS. These findings support the clinical utility of disease severity indices as practical tools for identifying patients at increased risk of short-term functional decline. Early risk stratification using these scores may help guide more individualized monitoring and treatment strategies.

065

Comparison of Multiple Sclerosis Severity Score and Age-Related Multiple Sclerosis Severity Score in a Large Real-World Multiple Sclerosis Cohort

Tuncay Basaran, Can Caliskan, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND The Multiple Sclerosis Severity Score (MSSS) and the Age-Related Multiple Sclerosis Severity Score (ARMSSS) are widely used tools for benchmarking disability severity in multiple sclerosis (MS). While MSSS adjusts disability according to disease duration, ARMSSS uses age as the reference, providing an alternative measure that is less dependent on accurate disease duration. However, data directly comparing the distribution and clinical performance of both scores in large real-world cohorts remain limited.

OBJECTIVES To characterize and compare the distributions of MSSS and ARMSSS in a large real-world MS cohort and to evaluate their ability to discriminate clinical subgroups according to sex and disease course.

METHODS Consecutive patients with relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS) who attended at least one outpatient visit after 2024 were included. Demographic and clinical data were extracted from the institutional registry. EDSS, MSSS, and ARMSSS were calculated for each participant. Severity scores were compared according to sex and disease course using effect size analyses.

RESULTS A total of 2,594 patients were included, of whom 71.3% were female. Mean age was 43.2±12.3 years, mean disease duration was 13.9±9.1 years, and mean EDSS was 1.52±2.04. Mean MSSS was 2.49±2.45, whereas ARMSSS, available for 2,105 patients with complete age data, averaged 2.52±2.52. Male patients demonstrated slightly higher EDSS, MSSS, and ARMSSS values than female patients (all $p \leq 0.003$), although effect sizes were small (Cohen's $d = 0.14$-0.16). In contrast, patients with SPMS exhibited markedly higher EDSS, MSSS, and ARMSSS values than those with RRMS, with very large effect sizes for all comparisons (all $p < 0.001$; Cohen's $d > 2.4$)

CONCLUSION MSSS and ARMSSS demonstrated comparable distributions and consistently distinguished patients according to disease course while identifying modest sex-related differences. These findings support the applicability of both severity measures for benchmarking disability in routine clinical practice and large real-world MS cohorts

066

Progression Independent of Relapse Activity as a Marker of Aggressive Disease Evolution in Multiple Sclerosis

Serkan Ozakbas, Ela Zengin, Can Caliskan, Yasemin Şimşek Aras, Ulvi Samadzade

BACKGROUND Progression independent of relapse activity (PIRA) refers to disability accumulation in multiple sclerosis (MS) occurring outside clinically evident relapses. Although considered relapse-independent, its clinical relevance in relapsing remitting MS (RRMS) remains unclear. Identifying factors associated with PIRA may help define patients with a more aggressive disease course and earlier progression.

OBJECTIVES To determine the frequency of PIRA at five years in patients with RRMS onset and to evaluate clinical, demographic, relapse-related, and treatment-related characteristics associated with its development.

METHODS Patients with RRMS onset and available five-year follow-up data were retrospectively analyzed. PIRA was defined as confirmed EDSS worsening not associated with a clinical relapse during the same period. Patients were stratified into PIRA and non-PIRA groups. Groups were compared in terms of age at disease onset, age at diagnosis, disease duration, time to treatment initiation, EDSS at diagnosis, relapse burden, annualized relapse rate, relapse topography, treatment duration, SPMS conversion, and immunological markers.

RESULTS A total of 1418 patients were included; 79 patients (5.6%) met PIRA criteria, while 1339 (94.4%) did not. Patients with PIRA had longer disease duration (15.92 ± 6.86 vs 12.23 ± 6.30 years, $p < 0.001$) and longer time from disease onset to treatment initiation (2.67 ± 4.43 vs 1.57 ± 2.74 years, $p = 0.002$). Age at onset and EDSS at diagnosis did not differ significantly. Relapse burden was higher in the PIRA group, with increased total relapses and annualized relapse rate (both $p < 0.001$), different time to first relapse ($p = 0.011$), and more frequent spinal and infratentorial relapses ($p = 0.022$ and $p = 0.001$). PIRA was associated with progressive disease phenotype, including higher current SPMS (21.5% vs 1.5%, $p < 0.001$) and SPMS conversion within five years (11.4% vs 0.7%, $p < 0.001$). Male sex was also more common in PIRA patients (41.8% vs 29.6%, $p = 0.022$).

CONCLUSION PIRA was identified in a small subset of patients with relapsing-remitting onset MS and was associated with longer disease duration, delayed treatment initiation, higher relapse burden, male sex, and increased SPMS conversion. Although defined as relapse-independent disability accumulation, its association with relapse characteristics and SPMS suggests a broader, more aggressive disease trajectory. These findings support PIRA as a clinically meaningful marker of high-risk MS with accelerated progression.

SECTION V

Age at Onset, Ageing and Sex

5 ABSTRACTS

067

A Potential Neurodevelopmental Transition Window in Multiple Sclerosis Onset: Clinical Evidence From Age-Stratified Analysis

Can Caliskan, Sudenur İnan, Said Alizada, Yasemin Şimşek Aras, Serkan Ozakbas

BACKGROUND MS onset before 18 years is classified as pediatric onset MS, whereas later onset is considered adult onset disease. However, brain maturation continues into young adulthood, suggesting that onset between 19 and 29 years may not fully align with either pediatric or typical adult patterns. This study evaluated whether this age range shows clinical features closer to pediatric onset or later adult onset MS and whether it may represent a neurodevelopmental transition zone.

OBJECTIVES To determine whether patients with MS onset between 19 and 29 years demonstrate clinical and disease activity patterns closer to POMS (≤18 years) or adult-onset MS (30-50 years), using a multinomial logistic regression approach.

METHODS This retrospective study included 1545 patients with relapsing remitting MS onset, including those later converting to SPMS, from a cohort of 4432 individuals. Patients were grouped by onset age as ≤18, 19 to 29, and 30 to 50 years. The 19 to 29 year group was the reference in multinomial logistic regression. The model included EDSS at diagnosis, five year EDSS, and five year ARR. Discriminatory variables were assessed using likelihood ratio tests, with odds ratios and Nagelkerke R2 used for group comparisons and model fit.

RESULTS A total of 1545 patients were included:190 (12.3%) with onset ≤18 years, 922 (59.7%) with onset at 19 to 29 years, and 433 (28.0%) with onset at 30 to 50 years. The multinomial model was significant but had low explanatory power ($\chi 2$ = 84.636, $p < 0.001$; Nagelkerke R2 = 0.063). EDSS at five years and five year ARR differentiated onset groups (both $p < 0.001$), whereas EDSS at diagnosis did-not ($p = 0.145$). Compared with the 19 to 29 year group, onset ≤18 years showed no significant differences. In contrast, onset at 30 to 50 years was associated with higher five year EDSS (OR = 1.312, 95% CI 1.188 to 1.450, $p < 0.001$) and lower five year ARR (OR = 0.257, 95% CI 0.155 to 0.425, $p < 0.001$), indicating a more disability dominant and less relapse active profile.

CONCLUSION Patients with MS onset between 19 and 29 years showed clinical features closer to pediatric onset MS than to later adult onset MS, especially in relapse activity and disability accumulation. In contrast, onset between 30 and 50 years was associated with higher disability progression and lower inflammatory activity, suggesting a more neurodegenerative disease profile. Despite limited explanatory power, these findings support a possible neurodevelopmental transition window in MS onset and should be considered exploratory rather than definitive.

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Ulvi Samadzade, Can Caliskan, Tuncay Basaran, Gözde Deniz Ünal, İrem Kara, Serkan Ozakbas

BACKGROUND Age at onset is a potential determinant of disease phenotype and disability accumulation in multiple sclerosis (MS), but longitudinal differences across pediatric-onset (POMS), adult-onset (AOMS), and late-onset MS (LOMS) remain insufficiently characterized.

OBJECTIVES To evaluate differences in clinical characteristics, CSF and radiological findings, treatment patterns, and disability trajectories across POMS, AOMS, and LOMS.

METHODS We retrospectively analyzed 780 MS patients with ≥3 years follow-up and baseline EDSS 2.0-3.0 (mild-to-moderate disability range), ensuring comparable baseline disability across groups. Patients were classified as POMS (n=29), AOMS (n=643), and LOMS (n=108). Group differences were assessed using Kruskal-Wallis and chi-square tests. Longitudinal EDSS changes were analyzed using repeated-measures GLM.

RESULTS Baseline EDSS was comparable across groups (p=0.387). Over follow-up, significant differences emerged in disability accumulation, with progressively higher EDSS change from POMS to LOMS (p<0.001). Repeated-measures analysis confirmed a significant time-by-group interaction (F=32.238, p<0.001), indicating distinct disability trajectories according to age at onset. LOMS showed the highest disability burden over time and a higher frequency of progressive disease phenotypes (p<0.001). POMS demonstrated lower disability accumulation but higher brainstem and cerebellar involvement (p=0.027). CSF oligoclonal band positivity differed between groups (p=0.010), whereas IgG index did not. Treatment step distribution differed significantly across groups at baseline and follow-up (both p<0.001).

CONCLUSION Age at onset is a key determinant of disease expression in MS. Despite comparable baseline disability, LOMS is associated with accelerated disability accumulation and a more progressive disease course, whereas POMS shows lower disability progression but distinct infratentorial involvement. These findings highlight age at onset as a major driver of long-term clinical trajectory in MS.

069

Pediatric-Onset Multiple Sclerosis Shows Higher Inflammatory Burden but Lower Disability Despite Similar Disease Duration Compared to Adult-Onset Disease

Ela Zengin, Can Caliskan, Said Alizada, Sudenur İnan, Yasemin Şimşek Aras, Serkan Ozakbas

BACKGROUND Pediatric-onset multiple sclerosis (POMS) is part of the MS disease spectrum but is thought to differ from adult-onset disease in terms of inflammatory activity and long-term disability accumulation. However, comparative data across age groups with balanced disease duration remain limited.

OBJECTIVES To compare clinical, radiological, cognitive, functional, laboratory, and treatment-related characteristics between pediatric- and adult-onset MS in a disease duration-matched cohort.

METHODS We retrospectively analyzed 671 patients with MS stratified by age at disease onset: pediatric-onset MS (POMS, n=74), 18-30 years (n=303), 30-40 years (n=194), and 40-50 years (n=100). Groups were compared in terms of sex distribution, lesion topography, treatment exposure, relapse measures, Expanded Disability Status Scale (EDSS), cognitive performance (SDMT, CVLT, BVMT), physical performance, and immunoglobulin indices. Disease duration was comparable across all groups.

RESULTS No significant differences were observed in sex distribution, lesion topography, treatment step, physical performance, or immunoglobulin indices between groups. POMS was associated with a higher cumulative relapse burden compared with the 30-40 and 40-50 year onset groups ($p=0.003$ and $p<0.001$, respectively). Despite this, final EDSS scores were lower in POMS compared with the 40-50 year onset group (0.34 ± 0.77 vs 0.76 ± 1.37, $p=0.045$). Cognitive performance was preserved in POMS, with higher SDMT scores compared with both the 30-40 and 40-50 year onset groups ($p<0.001$ for both), and higher CVLT and BVMT scores compared with the 40-50 year onset group.

CONCLUSION Despite comparable disease duration, pediatric-onset multiple sclerosis is characterized by a higher inflammatory burden but lower disability accumulation compared with later-onset disease. Cognitive performance appears relatively preserved in pediatric-onset disease, potentially reflecting earlier and comparable treatment exposure across onset groups. These findings support the concept of age-dependent disease trajectories in MS, with a more inflammatory but less disabling early course in pediatric-onset patients.

070

Inflammation Declines but Remains Clinically Relevant After Age 65 in Relapsing-Onset Multiple Sclerosis

Ulvi Samadzade, Orkhan Mammadov, Can Caliskan, Said Alizada, Tuncay Basaran, Serkan Ozakbas

BACKGROUND Inflammatory disease activity in multiple sclerosis (MS) is known to decline with aging; however, whether residual inflammatory activity continues to contribute to disability progression in older adults remains unclear.

OBJECTIVES To assess relapse activity, annualized relapse rate (ARR), MRI activity, and disability progression after age 65 in patients with relapsing-onset MS, and to examine the relationship between residual inflammatory activity and progression, with a focus on disease phenotype and SPMS conversion.

METHODS This single-center retrospective cohort study included patients with relapsing-remitting MS (RRMS) and SPMS who had at least 12 months of follow-up after age 65. Patients with primary progressive MS were excluded. Relapses were defined as new or worsening neurological symptoms lasting at least 24 hours in the absence of infection or fever. MRI activity was defined as the presence of new T2 or gadolinium-enhancing lesions.

RESULTS A total of 139 patients were included (78 RRMS, 61 SPMS), with a mean age of 73.55 years and a mean follow-up of 4.74 years after age 65. Inflammatory activity declined after age 65, with ARR decreasing from 0.25 to 0.06 (median 0.00); however, residual activity persisted, with 21.6% of patients experiencing relapses and 24.2% showing new MRI lesions. Disability progression occurred in 30.2% of patients and was significantly associated with ongoing inflammatory activity. Progression was more frequent in patients with relapses (50.0% vs 24.8%, $p=0.008$) and in those with new MRI lesions (43.5% vs 20.8%, $p=0.032$). SPMS patients had a higher rate of progression than RRMS patients (45.9% vs 17.9%, $p<0.001$). Among SPMS patients, those with relapses after age 65 had later SPMS conversion and longer disease duration at conversion ($p=0.002$ and $p=0.025$, respectively), suggesting sustained inflammatory activity in this subgroup.

CONCLUSION Inflammatory activity declines but persists after age 65 in relapsing-onset MS. Residual activity, reflected by relapses and MRI lesions, remains associated with disability progression, indicating a continued inflammatory contribution to disease worsening. Patients with later SPMS conversion and longer relapsing disease duration may represent a subgroup with sustained inflammation. These findings support ongoing, phenotype-specific monitoring of disease activity in older adults.

071

Male Sex Is Associated With Greater Disease Severity and Higher Treatment Escalation in Multiple Sclerosis

Can Caliskan, Tuncay Basaran, Güvenç Arslan, Ela Zengin, Yasemin Şimşek Aras, Serkan Ozakbas

BACKGROUND Sex differences in multiple sclerosis are well recognized. Although MS is more common in women, men often show a more aggressive disease course, with greater disability accumulation and more frequent progressive phenotypes. Large real world comparisons of disease severity indices and treatment patterns are needed to better characterize these differences.

OBJECTIVES To compare disability level, disease severity scores (EDSS, MSSS, ARMSSS), MS phenotype distribution, treatment escalation, and comorbidity profiles according to sex in a large cohort of patients with MS.

METHODS We retrospectively evaluated 2687 patients with MS followed after 2022. Variables included age, onset age, disease duration, EDSS, MSSS, ARMSSS, MS phenotype, treatment step, and comorbidities. Continuous variables were compared using the Mann Whitney U test due to non normal distribution, while categorical variables were analyzed using chi square tests.

RESULTS Among 2687 patients, 1895 (70.5%) were women and 792 (29.5%) were men. Age distribution was similar between sexes (median 43 years in both groups, $p = 0.579$). Age at disease onset was also comparable (median 29 years in both groups, $p = 0.900$), as was disease duration (median 13 years in both groups, $p = 0.690$). Despite similar demographic characteristics, male patients exhibited significantly higher disease severity. Median EDSS was higher in men than women (1.50 vs 1.00, $p < 0.001$). Similarly, ARMSSS (1.90 vs 1.33, $p < 0.001$) and MSSS (2.04 vs 1.35, $p < 0.001$) were significantly higher in male patients. Treatment escalation differed significantly by sex ($p < 0.001$). Third-line therapy use was more frequent in men (33.7% vs 25.4%), whereas second-line therapies were more common in women (47.1% vs 38.6%). MS phenotype distribution also differed significantly ($p < 0.001$), with a higher proportion of primary progressive MS in men compared with women (8.6% vs 3.9%). Comorbidity profiles showed similar rates of cardiovascular and neurological conditions between sexes. However, endocrine, autoimmune, and psychiatric comorbidities were more frequent in women.

CONCLUSION Male patients with MS had higher disability and disease severity scores than female patients, despite similar age, onset age, and disease duration. Higher treatment escalation and more frequent progressive MS further support a more aggressive disease profile in men. These findings indicate consistent sex related differences in MS severity across clinical, phenotypic, and treatment domains.

SECTION VI

Pregnancy, Parenthood and Familial MS

7 ABSTRACTS

072

The Postpartum Period as a Structured Inflammatory Rebound Window in Relapsing-Remitting Multiple Sclerosis

Said Alizada, Can Caliskan, Orkhan Mammadov, Yasemin Şimşek, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND The postpartum period is recognized as a time of increased inflammatory activity in relapsing-remitting multiple sclerosis (RRMS). However, the frequency, timing, and clinical determinants of postpartum relapse in contemporary real-world cohorts remain incompletely defined. In particular, it is unclear whether relapse occurrence follows a predictable clinical risk pattern or represents a stochastic post-pregnancy rebound phenomenon.

OBJECTIVES To evaluate the frequency, timing, and clinical predictors of relapse during the first postpartum year in women with RRMS.

METHODS We retrospectively analyzed 522 deliveries from 397 women with RRMS. Postpartum relapse was defined as any clinical relapse occurring within 12 months after delivery. Deliveries with and without postpartum relapse were compared in terms of maternal age, disease duration, diagnosis-to-pregnancy interval, preconception relapse activity, EDSS, and time to postpartum disease-modifying therapy (DMT) reinitiation. Breastfeeding duration was also assessed.

RESULTS Postpartum relapse occurred in 160 of 521 deliveries (30.7%), while 361 (69.3%) remained relapse-free. Among relapse-positive deliveries, the majority had a single relapse, while a smaller proportion experienced multiple relapses, corresponding to a total of 184 relapse events. Relapses clustered predominantly in the early postpartum period, with 19.2% occurring within the first 6 months and 13.6% between months 6 and 12. Compared with relapse-free deliveries, postpartum relapse was associated with younger maternal age (29.02 ± 4.82 vs 30.78 ± 4.81 years, $p < 0.001$), shorter disease duration (6.21 ± 4.86 vs 7.40 ± 4.63 years, $p = 0.008$), shorter diagnosis-to-pregnancy interval (3.85 ± 4.58 vs 5.35 ± 4.89 years, $p = 0.001$), higher preconception relapse activity (0.31 ± 0.54 vs 0.20 ± 0.46, $p = 0.022$), higher prepartum EDSS (1.54 ± 1.66 vs 0.88 ± 1.08, $p < 0.001$), and longer time to postpartum DMT reinitiation (182.58 ± 106.60 vs 112.92 ± 101.28 days, $p < 0.001$). Breastfeeding duration did not differ significantly between groups (9.83 ± 5.31 vs 10.90 ± 6.63 months, $p = 0.112$).

CONCLUSION Postpartum relapse occurred in nearly one-third of RRMS deliveries, mainly within 6 months, and was linked to younger age, higher preconception disease activity, greater disability, and delayed DMT restart, but not breastfeeding duration.

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Relapses During Pregnancy in Relapsing-Remitting Multiple Sclerosis: Frequency, Timing, Topography, and Clinical Determinants in a Real-World Cohort

Said Alizada, Orkhan Mammadov, Ulvi Samadzade, Can Caliskan, Yasemin Şimşek, Serkan Ozakbas

BACKGROUND Pregnancy generally reduces inflammatory activity in MS, but relapses may still occur in some women with RRMS, and their timing, characteristics, and predictors remain incompletely defined.

OBJECTIVES To evaluate the frequency, timing, topography, and clinical correlates of relapses during pregnancy in RRMS, including pre-pregnancy disease activity, disability, and DMT exposure.

METHODS We retrospectively analyzed 521 pregnancies from women with RRMS to evaluate relapse frequency, timing, trimester distribution, topography, and associations with pre-pregnancy clinical, relapse-related, disability, obstetric, and DMT exposure variables using multivariable logistic regression.

RESULTS Among 521 pregnancies, 56 (10.7%) had at least one relapse during pregnancy, whereas 465 (89.3%) remained relapse-free. Relapses were mostly single events: 53/56 (94.6%) had one relapse and 3/56 (5.4%) had two relapses, yielding 59 total events. First relapses occurred in the first, second, and third trimesters in 19/56 (33.9%), 21/56 (37.5%), and 16/56 (28.6%) pregnancies, respectively, with a median timing of 20.29 weeks (IQR 10.57-31.57). The overall pregnancy ARR was 0.14. Relapse topography was spinal in 28/56 (50.0%), multifocal/other in 11/56 (19.6%), infratentorial in 10/56 (17.9%), and optic in 7/56 (12.5%), without trimester-related variation. Relapse-positive pregnancies occurred in younger women than relapse-free pregnancies (28.98 vs 30.39 years, p=0.041), while disease duration, pre-pregnancy EDSS, previous-year relapse activity, pregnancy order, relapse burden, and DMT exposure were similar. In multivariable analysis, neither younger maternal age nor previous-year relapse burden independently predicted relapse during pregnancy.

CONCLUSION Relapses during pregnancy were uncommon, mostly single events distributed across all trimesters and frequently spinal, with no independent clinical, demographic, relapse-related, or treatment-related predictors, suggesting a partly stochastic pattern of disease reactivation during pregnancy.

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Repeated Pregnancies Do Not Increase Relapse Risk in Relapsing-Remitting Multiple Sclerosis

Said Alizada, Yasemin Şimşek Aras, Orkhan Mammadov, Can Caliskan, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND The effect of repeated pregnancies on pregnancy-related inflammatory disease activity in relapsing-remitting multiple sclerosis (RRMS) remains insufficiently understood.

OBJECTIVES To evaluate whether repeated pregnancies are associated with in-pregnancy and postpartum relapse activity in women with RRMS.

METHODS We retrospectively analyzed 421 pregnancies in women with RRMS, classified as first recorded or repeated pregnancies, and evaluated clinical, obstetric, treatment, in-pregnancy relapse, and first-year postpartum relapse variables using clustered generalized estimating equation models to account for repeated pregnancies.

RESULTS Among 421 pregnancies, 295 (70.1%) were first recorded and 126 (29.9%) were repeated pregnancies. Women with repeated pregnancies were older [32.0 (28.0-35.0) vs 29.0 (26.0-32.0) years; p<0.001] and had longer disease duration [8.0 (5.0-12.0) vs 6.0 (3.0-9.0) years; p<0.001], whereas prepregnancy EDSS and relapse activity were comparable between groups. Prepregnancy DMT exposure was present in 77.4% of pregnancies and DMT exposure during pregnancy in 45.4%. Term delivery occurred in 94.3%. In-pregnancy relapse occurred in 14.6% of first recorded pregnancies and 7.9% of repeated pregnancies (p=0.060). First-year postpartum relapse occurred in 32.5% and 27.0%, respectively (p=0.258). In multivariable GEE analyses, repeated pregnancy status was not independently associated with in-pregnancy relapse (adjusted OR 0.52, 95% CI 0.24-1.12; p=0.096) or postpartum relapse (adjusted OR 1.01, 95% CI 0.51-2.02; p=0.977). Younger maternal age, higher prepregnancy EDSS, and delayed postpartum DMT reinitiation independently predicted postpartum relapse activity.

CONCLUSION Repeated pregnancies were not associated with increased pregnancy-related inflammatory activity in RRMS, and postpartum relapse risk was driven mainly by baseline disability, younger age, and delayed DMT reinitiation rather than pregnancy recurrence itself.

075

Familial Aggregation in Multiple Sclerosis Reflects Disease Architecture Rather Than Disease Activity

Serkan Ozakbas, Said Alizada, Can Caliskan, Yasemin Şimşek, Ela Zengin

BACKGROUND Familial aggregation is a well-established feature of multiple sclerosis (MS), suggesting a genetic contribution to disease susceptibility. However, it remains unclear whether increasing familial MS burden is associated not only with disease risk but also with distinct clinical phenotypes and disease course characteristics. In particular, whether higher familial load influences disability accumulation, relapse activity, or disease subtype distribution remains uncertain.

OBJECTIVES To evaluate whether familial MS burden is associated with differences in clinical phenotype, disability, and relapse activity by comparing index cases from single-load and multiple-load families.

METHODS This retrospective single-center familial MS study classified families as single-load with two documented MS cases or multiple-load with ≥3 cases. The primary index-case cohort included 162 patients: 135 single-load (83.3%) and 27 multiple-load (16.7%), with similar female predominance between groups (71.9% vs 63.0%, p=0.356). Demographic, clinical, relapse, disability, and onset topography variables were compared using appropriate parametric, non-parametric, and Fisher's exact tests.

RESULTS In the index-case cohort, multiple-load and single-load groups did not differ significantly in age at onset (25.61 [21.96-32.67] vs 29.10 [21.97-36.97] years, p = 0.306), disease duration (18.11 [13.15-25.84] vs 15.32 [9.62-21.68] years, p = 0.101), baseline EDSS (3.50 [2.00-6.13] vs 2.50 [2.00-3.50], p = 0.051), or annualized relapse rate (0.239 [0.120-0.408] vs 0.222 [0.153-0.361], p = 0.746). Onset topography did not differ significantly between groups. However, disease subtype distribution differed significantly (p = 0.009). The multiple-load group showed a lower frequency of relapsing-remitting MS (55.6% vs 82.2%) and a higher proportion of secondary progressive MS (33.3% vs 14.1%) and primary progressive MS (11.1% vs 3.7%) compared with the single-load group. In the secondary whole-family analysis, which included 348 familial MS cases (263 in the single-load group and 85 in the multiple-load group), the same directional pattern was observed, but between-group differences were attenuated and did not reach statistical significance.

CONCLUSION Greater familial MS burden was not associated with onset age, disease duration, relapse activity, or onset topography, but was linked to enrichment of progressive MS phenotypes, suggesting that familial aggregation may shape disease architecture rather than inflammatory activity.

076

Gender Differences in Parenthood Patterns After Multiple Sclerosis Diagnosis: A Multigenerational Cohort Study

Yasemin Şimşek Aras, Can Caliskan, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Multiple sclerosis (MS) may influence reproductive decisions and family planning due to concerns related to disability progression, treatment exposure, and disease uncertainty. However, how parenthood patterns differ between women and men after MS diagnosis remains insufficiently characterized in large cohorts.

OBJECTIVES To evaluate parenthood patterns in people with MS (pwMS), with a focus on gender differences in timing of childbirth relative to disease onset and post-diagnosis reproductive behavior.

METHODS This single-center cohort included 757 pwMS and 1,055 children. Parenthood patterns were analyzed according to parental sex, total number of children, timing of childbirth relative to MS onset (pre vs post onset), and post-MS parenthood status. Group comparisons between male and female pwMS were performed using chi-square tests.

RESULTS The cohort consisted of 501 female (66.2%) and 256 male (33.8%) pwMS. Overall, 600 children were born before MS onset and 455 after MS onset. Significant gender differences were observed in multiple reproductive domains. Total number of children differed between female and male pwMS ($\chi 2 = 17.321$, $p = 0.002$). The number of children born before MS onset also differed significantly by sex ($\chi 2 = 33.317$, $p < 0.001$), as did the number of children born after MS onset ($\chi 2 = 11.742$, $p = 0.019$). Overall parenthood timing distribution (pre vs post MS parenthood patterns) differed between genders ($\chi 2 = 11.590$, $p = 0.003$). Higher-order parenthood patterns were almost exclusively observed in female pwMS; all individuals with four or five children were women. Female pwMS were more likely to have children after MS onset and to continue childbearing following diagnosis, whereas male pwMS more commonly had children only prior to disease onset.

CONCLUSION Parenthood patterns in multiple sclerosis demonstrate marked gender-specific differences. Female pwMS more frequently continued childbearing after disease onset and were more likely to have larger families, whereas male pwMS were more often limited to pre-diagnosis parenthood. These findings suggest that reproductive behavior in MS is shaped by gender-specific social and behavioral factors in addition to disease-related considerations. Understanding these differences may be relevant for counseling and long-term family planning discussions in clinical practic

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No Consistent Evidence of Adverse Overall Health Outcomes in Children of Parents With Multiple Sclerosis: A Multigenerational Cohort Study

Yasemin Şimşek Aras, Can Caliskan, Ulvi Samadzade, Ela Zengin, Serkan Ozakbas

BACKGROUND Concerns regarding long-term physical and mental health outcomes in children of individuals with multiple sclerosis (MS) are common in clinical practice. However, evidence beyond perinatal outcomes remains limited, particularly regarding broader pediatric and young adult health domains.

OBJECTIVES To evaluate physical health, mental health, and chronic disease burden in children of parents with MS in a large real-world multigenerational cohort.

METHODS This observational study included 756 parents with MS and 1,054 children. Data were obtained from parental reports and clinical records. Child-level variables included allergy, chronic disease, anxiety, depression, developmental status, and birth-related characteristics. Associations between categorical variables were assessed using chi-square tests.

RESULTS The cohort included 501 female (66.3%) and 255 male (33.7%) parents with MS. Among children, 517 (49.1%) were girls and 537 (50.9%) were boys. Mean age was 20.15±13.95 years, and mean birth weight was 3136.75±418.39 g. Overall, 24.9% (262/1054) of children had allergy, 37.4% (394/1054) anxiety, 20.0% (211/1054) depression, and 15.6% (164/1054) chronic disease. Allergy was associated with chronic disease (59.8% vs 18.4%, $p<0.001$), anxiety (41.1% vs 15.2%, $p<0.001$), depression (32.7% vs 22.9%, $p=0.003$), and prematurity (40.4% vs 24.1%, $p=0.008$). Anxiety was more frequent in girls than boys (41.4% vs 33.5%, $p=0.008$) and strongly associated with chronic disease (81.1% vs 29.3%, $p<0.001$), depression (70.6% vs 29.1%, $p<0.001$), and allergy (61.8% vs 29.3%, $p<0.001$). Depression was also more common in girls (24.4% vs 15.8%, $p=0.001$) and associated with chronic disease (36.6% vs 17.0%, $p<0.001$), anxiety (37.8% vs 9.4%, $p<0.001$), and allergy (26.3% vs 17.9%, $p=0.003$). Children born before MS onset showed higher rates of anxiety, depression, and chronic disease; however, this subgroup was significantly older, suggesting a strong age-period confounding effect.

CONCLUSION No consistent pattern of adverse long-term physical or mental health outcomes was identified in children of parents with MS. Although clustering among allergic, psychiatric, and chronic conditions was observed, these associations were not specific to parental MS and likely reflect broader biopsychosocial determinants of child health. These findings provide reassuring real-world evidence that parental MS is not associated with a distinct adverse long-term health profile in offspring.

078

Parental Multiple Sclerosis Is Not Associated With Adverse Academic Outcomes in Offspring: A Multigenerational Cohort Study

Yasemin Şimşek Aras, Can Caliskan, Güvenç Arslan, Ela Zengin, Serkan Ozakbas

BACKGROUND Multiple sclerosis (MS) may impose substantial physical and psychosocial burden on affected individuals and families. Concerns regarding the potential impact of parental disease severity, comorbidity burden, and treatment exposure on offspring developmental and academic outcomes persist, although robust population-level data remain limited.

OBJECTIVES To evaluate academic outcomes in children of people with MS (pwMS) and determine whether parental clinical characteristics, comorbidity burden, and treatment intensity are associated with offspring academic achievement.

METHODS This single-center cohort included 756 pwMS parents and 1,054 children. Demographic, clinical, developmental, and academic variables were analyzed. Academic achievement was categorized as low, normal, or high. Group comparisons were performed using Kruskal-Wallis and chi-square tests. Independent predictors were assessed using generalized estimating equation (GEE) models accounting for family clustering.

RESULTS Among 810 children with available academic data, 729 (90.1%) demonstrated normal academic achievement, while 57 (7.0%) had low and 23 (2.8%) had high academic achievement. Breastfeeding history, prematurity, developmental delay, chronic illness, allergy, depression, anxiety, and parental MS-related characteristics including disease duration, age at onset, comorbidity burden, treatment escalation, and timing of MS onset relative to childbirth were not associated with academic outcomes (all $p > 0.05$). In multivariable GEE analysis, child sex, child age, and parental current age were independently associated with academic outcome distribution (all $p < 0.05$). In contrast, parental comorbidity burden, chronic disease presence, anxiety, developmental delay history, and parental sex were not significant predictors. Despite substantial parental disease burden and frequent exposure to high-efficacy therapies, the vast majority of offspring demonstrated preserved academic performance.

CONCLUSION In this large multigenerational cohort, 90.1% of children of pwMS demonstrated normal academic achievement. Parental MS-related characteristics, including comorbidity burden, treatment intensity, and disease timing, were not associated with offspring academic performance. These findings provide reassuring evidence that parental MS is not linked to adverse academic outcomes despite substantial disease burden.

SECTION VII

Comorbidities

15 ABSTRACTS

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Psychiatric Comorbidity Is Linked to Divergent Disability Progression in Multiple Sclerosis: Clinician and Patient Reported Outcomes Over Three Years

Serkan Ozakbas, Can Caliskan, İrem Kara, Tuncay Basaran, Gözde Deniz Ünal, Ulvi Samadzade

BACKGROUND Psychiatric comorbidities are common in multiple sclerosis (MS) and may contribute to increased disability and functional burden. However, their effect on longitudinal disability progression remains unclear, particularly across clinician-rated and patient-reported measures.

OBJECTIVES To evaluate 3-year changes in disability and compare worsening rates in MS patients with and without psychiatric comorbidity.

METHODS This retrospective cohort study included 305 MS patients with baseline and 3-year Expanded Disability Status Scale (EDSS) and Patient-Determined Disease Steps (PDDS) assessments. Patients were stratified according to psychiatric comorbidity status. EDSS and PDDS were analyzed as continuous variables, and worsening was evaluated categorically. Between-group comparisons used Mann-Whitney U, chi-square, or Fisher's exact tests. Longitudinal changes were analyzed using repeated-measures GLM with group × time interaction.

RESULTS Among 305 patients, 86 (28.2%) had psychiatric comorbidity, most commonly depression (23.3%). Patients with psychiatric comorbidity were older and had longer disease duration and treatment exposure. They also had higher baseline EDSS (2.03 ± 1.88 vs 1.31 ± 1.72, $p < 0.001$) and PDDS scores (1.60 ± 1.89 vs 0.81 ± 1.49, $p < 0.001$), which remained higher at follow-up. EDSS worsening occurred more frequently in patients with psychiatric comorbidity (20.9% vs 10.0%, $p = 0.011$), as did PDDS worsening (18.6% vs 8.2%, $p = 0.010$). Repeated-measures GLM demonstrated a significant group × time interaction for EDSS ($F = 7.971$, $p = 0.005$), indicating different disability trajectories between groups, whereas no significant interaction was observed for PDDS ($F = 1.415$, $p = 0.235$).

CONCLUSION MS patients with psychiatric comorbidity show higher baseline disability and greater clinician-rated disability worsening over 3 years. However, this pattern is less evident in patient-reported disability measures, suggesting divergence between clinician-assessed and patient-perceived progression. These findings support a potential role of psychiatric comorbidity in disability trajectories, although baseline clinical differences likely contribute to observed effects.

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Psychiatric Comorbidity as a Marker of Increased Disease Burden in Multiple Sclerosis: A Real-World Cohort Study

Can Caliskan, Tuncay Basaran, Güvenç Arslan, Ulvi Samadzade, Ela Zengin, Serkan Ozakbas

BACKGROUND Psychiatric comorbidities are common in multiple sclerosis (MS) and may influence both subjective symptom burden and objective measures of disease severity and disability. However, their relationship with validated clinical indices in large real-world cohorts remains incompletely defined.

OBJECTIVES To evaluate the association between psychiatric comorbidity and demographic characteristics, disability, and disease severity in a large multiple sclerosis cohort.

METHODS We analyzed 2,687 patients with multiple sclerosis from a real-world clinical dataset. Patients were stratified according to the presence of psychiatric comorbidity. Age, disease onset age, disease duration, Expanded Disability Status Scale (EDSS), Age-Related Multiple Sclerosis Severity Score (ARMSSS), and Multiple Sclerosis Severity Score (MSSS) were compared between groups using the Mann-Whitney U test.

RESULTS Psychiatric comorbidity was present in 716 patients (26.6%). Patients with psychiatric comorbidity were older than those without (median 48 vs 41 years, $p<0.001$). Disease onset age was higher in the psychiatric comorbidity group (median 30 vs 28 years, $p<0.001$). Disease duration was also longer (median 17 vs 11 years, $p<0.001$). No significant difference was observed in time to secondary progressive MS conversion between groups (median 8 vs 10 years, $p=0.215$). Patients with psychiatric comorbidity showed significantly higher disability and disease severity. Median EDSS was 1.50 versus 1.00 ($p<0.001$). Median ARMSSS was 2.24 versus 1.28 ($p<0.001$), and median MSSS was 2.22 versus 0.98 ($p<0.001$).

CONCLUSION In this large real-world cohort of multiple sclerosis patients, psychiatric comorbidity was associated with older age, later disease onset, longer disease duration, and higher disability and disease severity across all validated scales. However, the lack of difference in time to secondary progressive conversion suggests that psychiatric comorbidity is not associated with accelerated disease progression but rather reflects accumulated disease burden. These findings support psychiatric comorbidity as a clinically meaningful component of overall multiple sclerosis disease burden and highlight the importance of its systematic assessment in routine clinical practice.

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Psychiatric Comorbidity in Multiple Sclerosis: Associations With Baseline Performance and Domain-Specific Longitudinal Change

Can Caliskan, Tuncay Basaran, İrem Kara, Gözde Deniz Ünal, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Psychiatric comorbidities are frequent in multiple sclerosis (MS) and have been associated with worse disability, cognitive impairment, and reduced physical functioning. However, their influence on longitudinal changes in objective motor and cognitive performance measures remains insufficiently characterized.

OBJECTIVES To evaluate longitudinal changes in physical performance, cognitive performance, and disability over a three-year period in patients with MS according to psychiatric comorbidity status.

METHODS A total of 384 patients with MS who completed baseline and three-year follow-up physical and cognitive assessments were retrospectively analyzed. Patients were grouped according to the presence or absence of psychiatric comorbidity at baseline.

RESULTS Psychiatric comorbidity was present in 95 patients (24.7%), most commonly depression (n = 78, 20.3%), while 289 patients (75.3%) had no psychiatric comorbidity. Patients with psychiatric comorbidity were older and had longer disease duration compared with those without psychiatric comorbidity. In multivariable regression ($F = 12.062$, $p < 0.001$), age ($\beta = 0.140$, $p = 0.026$), disease duration ($\beta = 0.158$, $p = 0.013$), and EDSS ($\beta = 0.209$, $p = 0.001$) were independently associated with psychiatric comorbidity, whereas cognitive test scores were not independent predictors. Over three years, significant time effects were observed for EDSS ($F = 19.410$, $p < 0.001$), BVMT-R ($F = 43.326$, $p < 0.001$), CVLT ($F = 90.005$, $p < 0.001$), and SDMT ($F = 32.432$, $p < 0.001$), but not for T25FW or DDPT. Psychiatric comorbidity was associated with overall worse performance across EDSS, all cognitive measures, and physical performance tests.A significant group-by-time interaction was observed only for SDMT ($F = 7.744$, $p = 0.006$), indicating differential longitudinal change in information processing speed between groups, while no interaction was found for EDSS or physical performance measures.

CONCLUSION Psychiatric comorbidity in MS is associated with older age, longer disease duration, higher disability, and globally worse cognitive and physical performance. However, over a three-year period, its impact on longitudinal decline is limited, with a selective effect observed only for information processing speed (SDMT). These findings suggest that psychiatric comorbidity primarily reflects baseline disease burden rather than driving accelerated motor or cognitive deterioration, with a potential domain-specific effect on processing speed.

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Depression Versus Other Psychiatric Comorbidities in Multiple Sclerosis: Associations with Disability and Disease Progression

Can Caliskan, Tuncay Basaran, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Psychiatric comorbidities are common in people with multiple sclerosis (MS) and are associated with worse clinical outcomes and reduced quality of life. Depression is the most prevalent psychiatric comorbidity, yet few studies have compared its clinical characteristics and impact on disability with those of other psychiatric disorders

OBJECTIVES To compare patients with depression and those with other psychiatric comorbidities regarding disability, relapse burden, disease duration, and disability progression.

METHODS We retrospectively analyzed 422 patients with MS and a documented psychiatric comorbidity. Patients were classified as having depression (n=317) or another psychiatric disorder (n=105). Clinical disability (EDSS), relapse burden, disease duration, and EDSS progression during the year preceding psychiatric comorbidity onset were compared between groups. Age-adjusted repeated-measures models were used to evaluate whether psychiatric comorbidity type was independently associated with disability level or progression.

RESULTS Depression was present in 317 patients (75.1%), while 105 patients (24.9%) had another psychiatric comorbidity. Patients with depression had higher EDSS scores one year before psychiatric comorbidity onset (2.24±1.82 vs 1.83±1.77, p=0.015), experienced more relapses during the preceding year (0.27±0.53 vs 0.13±0.39, p=0.011), had a higher cumulative relapse burden (4.34±3.19 vs 3.10±3.14, p<0.001), longer disease duration (16.74±9.03 vs 13.17±9.06 years, p<0.001), and higher final EDSS scores (2.16±2.31 vs 1.58±2.18, p=0.007). However, after adjustment for age in repeated-measures analyses, psychiatric comorbidity type was not independently associated with either EDSS level or disability progression.

CONCLUSION Patients with depression exhibited greater disability and disease burden than those with other psychiatric comorbidities in unadjusted analyses. However, these differences were largely explained by age, suggesting that depression itself was not an independent predictor of disability progression. These findings emphasize the importance of considering demographic and disease-related factors when evaluating the clinical impact of psychiatric comorbidities in MS.

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Endocrine Comorbidity Is Associated With Higher Disability but Not Adjusted Disease Severity in Multiple Sclerosis

Can Caliskan, Ela Zengin, Güvenç Arslan, Tuncay Basaran, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Endocrine comorbidities are frequent in multiple sclerosis (MS) and may contribute to increased clinical complexity and disability burden. However, their relationship with both raw disability measures and age- or disease duration-adjusted severity indices remains unclear.

OBJECTIVES To evaluate the association between endocrine comorbidity and disability as well as multiple sclerosis severity measures in a large real-world cohort.

METHODS We analyzed 2,687 patients with multiple sclerosis from a real-world dataset. Patients were grouped according to the presence of endocrine comorbidity. Demographic variables, disease characteristics, Expanded Disability Status Scale (EDSS), Age-Related Multiple Sclerosis Severity Score (ARMSSS), and Multiple Sclerosis Severity Score (MSSS) were compared using Mann-Whitney U tests.

RESULTS Endocrine comorbidity was present in 305 patients (11.4%). Patients with endocrine comorbidity were older than those without (median 51 vs 42 years, $p<0.001$). Disease onset age was higher (median 34 vs 28 years, $p<0.001$), and disease duration was longer (median 16 vs 12 years, $p<0.001$). No significant difference was observed in time to secondary progressive MS conversion (median 7 vs 10 years, $p=0.480$). Patients with endocrine comorbidity had higher disability as measured by EDSS (median 1.50 vs 1.00, $p<0.001$). In contrast, age- and disease duration-adjusted severity measures did not differ significantly between groups (ARMSSS median 1.69 vs 1.44, $p=0.500$; MSSS median 2.08 vs 1.38, $p=0.069$).

CONCLUSION In this large real-world multiple sclerosis cohort, endocrine comorbidity was associated with higher EDSS, reflecting greater current disability burden, alongside older age, later disease onset, and longer disease duration. However, the absence of significant differences in ARMSSS and MSSS suggests that endocrine comorbidity is not associated with accelerated multiple sclerosis-specific disease severity. These findings highlight an important dissociation between raw disability measures and adjusted disease severity indices, indicating that the impact of endocrine comorbidity on disability may be driven primarily by age- and duration-related factors rather than disease aggressiveness.

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Is It More Than a Coincidence? Increased Frequency of Familial Mediterranean Fever in Multiple Sclerosis and Its Possible Impact on Disability Progression

Ergi Kaya, Said Alizada, Can Caliskan, Serkan Ozakbas

BACKGROUND Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disease caused by mutations in the MEFV gene, characterised by dysregulation of innate immunity. Emerging evidence suggests that innate immune mechanisms may also contribute to the pathophysiology of multiple sclerosis (MS). However, data regarding the coexistence of FMF and MS and its clinical implications remain limited.

OBJECTIVES To determine the frequency of genetically confirmed FMF in a large MS cohort and to evaluate its potential impact on disease course.

METHODS A total of 3580 patients were screened retrospectively for FMF, and only those with genetically confirmed disease were included in the FMF-MS (F-MS) group. A control group (C-MS) was formed by randomly selecting MS patients without FMF. Data regarding age at MS onset and diagnosis, sex, family history, initial clinical presentation, oligoclonal band status, and IgG index, Expanded Disability Status Scale (EDSS) scores, relapse counts, radiological findings, and No Evidence of Disease Activity-3 (NEDA-3) status. These measures were assessed at baseline, at year 2, and at year 5. Disability progression was defined as a 1-point increase in EDSS for patients with a baseline EDSS below 5.5 and a 0.5-point increase for those with a baseline EDSS of 5.5 or higher.

RESULTS Genetically confirmed FMF was identified in 28 of 3580 pwMS (0.8%), corresponding to approximately 8 per 1000, which appears higher than expected compared to reported general population estimates. For the longitudinal analysis, 20 patients in the F-MS group and 53 randomly selected controls were included. Baseline demographic and clinical characteristics were similar between the two groups ($p>0.05$). At year 5, disability progression, as reflected by EDSS worsening, was observed more frequently in the F-MS group compared to controls (5/15 vs 3/36, $p=0.039$). Relapse rates, radiological activity, EDSS scores, and NEDA-3 at both year 2 and 5 did not differ significantly between the groups ($p>0.05$).

CONCLUSION FMF appears to be more frequent among pwMS in this high-prevalence population. While inflammatory disease activity measures were similar between groups, the increased rate of long-term disability progression in patients with FMF suggests a potential role of innate immune dysregulation in driving non-inflammatory disease worsening. These findings highlight a possible link between autoinflammatory mechanisms and progression in MS.

085

Does Bipolar Disorder Modify Disease Activity in Multiple Sclerosis? A Retrospective Cohort Study

Said Alizada, Ergi Kaya, Yasemin Şimşek, Can Caliskan, Serkan Ozakbas

BACKGROUND Psychiatric comorbidities are common in multiple sclerosis and may affect disease perception, treatment adherence, and clinical outcomes, but the specific impact of bipolar disorder on the MS disease course remains insufficiently defined despite shared neurobiological features such as white matter abnormalities and cortical involvement.

OBJECTIVES To determine the prevalence of bipolar disorder in an MS cohort and to evaluate its association with clinical and radiological outcomes over time.

METHODS This retrospective cohort study identified patients with MS and a documented history of bipolar disorder (B-MS) from a large MS population. A control group of patients with MS without bipolar disorder (C-MS) was randomly selected. Demographic and clinical characteristics were collected. Outcomes included relapse rates, Expanded Disability Status Scale (EDSS) scores, radiological activity, and No Evidence of Disease Activity-3 (NEDA-3) status at two and five years. Disability progression was defined as a 1-point EDSS increase for EDSS <5.5 and a 0.5-point increase for EDSS ≥5.5. Between-group comparisons were performed using appropriate statistical analyses.

RESULTS Among 3580 patients with MS, 52 (1.4%) had a history of bipolar disorder; 39 (75%) were female. For outcome analyses, 29 B-MS patients and 61 C-MS patients were included. Baseline characteristics were comparable between groups, including age at onset, diagnostic age, initial EDSS score, relapse history prior to diagnosis, cerebrospinal fluid findings, and disease-modifying treatment exposure ($p>0.05$ for all). In the first two years, relapse rates were lower in the B-MS group compared to C-MS (median [IQR]: 0 [0] vs 0 [1], $p=0.039$). However, there were no significant differences between groups in EDSS progression, radiological activity, or NEDA-3 status at two years ($p>0.05$). Similarly, at five years, no between-group differences were observed in disability progression, radiological outcomes, or NEDA-3 status ($p>0.05$).

CONCLUSION Bipolar disorder does not appear to significantly affect long-term disability progression, radiological activity, or composite disease control in MS. The lower early relapse rate in patients with bipolar disorder may reflect behavioral, therapeutic, or reporting-related factors rather than a true biological effect, highlighting the need for prospective studies incorporating treatment patterns, mood state, and adherence.

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Differential Associations of the Multiple Sclerosis Severity Score and Age-Related Multiple Sclerosis Severity Score With Cardiovascular Comorbidity in Multiple Sclerosis

Tuncay Basaran, Can Caliskan, Ela Zengin, Yasemin Şimşek Aras, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Cardiovascular comorbidities are associated with increased disability and worse clinical outcomes in multiple sclerosis (MS). The Multiple Sclerosis Severity Score (MSSS) and the Age-Related Multiple Sclerosis Severity Score (ARMSSS) are widely used metrics to quantify disease severity, but they differ in their adjustment for age and disease duration. Whether these measures show differential associations with cardiovascular comorbidity burden remains unclear.

OBJECTIVES To evaluate the association between cardiovascular comorbidity and EDSS, MSSS, and ARMSSS, and to compare the strength of these associations between MSSS and ARMSSS in patients with MS.

METHODS We retrospectively analyzed 2687 patients with MS followed in our clinic after 2022. Demographic and clinical variables included age, age at disease onset, disease duration, Expanded Disability Status Scale (EDSS), MSSS, ARMSSS, MS subtype, and cardiovascular comorbidity status. Multivariable regression analysis was conducted to evaluate the independent associations of age, age at disease onset, MSSS, and ARMSSS with cardiovascular comorbidity.

RESULTS Among 2687 patients, 353 (13.1%) had cardiovascular comorbidity. Disability and disease severity measures were higher in patients with cardiovascular comorbidity. Median EDSS was significantly higher in the comorbidity group (1.50 vs 1.00; $p < 0.001$). ARMSSS showed a small but statistically significant difference between groups (1.52 vs 1.44; $p = 0.019$). MSSS showed a more pronounced difference (2.36 vs 1.38; $p = 0.004$). In multivariable regression analysis, age was significantly associated with cardiovascular comorbidity ($B = 0.010$, $SE = 0.001$, $\beta = 0.368$, $p < 0.001$). Age at disease onset was not significant ($p = 0.119$). ARMSSS was not independently associated with cardiovascular comorbidity ($B = 0.018$, $SE = 0.012$, $\beta = 0.141$, $p = 0.127$). In contrast, MSSS remained significantly associated with cardiovascular comorbidity ($B = -0.028$, $SE = 0.012$, $\beta = -0.220$, $p = 0.020$).

CONCLUSION Cardiovascular comorbidity in multiple sclerosis is associated with older age, later disease onset, longer disease duration, and higher disability. Although both MSSS and ARMSSS were associated with cardiovascular comorbidity in univariate analyses, only MSSS remained independently associated in multivariable models. These findings indicate differential associations of MSSS and ARMSSS with cardiovascular comorbidity burden in multiple sclerosis, without implying causal relationships or superiority of either metric.

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Comorbidity Burden Is Associated With Distinct Clinical Characteristics Among People With Multiple Sclerosis Reaching Moderate to Severe Disability Within Five Years

Yasemin Şimşek Aras, Can Caliskan, Tuncay Basaran, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Comorbidities are increasingly recognized as modifiers of disease course and treatment in multiple sclerosis (MS). However, whether comorbidity burden identifies distinct clinical profiles among people who develop moderate-to-severe disability early in the disease course remains unclear.

OBJECTIVES To determine whether comorbidity burden is associated with distinct clinical characteristics among people with MS who reached an Expanded Disability Status Scale (EDSS) score ≥4.5 within five years.

METHODS This retrospective cohort study included 181 people with MS who had an EDSS score <4.5 at baseline and reached EDSS ≥4.5 after five years of follow-up. Participants were categorized according to physician-documented comorbidity burden as having no comorbidity, one comorbidity, or multiple comorbidities.A multivariable general linear model was used to evaluate whether comorbidity burden was independently associated with five-year EDSS after adjustment for age, sex, disease duration, and treatment category.

RESULTS Among the 181 participants, 75 (41.4%) had no comorbidity, 54 (29.8%) had one comorbidity, and 52 (28.7%) had multiple comorbidities. Patients with multiple comorbidities demonstrated a significantly greater cumulative relapse burden than those without comorbidities (p=0.026) and were more frequently treated with high-efficacy disease-modifying therapies (p=0.016). Brainstem/cerebellar lesion involvement also differed significantly across comorbidity groups (p=0.004). In contrast, age, disease duration, age at disease onset, age at diagnosis, and five-year EDSS were comparable across comorbidity groups (all p>0.05). After adjustment for age, sex, disease duration, and treatment category, comorbidity burden was not independently associated with disability severity at five years (p=0.882). Disease duration remained the only independent predictor of five-year EDSS (p=0.006).

CONCLUSION Among people with MS who reached moderate-to-severe disability within five years, greater comorbidity burden was associated with higher cumulative relapse burden, more frequent use of high-efficacy therapies, and differences in lesion topography. However, comorbidity burden was not independently associated with disability severity within this clinically homogeneous group. These findings suggest that comorbidity burden identifies distinct clinical profiles rather than greater disability severity among people with early moderate- to-severe disability.

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Comorbidity Burden in Multiple Sclerosis: Associations with Clinical Profile, Cumulative Relapse Burden, Treatment Escalation and Disability

Yasemin Şimşek Aras, Tuncay Basaran, Can Caliskan, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Comorbidities may complicate the clinical management of people with multiple sclerosis (MS) and influence disease outcomes. However, whether the number of comorbidities is independently associated with relapse burden, treatment intensity and disability beyond major confounding factors such as age and disease duration remains unclear.

OBJECTIVES To evaluate the association of comorbidity burden with demographic and clinical characteristics, lesion topography, cumulative relapse burden, treatment escalation and disability in people with MS

METHODS We retrospectively analyzed data from 1,944 people with MS followed at a single tertiary MS center. Patients were categorized into three groups according to their medical history: no comorbidity, one comorbidity and multiple comorbidities. Demographic characteristics, lesion topography, age at disease onset, age at diagnosis, disease duration, cumulative relapse number, treatment category, IgG index and last Expanded Disability Status Scale (EDSS) score were compared between groups. Factors associated with last-visit EDSS were evaluated using an adjusted model including age and disease duration as covariates.

RESULTS Among 1,944 patients, 1,365 (70.2%) were women and 579 (29.8%) were men. Overall, 786 (40.4%) had no comorbidity, 564 (29.0%) had one, and 594 (30.6%) had multiple comorbidities. Patients with multiple comorbidities were older and had older age at disease onset and diagnosis (all $p \leq 0.003$). The proportion of women and patients receiving high-efficacy disease-modifying therapies increased with comorbidity burden (both $p<0.001$). Cumulative relapse number was higher in patients with multiple comorbidities than in those without comorbidities (4.41±2.96 vs. 3.91±2.71; $p=0.006$). However, last-visit EDSS did not differ between groups ($p=0.176$). In multivariable analysis, age, disease duration, sex, and treatment category were independently associated with last-visit EDSS, whereas comorbidity burden was not ($p=0.400$).

CONCLUSION Multiple comorbidities define a distinct clinical profile in people with MS, characterized by older age, later disease onset and diagnosis, greater cumulative relapse burden and more frequent use of high-efficacy therapies. However, after adjustment for age and disease duration, comorbidity burden was not independently associated with disability. These findings suggest that comorbidity burden should be regarded primarily as a marker of patient profile and treatment complexity rather than an independent determinant of disability.

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Differential Motor Impairment Patterns Associated With Vascular Comorbidities in Multiple Sclerosis

Güvenç Arslan, Can Caliskan, Yasemin Şimşek Aras, Ela Zengin, Serkan Ozakbas

BACKGROUND Vascular comorbidities may contribute to disability accumulation and physical decline in Multiple Sclerosis (MS). Type 2 diabetes mellitus (DM2), hypertension (HT), and hyperlipidemia (HL) have been associated with worse outcomes through endothelial dysfunction, impaired perfusion, chronic inflammation, and neurovascular injury. DM2 may additionally impair motor performance through peripheral sensory and motor dysfunction. Whether these comorbidities show distinct motor patterns in MS remains unclear.

OBJECTIVES To compare the relative associations of DM2, HT, and HL with ambulatory and upper extremity motor performance in patients with MS

METHODS We retrospectively analyzed 463 patients with MS. Physical performance was assessed using the Timed 25-Foot Walk (T25FW) and dominant-hand dexterity performance testing (DDPT). T25FW and DDPT were entered as within-subject repeated measures in separate GLM analyses for DM2, HT, and HL status

RESULTS In the HT model, 171 patients had HT and 292 did not. HT was associated with worse T25FW (26.04±54.74 vs 9.60±27.14) and DDPT (26.77±21.29 vs 22.44±17.19), with significant overall effect ($F=17.217$, $p<0.001$, partial $\eta2=0.036$). Associations were significant for T25FW ($B=16.446$, $p<0.001$) and DDPT ($B=4.335$, $p=0.017$), with significant test-type interaction ($F=13.853$, $p<0.001$), indicating stronger ambulatory involvement. In the HL model, 113 patients had HL and 350 did not. HL was associated with worse T25FW (24.63±53.88 vs 12.78±34.52) and DDPT (28.90±28.97 vs 22.47±13.91), with significant overall effect ($F=10.410$, $p=0.001$, partial $\eta2=0.022$). Associations were significant for T25FW ($B=11.856$, $p=0.007$) and DDPT ($B=6.431$, $p=0.002$), without test-type interaction ($p=0.144$). In the DM2 model, 210 patients had DM2 and 253 did not. DM2 was associated with worse T25FW (21.60±49.01 vs 10.75±30.69) and DDPT (27.83±26.95 vs 20.90±5.52), with significant overall effect ($F=13.308$, $p<0.001$, partial $\eta2=0.028$). Associations were significant for T25FW ($B=10.857$, $p=0.004$) and DDPT ($B=6.928$, $p<0.001$), without test-type interaction ($p=0.220$).

CONCLUSION DM2, HT, and HL were associated with worse physical performance, affecting ambulation and upper extremity dexterity. HT showed the strongest overall association and preferentially affected ambulation, whereas DM2 and HL showed broader associations across both motor domains. These findings suggest that vascular comorbidities may contribute to distinct motor performance profiles in MS and highlight vascular risk assessment and management.

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Type 2 Diabetes Mellitus Is Linked to a Motor-Predominant Disability Profile in Multiple Sclerosis

Güvenç Arslan, Can Caliskan, Yasemin Şimşek Aras, Ela Zengin, Serkan Ozakbas

BACKGROUND Cognitive and motor dysfunction in multiple sclerosis (MS) are influenced not only by disease-related neurodegeneration but also by vascular comorbidities. Hypertension (HT) and type 2 diabetes mellitus (DM2) have both been associated with adverse neurological outcomes in the general population. However, their relative impact on cognitive versus motor disability in MS remains insufficiently characterized

OBJECTIVES To compare the differential associations of HT and DM2 with cognitive and motor performance in patients with MS

METHODS We retrospectively analyzed patients with MS categorized into three groups: healthy controls, HT-only, and DM2-only. Cognitive performance was assessed using the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test (CVLT), and Brief Visuospatial Memory Test (BVMT). Motor performance was evaluated using the Timed 25-Foot Walk (T25FW) and 9-Hole Peg Test (9HPT). Logistic and multinomial regression analyses were performed using IBM SPSS Statistics version 27.0

RESULTS A total of 336 patients were included in descriptive analyses (54 HT-only, 104 DM2-only, 178 healthy controls). Cognitive scores (SDMT, CVLT, BVMT) were lower in the HT group, while motor performance measures (T25FW and 9HPT) were worse in both HT and DM2 groups. In the multinomial regression model including cognitive variables (n=323), the overall model was not significant ($\chi2$=12.086, df=9, p=0.208), with limited explanatory power (Nagelkerke R2=0.041). In contrast, direct comparison between HT-only and DM2-only groups (n=134) yielded a significant model ($\chi2$=16.360, df=6, p=0.012; Nagelkerke R2=0.156). Compared with HT, DM2 was associated with significantly worse upper extremity motor performance (9HPT; B=0.097, p=0.037, OR=1.102) and modestly higher SDMT scores (B=0.039, p=0.045, OR=1.040). T25FW showed a trend toward impairment in DM2 (p=0.054), whereas EDSS, CVLT, and BVMT were not significantly different between groups

CONCLUSION Although both HT and DM2 are associated with neurological impairment in MS, DM2 appears to be more strongly linked to physical disability, particularly upper extremity motor dysfunction, whereas cognitive effects are less pronounced and inconsistent. These findings suggest that DM2 may exert a more motor-predominant disability profile in MS compared with hypertension

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Upper Extremity Function Is Preferentially Impaired With Increasing Vascular Comorbidity Burden in Multiple Sclerosis

Ela Zengin, Güvenç Arslan, Can Caliskan, Yasemin Şimşek Aras, Serkan Ozakbas

BACKGROUND Motor dysfunction is a major contributor to disability in multiple sclerosis (MS). Beyond MS-related neurodegeneration, vascular comorbidities such as type 2 diabetes mellitus, hypertension, and hyperlipidemia may exacerbate functional impairment through chronic inflammation and microvascular injury. However, whether cumulative vascular comorbidity burden differentially affects upper and lower extremity motor performance remains insufficiently understood

OBJECTIVES To evaluate the association between vascular comorbidity burden and upper and lower extremity motor function in patients with MS.

METHODS We retrospectively analyzed 463 patients with MS categorized into three groups: no comorbidity, one comorbidity, and two or more comorbidities (type 2 diabetes mellitus, hypertension, hyperlipidemia). Motor performance was assessed using the Timed 25-Foot Walk (T25FW) for lower extremity function and the Nine-Hole Peg Test (9HPT/DDPT) for upper extremity function. Multinomial logistic regression was performed with comorbidity burden as the dependent variable and motor performance measures as independent variables. Statistical analyses were conducted using IBM SPSS Statistics version 27.0

RESULTS Among 463 patients, 159 (34.3%) had no comorbidity, 161 (34.8%) had one comorbidity, and 143 (30.9%) had two or more comorbidities. The overall model was significant ($\chi 2$=35.301, df=4, p<0.001), with modest explanatory power (Nagelkerke R2=0.083; McFadden R2=0.035). Likelihood ratio testing demonstrated a significant contribution of 9HPT/DDPT ($\chi 2$=11.938, df=2, p=0.003) and a weaker contribution of T25FW ($\chi 2$=7.311, df=2, p=0.026). Compared with patients without comorbidity, both one and ≥2 comorbidity groups showed significantly worse upper extremity performance. One comorbidity was associated with higher 9HPT/DDPT scores (B=0.066, p=0.007, OR=1.068, 95% CI 1.018-1.121), with a slightly stronger effect in patients with ≥2 comorbidities (B=0.070, p=0.004, OR=1.072, 95% CI 1.022-1.125). In contrast, T25FW was not significant in the one-comorbidity group (p=0.684) and showed borderline association in the ≥2 comorbidity group (p=0.074)

CONCLUSION Increasing vascular comorbidity burden in MS is preferentially associated with impairment in upper extremity motor performance, while associations with gait are weaker and less consistent. Notably, upper extremity dysfunction is evident even in the presence of a single comorbidity, suggesting that fine motor function may represent a more sensitive and early marker of vascular comorbidity-related motor vulnerability in MS

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Vascular Comorbidity Burden Drives Selective Decline in Processing Speed in Multiple Sclerosis

Güvenç Arslan, Can Caliskan, Gözde Deniz Ünal, Ela Zengin, Serkan Ozakbas

BACKGROUND Cognitive impairment in multiple sclerosis (MS) is driven by both neurodegenerative and systemic vascular mechanisms. Type 2 diabetes mellitus, hypertension, and hyperlipidemia are increasingly recognized as modifiers of brain health through endothelial dysfunction, chronic inflammation, and microvascular injury. However, whether cumulative vascular comorbidity exerts domain-specific effects on cognition in MS remains insufficiently defined

OBJECTIVES To determine the impact of vascular comorbidity burden on domain-specific cognitive performance in MS.

METHODS We retrospectively evaluated 458 patients with MS stratified by vascular comorbidity burden: no comorbidity, one comorbidity, and ≥2 comorbidities (type 2 diabetes mellitus, hypertension, hyperlipidemia). Cognitive performance was assessed using the Brief International Cognitive Assessment for MS (BICAMS), including Symbol Digit Modalities Test (SDMT), California Verbal Learning Test (CVLT), and Brief Visuospatial Memory Test (BVMT). Multinomial logistic regression was used to examine associations between comorbidity burden and cognitive performance

RESULTS Among 458 patients, 159 (34.7%) had no comorbidity, 164 (35.8%) had one, and 135 (29.5%) had ≥2 comorbidities. The overall model was significant ($\chi 2$=28.174, df=6, p<0.001), with modest explanatory power (Nagelkerke R2=0.067; McFadden R2=0.028). SDMT emerged as the only cognitive domain significantly associated with vascular comorbidity burden. Likelihood ratio analysis confirmed a robust contribution of SDMT in discriminating comorbidity groups ($\chi 2$=11.393, df=2, p=0.003), whereas CVLT (p=0.240) and BVMT (p=0.202) showed no significant associations. Compared with patients without comorbidity, those with ≥2 vascular comorbidities demonstrated significantly reduced SDMT performance (p=0.001, OR=0.961, 95% CI 0.938-0.984). No significant differences were observed in patients with a single comorbidity

CONCLUSION Vascular comorbidity burden in MS is selectively associated with impaired information processing speed, while memory-related domains remain preserved. These findings support a domain-specific vulnerability of processing speed to cumulative vascular burden, suggesting that systemic vascular pathology may disproportionately affect fronto-subcortical cognitive efficiency in MS.

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Differential Domain-Specific Cognitive Effects of Diabetes, Hyperlipidemia, and Hypertension in Multiple Sclerosis

Güvenç Arslan, Can Caliskan, Yasemin Şimşek Aras, Ela Zengin, Serkan Ozakbas

BACKGROUND Cognitive impairment is a frequent and disabling manifestation of multiple sclerosis (MS). Vascular comorbidities, including type 2 diabetes mellitus (DM2), hyperlipidemia (HL), and hypertension (HT), may contribute to cognitive dysfunction through distinct vascular and metabolic mechanisms. However, their differential associations with specific cognitive domains remain incompletely understood.

OBJECTIVES To investigate domain-specific cognitive associations of DM2, HL, and HT in patients with MS

METHODS We retrospectively analyzed 458 patients with MS. Cognitive performance was assessed using the Brief International Cognitive Assessment for MS (BICAMS), including the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test (CVLT), and Brief Visuospatial Memory Test (BVMT). Separate analyses were performed for DM2, HL, and HT groups using repeated-measures and regression-based models. Statistical analyses were conducted using IBM SPSS Statistics version 27.0.

RESULTS DM2 was present in 208 patients and was associated with a selective reduction in processing speed. Although no overall cognitive interaction was observed ($F=3.371$, $p=0.067$), DM2 was independently associated with lower SDMT scores ($p=0.019$), with no significant effects on CVLT or BVMT. HL ($n=108$) showed a significant overall cognitive effect ($F=11.022$, $p=0.001$) and was associated with reduced SDMT ($p<0.001$) and BVMT ($p<0.001$), while CVLT remained unaffected. HT ($n=163$) demonstrated the strongest and most widespread cognitive impact ($F=21.522$, $p<0.001$), with significant reductions in SDMT ($p<0.001$), BVMT ($p<0.001$), and CVLT ($p=0.016$), indicating broader multi-domain involvement. Across all comorbidities, SDMT consistently showed the most robust association with vascular risk status

CONCLUSION Vascular comorbidities in MS demonstrate distinct domain-specific cognitive signatures: DM2 is primarily associated with processing speed decline, HL with combined processing speed and visuospatial impairment, and HT with broad multi-domain cognitive involvement. Despite these differences, processing speed consistently emerges as the most sensitive cognitive domain across vascular risk factors, supporting SDMT as a potential universal marker of vascular-related cognitive vulnerability in MS

SECTION VIII

Radiologically Isolated Syndrome and First Demyelinating Attack

10 ABSTRACTS

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Does Age at Onset Matter in Radiologically Isolated Syndrome? A Comparative Study of Early Onset and Adult-Onset Cases

Ergi Kaya, Can Caliskan, Alp Sariteke, Yasemin Şimşek Aras, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Radiologically isolated syndrome (RIS) represents a preclinical stage of multiple sclerosis (MS), defined by incidental findings suggestive of demyelination. While early-onset MS demonstrates distinct clinical and radiological behaviour compared to adult-onset disease, whether similar differences exist in RIS remains unknown

OBJECTIVES To compare demographic characteristics, radiological findings, and disease outcomes between early-onset RIS (E-RIS) and adult-onset RIS (A-RIS).

METHODS This retrospective cohort study included patients with RIS classified according to age at radiological onset (<18 years as early-onset, ≥18 years as adult-onset). Demographic data, brain and spinal cord involvement, oligoclonal band status, annualized relapse rates, EDSS scores, and conversion to MS were assessed. Between-group comparisons were performed using appropriate statistical methods.

RESULTS A total of 147 patients with RIS were included, of whom 21 were classified as E-RIS and 126 as A-RIS. Baseline characteristics, including sex distribution, lesion localization, oligoclonal band positivity, and family history, were similar between groups ($p>0.05$ for all). E-RIS patients had lower ages at RIS and MS diagnosis by definition ($p<0.05$), while no significant differences were observed in radiological lesion burden, development of new radiological activity during follow-up, or transition to MS between groups ($p>0.05$). Furthermore, no significant differences were found in EDSS scores at baseline or follow-up, annualized relapse rates, or radiological activity after MS conversion between E RIS and A-RIS groups ($p>0.05$ for all comparisons).

CONCLUSION Early-onset radiologically isolated syndrome demonstrates a clinical and radiological course comparable to adult onset RIS. These findings suggest that age at radiological onset may not significantly influence disease evolution in the preclinical stage of MS. However, further prospective studies are needed to clarify whether earlier detection of demyelination has implications for long-term disease monitoring and intervention strategies

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Radiologically and Clinically Isolated Syndromes Converge Into Similar Clinical and Radiological Trajectories After Conversion to Multiple Sclerosis

Ergi Kaya, Can Caliskan, Said Alizada, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Multiple sclerosis (MS) is often preceded by distinct pre-diagnostic entities, including radiologically isolated syndrome (RIS) and clinically isolated syndrome (CIS). Although these entities differ in clinical presentation at baseline, it remains unclear whether such differences persist after conversion to MS. Understanding this transition may clarify whether pre-diagnostic heterogeneity has long-term prognostic significance.

OBJECTIVES To compare the clinical and radiological prognosis of patients with radiologically isolated syndrome (RIS) and clinically isolated syndrome (CIS) after conversion to multiple sclerosis.

METHODS This retrospective cohort study included 115 patients with multiple sclerosis, consisting of 66 CIS and 49 RIS patients. Multiple Sclerosis/CIS diagnoses were established using the 2017 McDonald criteria. Data collected included sex, age at diagnosis, disease duration, first symptom localisation, oligoclonal band status, baseline MRI lesion localisation, new or enlarging lesion activity within the first two years, treatment type and duration, Expanded Disability Status Scale (EDSS) at baseline and year two, relapse number before and after diagnosis, and NEDA-3 status. Appropriate statistical tests were used for group comparisons.

RESULTS No significant differences were observed between RIS and CIS in terms of sex, family history, age at MS diagnosis, oligoclonal band, or baseline involvement of optic nerve and brainstem (all $p > 0.05$). However, CIS patients more frequently presented with supratentorial and spinal cord involvement compared with RIS patients (supratentorial: 45.5% vs 18.4%, $p = 0.002$; spinal cord: 40.9% vs 8.2%, $p < 0.001$). Baseline EDSS was significantly higher in CIS compared with RIS patients (1.12 ± 1.32 vs 0.42 ± 0.69, $p < 0.001$). Importantly, at two-year follow-up, no significant difference was observed in EDSS between groups ($p > 0.05$). Similarly, no differences were found in relapse number, radiological activity, or NEDA-3 status during the first two years after MS diagnosis (all $p > 0.05$). Treatment type and duration were also comparable between groups ($p > 0.05$).

CONCLUSION Although clinically isolated syndrome is associated with higher disability and different symptom localization at baseline compared with radiologically isolated syndrome, these differences do not persist after conversion to multiple sclerosis. These findings suggest that despite distinct pre-diagnostic phenotypes, RIS and CIS converge into a unified clinical and radiological disease course once multiple sclerosis is established.

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Oligoclonal Band Positivity as a Prognostic Marker in Radiologically Isolated Syndrome and Its Impact After Conversion to Multiple Sclerosis

Ergi Kaya, Can Caliskan, Alp Sariteke, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Radiologically isolated syndrome (RIS) represents a preclinical stage of multiple sclerosis (MS) in which incidental magnetic resonance imaging findings suggest demyelinating disease in the absence of clinical symptoms. A proportion of individuals with RIS convert to clinically definite MS over time. Oligoclonal bands (OCBs) are an established cerebrospinal fluid biomarker in MS, but their prognostic value in RIS and their relationship with disease activity after conversion remain incompletely understood.

OBJECTIVES To evaluate the prognostic significance of OCB positivity in RIS, including its association with conversion to MS and subsequent clinical and radiological disease activity.

METHODS This retrospective cohort study included patients diagnosed with RIS and followed by a single MS specialist. Conversion to MS was determined according to the 2017 McDonald criteria. Demographic, clinical, radiological, and cerebrospinal fluid data were collected. OCB status was classified as positive (type 2 or 3) or negative (type 1 or 4). Groups were compared in terms of time to conversion, radiological activity during RIS, and post-conversion clinical and radiological outcomes using appropriate statistical analyses.

RESULTS A total of 110 patients with RIS (80% female) were included; 74 were OCB-positive, and 36 were OCB-negative. Baseline characteristics, including age at RIS diagnosis, age at MS conversion, follow-up duration, and family history, were comparable between groups ($p>0.05$). The IgG index was significantly higher in the OCB-positive group ($p<0.01$). During the RIS phase, no significant difference in new radiological activity was observed between groups ($p>0.05$). However, conversion to MS was more frequent in OCB-positive than in OCB-negative patients (79.7% vs 52.7%, $p=0.003$). After MS conversion, all observed relapses occurred in the OCB-positive group ($p<0.05$). Additionally, the number of new radiological lesions after MS diagnosis was higher in OCB-positive patients compared with OCB-negative patients ($p=0.024$), while overall radiological activity rates were similar between groups.

CONCLUSION OCB positivity is associated with an increased likelihood of conversion from RIS to MS and may also identify patients with a more active disease course following conversion. These findings support the role of OCBs as a prognostic biomarker not only in the preclinical RIS stage but also in early MS disease characterisation.

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Predicting Conversion from Radiologically Isolated Syndrome to Multiple Sclerosis Using Machine Learning: A Comparative Study of Classification and Regression Models

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BACKGROUND Radiologically Isolated Syndrome (RIS) refers to the incidental detection of demyelinating lesions on brain MRI in the absence of clinical neurological symptoms. Approximately one-third of RIS patients develop clinically definite Multiple Sclerosis (MS) within five years, yet the time course is highly variable.

OBJECTIVES This study aimed to predict both MS development and the time to MS conversion in patients with RIS using machine learning (ML) approaches.

METHODS Retrospective baseline and follow-up demographic, clinical and radiological data from 147 RIS patients were analysed. Two modelling tasks were defined: (1) a binary classification task predicting MS diagnosis (yes/no) using Random Forest (RF), XGBoost, LightGBM, and Support Vector Machine (SVM) combined in a Soft Voting Ensemble; and (2) a regression task predicting time to MS conversion (months) using Ridge, Lasso, ElasticNet, and XGBoost combined in a Voting Ensemble. All models were evaluated with 5-fold cross-validation.

RESULTS In the classification task, RF achieved the highest AUC (0.928 ± 0.041); the Soft Voting Ensemble demonstrated the most balanced performance (AUC=0.918, F1=0.884, Precision=0.902). In the regression task, Lasso yielded near-perfect accuracy (R2=0.999, MAE=0.8 mo), while the Voting Ensemble offered robust generalisation (R2=0.984, MAE=3.5 mo, RMSE=5.8 mo). Spinal cord involvement, positive oligoclonal bands (OCB), and new lesion development were consistently the most important predictors.

CONCLUSION ML models show promise for predicting both MS conversion and its timing in patients with RIS. These findings highlight the clinical potential of ML-based risk stratification tools to support early individualised treatment decisions.

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Clinical, Radiological and Demographic Predictors of Conversion from Radiologically Isolated Syndrome to Multiple Sclerosis

Ergi Kaya, Ulvi Samadzade, Alp Sariteke, Serkan Ozakbas

BACKGROUND Radiologically isolated syndrome (RIS) is an important early stage of central nervous system demyelinating disease. A proportion of these individuals is diagnosed with Multiple Sclerosis (MS) during follow-up. Identifying risk factors for this conversion is crucial to preventing future disabilities, drug side effects and costs. However, knowledge of the factors associated with conversion remains incompletely understood.

OBJECTIVES To determine the contributing factor in RIS to MS conversion in a real-world cohort.

METHODS This retrospective study included 147 patients (114 females) who met the 2023 revised RIS criteria. Baseline and follow-up demographic, clinical and radiological data were collected. MS diagnosis was made by an expert using the 2017 McDonald Diagnostic criteria. Appropriate statistical analyses were performed.

RESULTS During follow-up, 93 (63%) RIS patients were diagnosed with MS. The median follow-up time was 27 months (IQR: 48) across all participants. The median time to conversion to MS was 24 months (IQR: 51) in this group. There was no difference between the MS and RIS groups in terms of gender, RIS follow-up duration, family history, or baseline radiological contrast-enhanced lesion ($p>0.05$). However, baseline radiological T1 hypointense lesions (MS vs RIS: 18/93 vs 2/54) and spinal cord involvement (MS vs RIS: 28/93 vs 5/54) were more frequent in the MS group ($p<0.01$ for both). Furthermore, new radiological lesions during follow-up were detected more frequently in the MS group (MS vs RIS: 28/93 vs 4/54, $p<0.01$). Oligoclonal band positivity was more frequent in the MS group (MS vs RIS: 59/78 vs 15/32, $p<0.01$). However, there was no difference between the MS and RIS groups in IgG index positivity (defined as IgG index >0.7; $p> 0.05$).

CONCLUSION In this cohort of patients with radiologically isolated syndrome, nearly two-thirds converted to multiple sclerosis during follow-up. Baseline T1 hypointense lesions, spinal cord involvement, the MRI activity during follow-up, and oligoclonal band positivity were associated with an increased risk of conversion to MS.

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Headache in Radiologically Isolated Syndrome Is Highly Prevalent but Not a Marker of Disease Activity or Conversion to Multiple Sclerosis

Said Alizada, Can Caliskan, Yasemin Şimşek, Ulvi Samadzade, Serkan Ozakbas

BACKGROUND Headache is a common neurological symptom and a frequent reason for brain MRI, often leading to incidental detection of radiologically isolated syndrome (RIS). However, its clinical relevance in RIS remains uncertain, particularly regarding its relationship with lesion distribution, disease activity, disability, and conversion to multiple sclerosis.

OBJECTIVES To evaluate the frequency and timing of headache in patients with RIS and to investigate its associations with demographic features, MRI lesion distribution, conversion to relapsing-remitting multiple sclerosis (RRMS), disability measures, relapse burden, treatment exposure, and immunological indices.

METHODS A total of 156 RIS patients were retrospectively analyzed for headache status and timing, clinical and MRI-related variables, RRMS conversion, relapse burden, treatment exposure, IgG index, and OCB positivity, with group comparisons and converter subgroup analyses performed using t tests and chi-square tests.

RESULTS Headache was present in 118 of 156 patients (75.6%), while 38 patients (24.4%) had no headache. The cohort was predominantly female (78.2%), and headache was significantly more frequent in women than in men (79.5% vs 61.8%, $p = 0.033$). Headache most commonly preceded RIS diagnosis (55.8%), while smaller proportions occurred at RIS detection (5.8%) or between RIS and RRMS conversion (14.1%). RRMS conversion occurred in 93 patients (59.6%), with similar rates in patients with and without headache (60.2% vs 57.9%, $p = 0.805$). Time to conversion was also comparable between groups (3.48 ± 3.83 vs 3.41 ± 3.46 years, $p = 0.939$). No significant associations were observed between headache status and lesion topography, including spinal cord, infratentorial, supratentorial, or optic pathway involvement (all $p > 0.05$). Similarly, no differences were found in EDSS at RRMS onset or follow-up, relapse burden, annualized relapse rate, treatment exposure, or immunological markers including IgG index and OCB positivity (all $p > 0.05$). Although total relapse count and IgM index showed numerically lower values in the headache group, these differences were not statistically significant.

CONCLUSION Headache is common in RIS, particularly among women, but is not associated with lesion distribution, MS conversion, disability, relapse burden, treatment exposure, or immunological markers, suggesting a frequent non-specific comorbidity partly influenced by MRI referral bias.

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Spinal Cord Lesions in Radiologically Isolated Syndrome: A Strong Predictor of Conversion to Multiple Sclerosis but Not of Disease Course

Ergi Kaya, Can Caliskan, Alp Sariteke, Said Alizada, Yasemin Şimşek, Serkan Ozakbas

BACKGROUND Radiologically isolated syndrome (RIS) is often identified incidentally on brain MRI, and a proportion of patients later develop clinically definite multiple sclerosis (MS). While spinal cord lesions are recognized as a prognostic factor in MS, their role in RIS remains incompletely understood.

OBJECTIVES To evaluate the prognostic significance of spinal cord lesions in patients with RIS, with respect to conversion to MS and subsequent clinical outcomes.

METHODS This retrospective cohort study included patients diagnosed with RIS and followed longitudinally. Patients were categorized according to the presence (S group) or absence (B group) of spinal cord lesions at baseline. Demographic, clinical, and radiological data were collected. Outcomes included conversion to MS, EDSS at diagnosis and last follow-up, annualized relapse rate after MS conversion, and post-conversion radiological activity. Between-group comparisons were performed using appropriate statistical analyses.

RESULTS A total of 147 patients with RIS (77.5% female) were included; 33 had spinal cord lesions (S group) and 114 had no spinal cord involvement (B group). Baseline characteristics, including age at RIS diagnosis, sex distribution, follow-up duration, family history, and radiological activity during RIS phase, were similar between groups ($p>0.05$ for all). Patients in the S group were significantly more likely to convert to MS during follow-up compared with the B group (84.8% vs 57.0%, $p=0.003$). Additionally, spinal cord involvement as the first clinical manifestation was more frequent in the S group (21.2% vs 7.0%, $p=0.043$). However, no significant differences were observed between groups in EDSS at diagnosis or follow-up, annualized relapse rate after MS conversion, or post-conversion radiological activity ($p>0.05$ for all comparisons).

CONCLUSION Spinal cord lesions in radiologically isolated syndrome are strongly associated with an increased risk of conversion to multiple sclerosis and may predict spinal cord involvement at clinical onset. However, they do not appear to influence subsequent disease severity or progression after conversion. These findings suggest that spinal cord involvement in RIS primarily reflects a marker of disease conversion risk rather than long-term disease aggressiveness.

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Radiologically Isolated Syndrome Is Not Radiologically Isolated: Comorbidity Burden and Clinical Heterogeneity

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BACKGROUND Radiologically isolated syndrome (RIS) is traditionally defined as incidental MRI findings suggestive of central nervous system demyelination without clinical symptoms. However, growing evidence suggests RIS may represent a broader clinical continuum influenced by systemic factors. Comorbidities, particularly neurological and psychiatric disorders, may affect clinical trajectories and disease evolution in RIS.

OBJECTIVES To evaluate comorbidity burden in RIS and investigate its association with clinical characteristics, headache prevalence, and disease evolution, including time to conversion to multiple sclerosis.

METHODS This retrospective cohort study included 156 RIS patients. Demographic features, comorbidity burden, headache presence, lesion characteristics, IgG and IgM indices, EDSS scores, relapse-related variables, disease duration, and conversion outcomes were analyzed. Patients were stratified according to comorbidity status.

RESULTS A total of 156 RIS patients were included (mean age 37.42 ± 10.90 years; 78.2% female). Comorbidities were highly prevalent, with 90.4% of patients having at least one comorbid condition. Neurological comorbidities were most frequent (85.3%), followed by psychiatric (10.9%) and cardiometabolic disorders (8.3%). Headache was more frequent in patients with comorbidity (79.4% vs 40.0%). Patients with comorbidity showed significantly longer RIS disease duration (8.50 ± 5.13 vs 4.53 ± 4.16 years, $p = 0.004$) and longer time to MS conversion (3.65 ± 3.81 vs 1.14 ± 0.90 years, $p < 0.001$). No significant differences were observed in EDSS scores, IgG/IgM indices, relapse-related variables, or conversion to RRMS.

CONCLUSION Comorbidity burden is highly prevalent in RIS and is associated with longer disease duration and delayed conversion to multiple sclerosis. Although disability and immunological markers did not differ between groups, comorbidity status appears to influence disease evolution dynamics. These findings support the concept that RIS should not be regarded solely as a radiological entity, but rather as a clinically heterogeneous condition influenced by systemic factors along the preclinical spectrum of multiple sclerosis.

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Subclinical Disease Activity Despite Sustained Minimal Disability After a Single Demyelinating Attack

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BACKGROUND A single demyelinating attack with sustained minimal disability suggests a favorable course, but radiological progression and CSF inflammatory activity may persist despite excellent clinical outcomes.

OBJECTIVES To characterize radiological and CSF inflammatory activity in patients with a single clinical attack and sustained minimal disability at 5 years.

METHODS We retrospectively analyzed patients with a single documented clinical attack and EDSS 0-1.5 at year 5, evaluating demographic and disease-related characteristics, EDSS course, initial attack localization, post-attack MRI activity, OCB pattern, and IgG index; exploratory subgroup analyses were performed according to the presence of new MRI lesions after the initial attack.

RESULTS A total of 230 patients were included, of whom 72% were female. Mean age was 42 years, and mean age at disease onset was 31 years. Diagnostic delay was minimal, with a median interval of 0 years from symptom onset to diagnosis. Median follow-up duration was 7 years. Clinical outcomes were overall favorable, with sustained minimal disability across the cohort and a median EDSS score of 0 at year 5. Despite this favorable clinical phenotype, subclinical disease activity remained common. Post-attack MRI activity was observed in 52% of patients, indicating ongoing radiological activity despite preserved low disability. CSF inflammatory findings were also frequent: type 2 OCB positivity was present in 58% of patients with available OCB data, while elevated IgG index was observed in 53% of patients with available IgG index data. Initial attack localization was heterogeneous, with brainstem-cerebellar involvement representing the most common presentation, followed by supratentorial, spinal cord, and optic pathway involvement. Patients with post-attack MRI activity demonstrated a more inflammatory paraclinical profile. Type 2 OCB positivity was more frequent among patients with MRI activity, whereas type 1 OCB pattern was more common in patients without new MRI lesions. Brainstem-cerebellar onset was also more frequent among patients with post-attack MRI activity. Nevertheless, disability remained minimal across both groups throughout follow-up.

CONCLUSION Patients with a single demyelinating attack and sustained minimal disability showed a favorable long-term clinical course, but the persistence of radiological activity and CSF inflammatory markers despite low EDSS suggests that clinical stability may coexist with ongoing subclinical disease activity, underscoring the complementary value of MRI and CSF assessment.

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Earlier or Overdiagnosis? Impact of the 2024 McDonald Criteria in Radiologically Isolated Syndrome

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BACKGROUND The 2024 McDonald Criteria aim to facilitate an earlier diagnosis of multiple sclerosis (MS) by incorporating updated radiological and biological markers. This shift may be particularly relevant for individuals with radiologically isolated syndrome (RIS), who are at risk of developing MS. However, whether earlier diagnosis reflects clinically meaningful disease activity or primarily represents a lowering of diagnostic thresholds remains uncertain.

OBJECTIVES To compare the diagnostic yield and time to diagnosis between the 2017 and 2024 McDonald criteria in a cohort of patients with RIS, and to explore the relationship between earlier diagnosis and subsequent radiological activity.

METHODS This retrospective study included 108 patients fulfilling the 2023 criteria. Demographic and radiological follow-up data were collected. The 2017 and 2024 McDonald criteria were applied to all participants based on available data. Variables were analysed using appropriate statistical methods.

RESULTS The cohort consisted of 108 RIS (79.6% female), with a mean age of 36.91±11.26 years. According to the 2017 criteria, 61 patients were diagnosed with MS, whereas 91/ 108 patients fulfilled the 2024 criteria. All patients diagnosed under the 2017 criteria also met the 2024 criteria, while 44 of the remaining 61 patients (72.1%) were newly classified as MS under the 2024 criteria ($p<0.001$). The mean time from RIS identification to MS diagnosis was reduced from 48.8±47.6 months (2017 criteria) to 36.8±42.2 months (2024 criteria), corresponding to an earlier diagnosis of approximately 12 months. Notably, none of the patients who did not meet the 2024 criteria developed new radiological lesions during follow-up. Among those classified as MS by the 2024 criteria, 19 patients subsequently demonstrated radiological activity during their RIS follow-up period as defined by the 2017 framework.

CONCLUSION The 2024 McDonald criteria substantially increase the diagnostic yield of MS in individuals with RIS and enable an earlier diagnosis. While this shift may allow earlier identification, it may also reflect a lowering of diagnostic thresholds rather than the detection of clinically meaningful disease in all cases. The absence of radiological activity in patients not meeting the 2024 criteria supports their potential negative predictive value. However, the clinical implications of earlier diagnosis, including the risk of overdiagnosis and its impact on long-term outcomes, require confirmation in prospective studies.

SECTION IX

Treatment and Real-World Evidence

8 ABSTRACTS

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Repeated Treatment Discontinuation Is Associated With Higher Relapse Activity in Multiple Sclerosis

Ergi Kaya, Orkhan Mammadov, Can Caliskan, Yasemin Şimşek Aras, Ela Zengin, Serkan Ozakbas

BACKGROUND Long-term adherence to disease-modifying treatment (DMT) is a key component of multiple sclerosis (MS) management. Treatment discontinuation may result in renewed inflammatory disease activity. Understanding the clinical impact of recurrent non-adherence may help identify patients at higher risk of disease reactivation.

OBJECTIVES To evaluate the clinical consequences of repeated DMT discontinuation due to non-adherence or personal choice in patients with MS.

METHODS This retrospective study included patients with MS who discontinued DMT because of non-adherence or personal preference. Patients who discontinued treatment only once were classified as single-discontinuation (O-D), whereas those with more than one discontinuation episode were classified as repeated-discontinuation (R-D). Demographic and clinical variables, Expanded Disability Status Scale (EDSS) scores, annualized relapse rates (ARR), and treatment characteristics were collected. EDSS worsening was defined as a 1.5-point increase for baseline EDSS 0, a 1-point increase for EDSS 1-5, and a 0.5-point increase for EDSS ≥5.5. Clinical outcomes after treatment discontinuation were compared between groups.

RESULTS A total of 311 patients with MS were included. Among them, 64 patients experienced repeated DMT discontinuation (R-D), while 247 discontinued treatment only once (O-D). Age at diagnosis, follow-up duration after discontinuation, DMT category, and EDSS score at discontinuation were comparable between groups (all $p > 0.05$). Repeated discontinuation was more frequent among female patients and among those with relapsing-remitting MS (68% vs 53.1%, $p = 0.026$; and 13.7% vs 3%, $p = 0.018$, respectively). Patients in the R-D group also had a higher number of relapses before diagnosis (median [IQR]: 2 [1.75] vs 1 [1], $p = 0.004$). During follow-up, no significant differences were observed between groups regarding final EDSS scores or EDSS worsening after treatment discontinuation. However, inflammatory disease activity was higher among O-D. The ARR after DMT discontinuation was significantly higher in the R-D group (median [IQR]: 0.16 [0.33] vs 0 [0.23], $p = 0.020$).

CONCLUSION Repeated discontinuation of DMT due to non-adherence or personal choice was associated with increased relapse activity in patients with MS. These findings highlight the clinical importance of sustained treatment adherence. Early patient education and continuous communication regarding treatment-related concerns may help reduce recurrent discontinuation behavior.

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Impact of Ocrelizumab Dose Delay on Relapse Activity and Disability Outcomes in Multiple Sclerosis: A Three-Year Real-World Study

Ergi Kaya, Güvenç Arslan, Yasemin Şimşek Aras, Can Caliskan, Serkan Ozakbas

BACKGROUND Ocrelizumab (OCR) is an effective treatment administered every six months for people with multiple sclerosis (MS). In routine clinical practice, treatment delays may occur because of infection concerns, healthcare access, or other logistical factors. Although several real-world studies have examined delayed OCR dosing, evidence regarding its long-term clinical consequences remains limited.

OBJECTIVES To evaluate the impact of ocrelizumab dose delay on relapse activity and disability outcomes in people with MS.

METHODS This retrospective real-world study included 184 people with MS (65% female) treated with ocrelizumab. Dose delay was defined as at least one OCR infusion administered more than three months after the scheduled treatment date. Patients were classified into a regular ocrelizumab (RO) group and a delayed ocrelizumab (DO) group. Demographic and clinical characteristics, including Expanded Disability Status Scale (EDSS) scores at baseline and three years, relapse activity, and disability progression, were evaluated. Confirmed disability worsening was defined as an EDSS increase of ≥1.5 points for baseline EDSS 0, ≥1.0 point for baseline EDSS 1.0- 5.0, and ≥0.5 point for baseline EDSS ≥5.5. Continuous and categorical variables were compared using appropriate statistical tests.

RESULTS Among 184 participants, 141 received regular OCR dosing and 43 experienced at least one delayed infusion. The groups were comparable regarding sex, age at OCR initiation, baseline relapse history, and baseline EDSS score (all $p>0.05$). Patients in the RO group were more likely to have progressive MS, whereas those in the DO group were older at disease onset (median age at diagnosis: 37 vs 32 years; both $p<0.05$). After three years, EDSS scores and rates of disability progression were similar between the RO and DO groups (both $p>0.05$). However, patients in the DO group experienced significantly higher relapse frequency during follow-up than those receiving regular dosing ($p=0.046$). The proportion of patients with disability worsening did not differ significantly between groups.

CONCLUSION Ocrelizumab dose delay of more than three months was associated with increased relapse activity but not with greater disability progression over three years. These findings suggest that prolonged treatment delays may compromise inflammatory disease control despite similar short-term disability outcomes. Prospective studies with larger cohorts are warranted to determine the long-term clinical consequences of delayed ocrelizumab dosing.

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Maintained Disease Control After Switching to Extended Interval Dosing of Natalizumab in Relapsing-Remitting Multiple Sclerosis: Within-Patient Real-World Evidence

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BACKGROUND Extended interval dosing (EID) of natalizumab is increasingly adopted to optimize long-term safety, yet concerns remain regarding potential loss of disease control after switching.

OBJECTIVES To determine whether switching from standard interval dosing (SID) to EID is associated with loss of clinical or radiological disease control in a real-world RRMS cohort.

METHODS In this retrospective, single-center study, adult RRMS patients treated with natalizumab were evaluated. Patients who switched from SID (every 4 weeks) to EID (every 6 weeks) underwent within-patient comparison of disease activity before and after switching. A parallel SID cohort was analyzed as a reference group. Outcomes included annualized relapse rate (ARR), Expanded Disability Status Scale (EDSS), and no evidence of disease activity (NEDA-3), defined as absence of relapses, confirmed disability progression, and MRI activity (new/enlarging T2 or gadolinium-enhancing lesions on annual scans).

RESULTS Ninety-four patients were included (87.2% female; mean age 36.5 ± 7.6 years), of whom 17 (18.1%) switched to EID after prolonged disease stability. Patients in the EID group had longer natalizumab exposure prior to switching, consistent with a clinically stable, treatment-responsive subgroup. Across the cohort, natalizumab treatment was associated with sustained suppression of inflammatory disease activity. In the EID group, no increase in ARR was observed following the switch, with no relapses recorded during a mean follow-up of 21.0 ± 6.3 months. Disability remained stable, with no significant change in EDSS after switching (p=0.201). Importantly, all patients maintained NEDA-3 status during the EID period, indicating preserved composite disease control. Findings were consistent with persistently low disease activity observed in the SID reference group. No cases of progressive multifocal leukoencephalopathy occurred.

CONCLUSION In this real-world cohort, switching from SID to EID of natalizumab did not compromise disease control, with complete preservation of clinical and radiological stability over follow-up. These within-patient findings support EID as an effective risk-mitigation strategy in carefully selected, stable

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Consistent Multidomain Stability Across Clinical Subgroups with Ocrelizumab in Long-Standing Relapsing-Remitting Multiple Sclerosis

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BACKGROUND Ocrelizumab is a high-efficacy anti-CD20 therapy with a well-established effect on inflammatory disease activity in relapsing-remitting multiple sclerosis (RRMS). However, real-world data integrating disability, cognitive, and physical outcomes - particularly in patients with long-standing disease - remain limited.

OBJECTIVES To comprehensively evaluate the multidomain effectiveness of ocrelizumab and to determine the consistency of treatment response across key clinical subgroups in a large real-world RRMS cohort.

METHODS This retrospective, single-center study included 396 RRMS patients treated with ocrelizumab. Outcomes assessed at baseline and last follow-up included annualized relapse rate (ARR), Expanded Disability Status Scale (EDSS), cognitive performance (CVLT, SDMT, BVMT-R), and physical performance (T25FW, 9-HPT).

RESULTS The cohort was 69.2% female, with a mean age of 43.5 ± 12.0 years and a mean disease duration of 15.1 ± 8.1 years at treatment initiation. The mean time from disease onset to treatment was 11.7 ± 7.7 years, and mean follow-up was 3.35 ± 2.17 years. Ocrelizumab demonstrated a pronounced and consistent therapeutic effect across all evaluated domains. ARR decreased dramatically from 0.49 ± 0.40 to 0.02 ± 0.13 ($p < 0.001$), reflecting near-complete suppression of inflammatory disease activity. Disability remained stable over follow-up (EDSS 2.05 ± 1.57 vs 2.09 ± 1.66, $p = 0.183$), indicating effective prevention of clinical worsening at the group level. Cognitive and physical functions were preserved throughout follow-up. A small but statistically significant change was observed in CVLT scores ($p = 0.009$), while SDMT, BVMT-R, T25FW, and 9-HPT showed no significant change, supporting an overall pattern of functional stability. Importantly, treatment effects were highly consistent across all subgroups, with no meaningful differences according to disease duration, baseline disability, or prior treatment exposure. Although supratentorial involvement was associated with higher baseline ARR ($p = 0.026$), it did not impact treatment response.

CONCLUSION In this large real-world RRMS cohort with long disease duration, ocrelizumab showed high and consistent effectiveness, characterized by near-complete suppression of inflammatory activity and sustained stabilization of disability, cognitive, and physical function over more than three years of follow-up. These findings indicate that ocrelizumab delivers robust and durable disease control across multiple clinical domains, even in patients treated later in the disease course.

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Distinct Clinical Profiles of Secondary and Primary Progressive Multiple Sclerosis Under Ocrelizumab: A Real-World Cohort Study

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BACKGROUND Progressive multiple sclerosis (MS) comprises clinically heterogeneous phenotypes with differing inflammatory activity, disability trajectories, and anatomical involvement. Although ocrelizumab is widely used in both secondary progressive MS (SPMS) and primary progressive MS (PPMS), comparative real-world data between these phenotypes remain limited.

OBJECTIVES To compare demographic, clinical, and disease characteristics between patients with SPMS and PPMS receiving ocrelizumab in a real-world cohort.

METHODS This retrospective observational study included 428 patients with progressive MS treated with ocrelizumab. Demographic and clinical variables including age, age at onset, disease duration, relapse activity, Expanded Disability Status Scale (EDSS), and radiological involvement were extracted from medical records. Continuous variables were compared using the Mann-Whitney U test and categorical variables using chi-square analysis. Statistical significance was defined as $p<0.05$.

RESULTS Among 428 patients, 66.6% had SPMS and 33.4% had PPMS. Age was comparable between groups ($p=0.699$). Compared with PPMS, SPMS patients had significantly longer disease duration and initiated ocrelizumab later in the disease course (both $p<0.001$). PPMS patients demonstrated significantly older age at disease onset ($p<0.001$). Pre-treatment relapse activity was significantly higher in SPMS ($p<0.001$), whereas relapse frequency decreased following ocrelizumab treatment in both groups ($p=0.032$). Spinal cord involvement was significantly more common in PPMS patients ($p<0.001$). Baseline and follow-up EDSS scores were significantly higher in SPMS patients ($p=0.025$ and $p<0.001$, respectively), consistent with their longer cumulative disease duration.

CONCLUSION SPMS and PPMS exhibit distinct clinical phenotypes despite shared classification as progressive MS. SPMS was associated with greater inflammatory burden and higher disability accumulation, whereas PPMS demonstrated later disease onset and more prominent spinal cord involvement. These findings underscore the biological and clinical heterogeneity of progressive MS and support phenotype-specific approaches to monitoring and treatment strategies.

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Motor-Cognitive Dissociation in Progressive Multiple Sclerosis Under Ocrelizumab: A Real-World Phenotype Comparison of Secondary and Primary Disease

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BACKGROUND Progressive multiple sclerosis (MS) leads to accumulating disability affecting both motor and cognitive domains. Although ocrelizumab is widely used in both secondary progressive MS (SPMS) and primary progressive MS (PPMS), real-world data comparing functional outcomes across these phenotypes remain limited.

OBJECTIVES To compare physical and cognitive performance between SPMS and PPMS patients treated with ocrelizumab in a real-world cohort, and to explore phenotype-specific functional patterns under treatment.

METHODS This retrospective observational study included 428 patients with progressive MS treated with ocrelizumab. Physical performance was assessed using the Timed 25-Foot Walk (T25FW) and 9-Hole Peg Test (9-HPT). Cognitive function was evaluated using the Symbol Digit Modalities Test (SDMT), Brief Visuospatial Memory Test (BVMT), and California Verbal Learning Test (CVLT). Baseline and follow-up data were compared between groups using the Mann-Whitney U test, with statistical significance set at $p<0.05$.

RESULTS Among 428 patients, 66.6% had SPMS and 33.4% had PPMS. While age was comparable between groups, SPMS patients had longer disease duration and initiated ocrelizumab later in the disease course (both $p<0.001$). PPMS patients showed significantly older age at disease onset ($p<0.001$). Physical performance differed mainly in ambulatory function. T25FW was significantly worse in PPMS at both baseline and follow-up (both $p<0.001$), indicating more pronounced walking impairment. This finding was consistent with a higher frequency of spinal cord involvement at disease onset in PPMS ($p<0.001$). In contrast, upper extremity function (9-HPT) did not differ between groups ($p>0.05$). Cognitive performance was largely comparable. SDMT and CVLT scores showed no significant differences at baseline or follow-up ($p>0.05$). BVMT was lower in PPMS at baseline ($p=0.024$), but this difference was not sustained at follow-up ($p=0.978$), suggesting limited and non-persistent group variation in visuospatial memory.

CONCLUSION SPMS and PPMS demonstrate distinct functional profiles under ocrelizumab treatment, with PPMS characterized by greater ambulatory impairment and more frequent spinal cord involvement, while cognitive performance remains broadly similar between phenotypes. These findings suggest that physical disability in progressive MS is phenotype-dependent and likely driven by differential anatomical burden, whereas cognitive involvement appears more uniformly distributed across progressive subtypes.

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Disease Burden and Fatigue Characteristics According to Baseline Treatment Step in Multiple Sclerosis

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BACKGROUND In multiple sclerosis (MS), treatment step is generally determined by clinical phenotype, disease activity, and disability level. Therefore, it should be interpreted as a marker of underlying disease burden rather than a causal determinant of fatigue or disability outcomes.

OBJECTIVES To compare demographic characteristics, disability status, fatigue profiles, physical activity, sleepiness, and disease phenotype according to baseline treatment step in patients with MS.

METHODS Patients with MS and available baseline treatment step data were classified into first-, second-, and third-step treatment groups. Continuous variables were expressed as mean ± standard deviation and compared using one-way analysis of variance. Categorical variables were analyzed using Pearson chi-square test. Tukey and Bonferroni post hoc analyses were applied where appropriate. Statistical analyses were performed using IBM SPSS Statistics Version 27.0, with $p < 0.05$ considered statistically significant.

RESULTS A total of 212 patients were included: 103 (48.6%) in the first-step group, 51 (24.1%) in the second-step group, and 58 (27.4%) in the third-step group. Age, disease duration, and baseline EDSS increased progressively across treatment steps. Mean age was 35.51 ± 11.48 years in the first-step group, 38.63 ± 10.37 in the second-step group, and 46.11 ± 11.81 in the third-step group. Disease duration was 6.55 ± 12.65, 9.58 ± 5.89, and 16.88 ± 8.36 years, respectively. Baseline EDSS scores were 1.42 ± 1.35, 3.07 ± 2.14, and 5.26 ± 1.80, respectively. Total fatigue impact score ($F = 7.522$, $p = 0.001$), physical fatigue ($F = 12.910$, $p < 0.001$), and psychosocial fatigue ($F = 10.419$, $p < 0.001$) differed significantly between groups at baseline, while cognitive fatigue, physical activity (Godin score), and sleepiness (Epworth scale) did not. At two-year follow-up, EDSS ($F = 51.581$, $p < 0.001$), total fatigue impact score ($F = 12.968$, $p < 0.001$), and physical fatigue ($F = 23.797$, $p < 0.001$) remained significantly different across treatment steps. Baseline treatment step was also significantly associated with both two-year treatment step and MS phenotype (both $p < 0.001$).

CONCLUSION Higher baseline treatment step was associated with older age, longer disease duration, higher disability, and greater fatigue burden, particularly in the physical domain. These findings suggest that treatment step primarily reflects underlying disease severity and clinical phenotype rather than exerting an independent effect on fatigue or disability outcomes.

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Impact of Disease-Modifying Therapy Change on Pain Severity in Multiple Sclerosis

Ergi Kaya, Can Caliskan, Güvenç Arslan, Serkan Ozakbas

BACKGROUND People with multiple sclerosis (pwMS) frequently experience a wide range of pain syndromes, many of which can be severe. The pathophysiology of pain in MS is multifactorial and involves inflammatory mechanisms. Disease-modifying therapies (DMT) reduce inflammatory disease activity and may consequently alleviate MS-related pain. However, evidence regarding their effect on pain remains scarce.

OBJECTIVES To investigate whether switching from low- to high-efficacy DMTs influences pain severity in pwMS

METHODS This retrospective study included 227 (68.3% female) individuals with multiple sclerosis who had PainDETECT scores available at baseline and at the one-year follow-up. Disease-modifying therapies were classified as either low- or high-efficacy. Participants were categorised into three groups: those who remained on low efficacy treatment, those who switched to high efficacy treatment, and those who remained on high efficacy treatment. Demographic and clinical variables were recorded. Group comparisons were performed using Mann-Whitney U, Kruskal-Wallis and chi-square. Additionally, changes in PainDETECT scores were evaluated using a repeated measures general linear model. Statistical significance was set at $p<0.05$.

RESULTS The mean age of the participants was 40.43±10.85, and the mean EDSS was 2.94±2.36. At baseline, 178 participants received low-efficacy DMT and 49 received high-efficacy DMT. During follow-up, 144 patients escalated from low- to high-efficacy therapies, 34 participants continued on low-efficacy therapies, and 49 participants continued on high-efficacy therapies. Mean PainDETECT scores were 5.08±6.49 at baseline and 5.06±6.54 after one year. No significant differences were observed in PainDETECT scores between the low-efficacy and high-efficacy groups, either at baseline or after one year (all $p > 0.05$). Likewise, participants who escalated to high-efficacy therapy did not differ from those who remained at the same treatment-efficacy level ($p>0.05$).

CONCLUSION Treatment escalation from low- to high-efficacy DMTs was not associated with lower pain severity than remaining at the same treatment-efficacy level. However, studies with longer follow-up and large populations are needed.

SECTION X

Imaging, Optical Coherence Tomography and the Visual System

8 ABSTRACTS

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Association of BrainAgeR-Derived Brain Age with Clinical Disease Burden, Brain Volumes, and Retinal Neuroaxonal Measures

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BACKGROUND Machine learning-based brain age estimates have emerged as potential imaging biomarkers of biological brain aging and neurodegeneration in multiple sclerosis. However, the relationships between brain age, clinical disability, brain atrophy, and retinal neuroaxonal loss remain incompletely understood.

OBJECTIVES To investigate the associations between BrainAgeR-derived brain age and clinical disease burden, brain volumes, physical and cognitive performance, and retinal neuroaxonal measures in individuals with relapsing-remitting multiple sclerosis (RRMS).

METHODS This cross-sectional study included 25 individuals with RRMS. Brain age was estimated using BrainAgeR. Brain tissue volumes were quantified using Quantib and FreeSurfer, and retinal layer thicknesses were measured by optical coherence tomography. Clinical variables included age, disease duration, Expanded Disability Status Scale (EDSS) score, total relapse count, and annualized relapse rate. Physical and cognitive performance measures were analyzed in the subset of participants with available data. Associations were evaluated using Pearson or Spearman correlation analyses, as appropriate.

RESULTS This cross-sectional study included 25 individuals with RRMS. Brain age was estimated using BrainAgeR. Brain tissue volumes were quantified using Quantib and FreeSurfer, and retinal layer thicknesses were measured by optical coherence tomography. Clinical variables included age, disease duration, Expanded Disability Status Scale (EDSS) score, total relapse count, and annualized relapse rate. Physical and cognitive performance measures were analyzed in the subset of participants with available data. Associations were evaluated using Pearson or Spearman correlation analyses, as appropriate.

CONCLUSION BrainAgeR-derived brain age was associated with greater clinical disease burden and retinal neuroaxonal thinning, but not with brain volumes or physical and cognitive performance in this cohort. These findings suggest that BrainAgeR-derived brain age may serve as a complementary imaging biomarker reflecting clinical disability and retinal neuroaxonal damage in RRMS.

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Associations of White Matter Lesion Volume with Clinical, Brain Volumetric, and Retinal Neuroaxonal Measures in Relapsing-Remitting Multiple Sclerosis

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BACKGROUND White matter lesion burden is a hallmark of inflammatory disease activity in multiple sclerosis (MS). However, its relationships with clinical disability, cognitive performance, brain atrophy, and retinal neuroaxonal degeneration remain incompletely understood. Clarifying these associations may improve understanding of the pathological relevance of lesion burden.

OBJECTIVES To investigate the associations of automatically quantified white matter lesion volume with clinical disease burden, cognitive and physical performance, brain volumetric measures, and retinal neuroaxonal thicknesses in individuals with relapsing-remitting MS.

METHODS This cross-sectional study included 25 individuals with relapsing-remitting MS. White matter lesion count and volume were automatically quantified using Quantib. Brain volumetric measures were obtained using Quantib and FreeSurfer, while retinal layer thicknesses were measured using optical coherence tomography. Clinical assessments included disease duration, Expanded Disability Status Scale (EDSS), relapse burden, cognitive performance (SDMT, CVLT-II, and BVMT-R), and physical performance (T25FW and 9HPT). Associations were evaluated using Spearman correlation analysis.

RESULTS Greater white matter lesion volume was associated with longer disease duration (ρ=0.452, p=0.023) and lower macular retinal nerve fibre layer (mRNFL) thickness (ρ=−0.479, p=0.038). No statistically significant associations were observed between lesion volume and EDSS, relapse burden, cognitive performance, physical performance, total brain volume, or cortical thickness.

CONCLUSION In this cohort, greater white matter lesion volume was associated with longer disease duration and retinal neuroaxonal thinning but not with other clinical or brain volumetric measures. These findings suggest that conventional lesion burden alone may not fully capture the multidimensional pathological changes in MS. However, given the limited sample size, these results should be interpreted cautiously and require confirmation in larger, adequately powered studies.

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Association of Mean Cortical Thickness with Cognitive Performance, Brain Volumes, and Clinical Measures in Relapsing Multiple Sclerosis

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BACKGROUND Cortical thinning is an important imaging marker of neurodegeneration in multiple sclerosis. However, its associations with cognitive performance, physical function, brain tissue volumes, and retinal neuroaxonal measures remain incompletely understood in relapsing-remitting multiple sclerosis (RRMS).

OBJECTIVES To investigate the associations between mean cortical thickness and cognitive performance, physical function, clinical disease burden, brain tissue volumes, and retinal neuroaxonal measures in individuals with RRMS

METHODS This cross-sectional study included 25 individuals with RRMS. Mean cortical thickness was calculated using FreeSurfer. Brain tissue volumes and white matter hyperintensity volume were quantified using automated MRI analysis. Cognitive performance data were available for 19 participants and physical performance data for 20 participants. Cognitive and physical performance were assessed using standardized tests, and retinal neuroaxonal measures were obtained using optical coherence tomography. Associations were evaluated using Pearson or Spearman correlation analyses, as appropriate.

RESULTS Mean cortical thickness was 2.459 ± 0.101 mm. Greater cortical thickness was associated with better Symbol Digit Modalities Test (SDMT) performance ($\rho = 0.464$; $p = 0.045$; $n = 19$) and greater gray matter volume ($\rho = 0.512$; $p = 0.009$). Increasing age was associated with lower cortical thickness ($\rho = -0.443$; $p = 0.027$). No significant associations were observed between cortical thickness and other cognitive tests, physical performance measures, clinical disease burden, retinal neuroaxonal measures, or white matter hyperintensity volume. Mean cortical thickness did not differ significantly between participants receiving low efficacy and high-efficacy disease-modifying therapies ($p = 0.559$)

CONCLUSION Greater mean cortical thickness was associated with better information processing speed and greater gray matter volume in individuals with RRMS. No significant associations were observed with other cognitive domains, physical performance, clinical disease burden, or retinal neuroaxonal measures. These findings support the potential role of cortical thickness as a complementary imaging marker of neurodegeneration in RRMS, although confirmation in larger longitudinal studies is warranted

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Retinal Structural Measurements Are Associated with Two-Year Upper Extremity Motor Decline but Not Walking Performance in Multiple Sclerosis

Güvenç Arslan, Can Caliskan, Ela Zengin, Serkan Ozakbas

BACKGROUND Retinal layer thinning measured by optical coherence tomography (OCT) is an established marker of neuroaxonal damage in multiple sclerosis (MS). Although retinal structural measurements have been associated with physical disability, their relationship with longitudinal changes in specific domains of physical performance remains unclear.

OBJECTIVES To determine whether retinal structural measurements are associated with two-year changes in walking and upper extremity motor performance in people with MS.

METHODS This retrospective longitudinal study included 102 people with MS. Physical performance was assessed approximately two years apart using the Timed 25-Foot Walk (T25FW) and the Nine-Hole Peg Test (9HPT). Change scores were calculated as follow-up minus baseline values. OCT measurements included macular ganglion cell layer (GCL), ganglion cell-inner plexiform layer (GCIPL), macular retinal nerve fiber layer (mRNFL), and global and sectoral peripapillary retinal nerve fiber layer (pRNFL) thicknesses. Associations between retinal measurements and physical performance changes were examined using Spearman rank correlation analyses.

RESULTS Mean two-year changes were 0.00±1.40 seconds for T25FW (n=78) and 1.70±14.05 seconds for 9HPT (n=81). Changes in walking performance (ΔT25FW) were not associated with any macular or peripapillary retinal layer measurement. In contrast, greater worsening in upper extremity motor performance (Δ9HPT) was associated with lower GCL (ρ=−0.349, p=0.003), GCIPL (ρ=−0.314, p=0.007), and mRNFL thicknesses (ρ=−0.313, p=0.007). Greater worsening in 9HPT performance was also associated with lower global pRNFL (ρ=−0.244, p=0.039), superior pRNFL (ρ=−0.248, p=0.036), and temporal pRNFL thicknesses (ρ=−0.242, p=0.040), whereas no significant associations were observed with mean optic disc, inferior, or nasal pRNFL measurements. Worsening in 9HPT performance was associated with older age (ρ=0.282, p=0.011) but not with disease duration.

CONCLUSION Retinal structural measurements were selectively associated with longitudinal worsening of upper extremity motor performance but not walking performance. Macular retinal layers, particularly GCL and GCIPL, showed the strongest associations, suggesting that retinal neuroaxonal integrity may be more closely linked to fine motor decline than to gait deterioration in MS. Larger prospective studies incorporating serial OCT measurements are warranted to validate these findings.

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Optic System Involvement as a Marker of Cognitive-Motor Decline in Multiple Sclerosis

Gözde Deniz Ünal, İrem Kara, Ela Zengin, Tuncay Basaran, Ebru Isgandarli, Serkan Ozakbas

BACKGROUND Optic pathway involvement is frequent in multiple sclerosis (MS) and traditionally considered a visual deficit. However, visual integrity may also affect cognition, postural control, and dual-task performance. Whether baseline optic involvement identifies patients at risk of cognitive-motor decline and fall risk remains unclear.

OBJECTIVES To determine whether baseline optic system involvement is associated with longitudinal cognitive decline, dual-task performance, and fall risk in MS.

METHODS This longitudinal registry-based study included individuals with MS with available baseline EDSS visual functional system scores. Participants were classified as optic-involved (visual FS > 0) or non-involved (visual FS = 0). Baseline SDMT, CVLT-II, BVMT, and clinical measures were compared. Follow-up was the nearest visit to 5 years (range 4-6 years). Dual-task cost was derived from standard and cognitive Timed Up and Go performance. Longitudinal SDMT slope was calculated using within-subject linear trend estimation. Fall risk was defined as ABC score < 67. Group comparisons used non-parametric tests. Regression models adjusted for age, disease duration, baseline EDSS, and baseline cognitive scores assessed outcomes.

RESULTS A total of 2,186 individuals with MS were included; 192 (8.8%) had baseline optic system involvement. Baseline EDSS was higher in the optic-involved group (median 1.5 vs 1.0, $p < 0.001$), while age and disease duration were similar. At baseline, CVLT-II was lower in the optic-involved group ($p = 0.048$), SDMT showed borderline reduction ($p = 0.052$), and BVMT was comparable. At follow-up, SDMT remained significantly lower in the optic-involved group ($p = 0.042$). Although unadjusted SDMT change was not significantly different, optic involvement independently predicted worse SDMT slope ($\beta = -0.55$, $p = 0.046$) and greater worsening in dual-task cost ($\beta = 21.44$, $p = 0.029$). Fall risk was higher in the optic-involved group (40.0% vs 23.8%), with increased odds in adjusted logistic regression (OR = 4.01, $p = 0.049$).

CONCLUSION Baseline optic system involvement in MS is associated with a broader cognitive-motor vulnerability profile beyond visual dysfunction. Affected individuals show worse verbal learning at baseline, reduced SDMT performance over time, a steeper decline in processing speed, increased dual-task cost, and higher fall risk. These findings suggest that optic pathway involvement may serve as a clinically meaningful marker of global cognitive-motor decline in MS

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Clinical Burden and Cognitive Performance According to Visual Functional System Involvement in Multiple Sclerosis

Ela Zengin, Can Caliskan, Gözde Deniz Ünal, Serkan Ozakbas

BACKGROUND The Expanded Disability Status Scale Visual Functional System Score (Visual FSS) quantifies visual pathway impairment in multiple sclerosis (MS). However, its relationship with cognitive performance remains uncertain.

OBJECTIVES To compare the clinical and cognitive characteristics of people with MS according to Visual FSS (0-1 vs ≥2) and to identify factors independently associated with Visual FSS ≥2.

METHODS This retrospective cohort study included 1,218 people with MS classified according to their most recent Visual FSS. Cognitive performance was assessed using the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test (CVLT), and Brief Visuospatial Memory Test-Revised (BVMT-R). Binary logistic regression was performed to identify factors independently associated with Visual FSS ≥2.

RESULTS Visual FSS ≥2 was present in 227 participants (18.6%). Compared with participants with Visual FSS 0-1, those with Visual FSS ≥2 had higher EDSS scores (1.31±1.76 vs 0.93±1.61; p=0.002), longer disease duration (12.92±8.57 vs 11.27±8.03 years; p=0.006), more relapses (3.68±2.95 vs 2.74±2.25; p<0.001), younger age at disease onset (27.05±8.46 vs 28.53±9.19 years; p=0.027), and more frequent optic pathway onset (53.3% vs 15.3%; p<0.001). SDMT, CVLT, and BVMT-R scores did not differ significantly in univariable analyses. In the multivariable model (n=1,105), longer disease duration was independently associated with higher odds of Visual FSS ≥2 (OR 1.043, 95% CI 1.018-1.069; p=0.001), whereas higher BVMT-R scores were associated with lower odds (OR 0.966, 95% CI 0.941-0.993; p=0.013). The overall explanatory value of the model was modest (Nagelkerke R^2=0.028).

CONCLUSION Visual FSS ≥2 was associated with greater cumulative clinical disease burden but showed no evidence of consistent cognitive impairment across domains. The isolated association with BVMT-R should be interpreted cautiously, as this visually mediated test depends on intact visual perception and visuospatial encoding; lower scores may therefore reflect visual dysfunction itself rather than a specific impairment of visuospatial memory. The modest explanatory value of the multivariable model further supports that Visual FSS has only a limited independent association with cognitive performance.

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Associations Between Retinal Layer Thickness and Cognitive Performance in Multiple Sclerosis

Ela Zengin, Can Caliskan, Güvenç Arslan, Serkan Ozakbas

BACKGROUND Optical coherence tomography (OCT) provides non-invasive measures of retinal neuroaxonal integrity and has emerged as a potential biomarker of neurodegeneration in multiple sclerosis (MS). Although peripapillary retinal nerve fibre layer (pRNFL) thinning has been linked to cognitive impairment, less is known about the relationships of individual macular retinal layers - including the ganglion cell layer (GCL), ganglion cell-inner plexiform layer (GCIPL), and macular retinal nerve fibre layer (mRNFL) - with specific cognitive domains.

OBJECTIVES To investigate the associations between retinal layer thicknesses and information processing speed, verbal learning, and visuospatial memory in people with MS.

METHODS This cross-sectional study included 92 people with MS who underwent OCT and cognitive assessment. Cognitive performance was evaluated using the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test (CVLT), and Brief Visuospatial Memory Test-Revised (BVMT-R). OCT measurements included GCL, GCIPL, mRNFL, global pRNFL, and sectoral pRNFL thicknesses. Associations between retinal measurements and cognitive performance were examined using Spearman correlation analysis.

RESULTS Greater global pRNFL thickness was associated with better performance on the SDMT (ρ=0.385, p<0.001), CVLT (ρ=0.242, p=0.024), and BVMT-R (ρ=0.365, p=0.001). Higher GCL thickness was associated with better SDMT (ρ=0.233, p=0.032) and BVMT-R performance (ρ=0.409, p<0.001), while higher GCIPL thickness correlated with SDMT (ρ=0.240, p=0.027), CVLT (ρ=0.216, p=0.044), and BVMT-R scores (ρ=0.396, p<0.001). Greater mRNFL thickness was similarly associated with better SDMT (ρ=0.247, p=0.022), CVLT (ρ=0.249, p=0.020), and BVMT-R performance (ρ=0.295, p=0.006). Temporal pRNFL thickness showed a weaker association with SDMT performance (ρ=0.224, p=0.040). Among the retinal measurements, GCL and GCIPL demonstrated the strongest associations with visuospatial memory.

CONCLUSION Retinal neuroaxonal integrity, reflected by both macular and peripapillary retinal layer thicknesses, was associated with cognitive performance in MS. While pRNFL showed expected associations with cognition, GCL, GCIPL, and mRNFL provided additional complementary information, with the strongest relationships observed between macular retinal layers and visuospatial memory. These findings support the potential value of detailed retinal layer analysis as an accessible biomarker of cognitive involvement in MS.

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Macular Ganglion Cell Thickness Is Selectively Associated with Two-Year Visuospatial Memory Change in Multiple Sclerosis

Ela Zengin, Can Caliskan, Güvenç Arslan, Serkan Ozakbas

BACKGROUND Optical coherence tomography (OCT)-derived retinal layer measurements are established markers of neuroaxonal damage in multiple sclerosis (MS). Although retinal thinning has been associated with cognitive impairment, its relationship with longitudinal changes across specific cognitive domains remains incompletely understood.

OBJECTIVES To determine whether retinal structural measurements are associated with two-year changes in information processing speed, verbal learning, and visuospatial memory in people with MS.

METHODS This retrospective longitudinal study included 102 people with multiple sclerosis. Cognitive performance was assessed at two evaluations approximately two years apart using the SDMT, CVLT II, and BVMT R. Cognitive change scores were calculated by subtracting baseline scores from follow up scores. OCT measurements included GCL, GCIPL, mRNFL, and pRNFL thicknesses. Associations between retinal measurements and cognitive change scores were examined using Spearman correlation analyses.

RESULTS The mean two year changes were 0.53 ± 11.26 points for ΔSDMT (n = 80), 1.90 ± 12.49 points for ΔCVLT (n = 81), and 0.57 ± 6.31 points for ΔBVMT R (n = 79). ΔSDMT was not significantly associated with GCL (ρ = 0.036; p = 0.765; n = 71), GCIPL (ρ = 0.074; p = 0.542; n = 71), mRNFL (ρ = 0.098; p = 0.415; n = 71), or pRNFL thickness (ρ = 0.043; p = 0.724; n = 71). Similarly, ΔCVLT was not associated with GCL (ρ = 0.124; p = 0.298; n = 72), GCIPL (ρ = 0.163; p = 0.171; n = 72), mRNFL (ρ = 0.176; p = 0.139; n = 72), or pRNFL thickness (ρ = 0.126; p = 0.293; n = 72). In contrast, ΔBVMT R was positively associated with GCL (ρ = 0.252; p = 0.035; n = 70) and GCIPL thickness (ρ = 0.347; p = 0.003; n = 70). No significant associations were found between ΔBVMT R and mRNFL (ρ = 0.125; p = 0.304; n = 70) or pRNFL thickness.

CONCLUSION Macular ganglion cell measurements, particularly GCIPL thickness, were selectively associated with two year changes in visuospatial memory but not with changes in information processing speed or verbal learning. These findings suggest that macular retinal integrity may serve as a structural marker of longitudinal visuospatial cognitive change in multiple sclerosis. Larger prospective studies incorporating serial OCT measurements are needed to confirm these observations

SECTION XI

Neuromyelitis Optica Spectrum Disorder

2 ABSTRACTS

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Phenotypic Heterogeneity With Convergent Outcomes in Aquaporin-4 Positive and Double-Negative Neuromyelitis Optica Spectrum Disorder

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BACKGROUND Neuromyelitis optica spectrum disorder (NMOSD) encompasses clinically and biologically heterogeneous disease entities. Aquaporin-4 antibody-positive (AQP4+) and double-negative (DN) NMOSD are recognized subgroups with distinct immunological characteristics. However, whether these biological and clinical differences translate into divergent long-term outcomes remains unclear.

OBJECTIVES To compare demographic and clinical characteristics of AQP4+ and double-negative NMOSD and to evaluate whether baseline phenotypic differences are associated with differences in relapse activity and disability progression.

METHODS This retrospective cohort study included 61 patients fulfilling the 2015 international NMOSD diagnostic criteria. Of these, 40 were AQP4+ and 21 were double-negative. Demographic data, comorbidities, Expanded Disability Status Scale (EDSS), annualized relapse rate (ARR), number of relapses before and after diagnosis, follow-up duration, and initial symptom localization were analyzed. Appropriate statistical tests were applied for group comparisons.

RESULTS Baseline EDSS was significantly higher in the AQP4+ group compared with the DN group (median 3.0 vs 2.0, $p = 0.002$). Female predominance was observed in the AQP4+ group, although this did not reach statistical significance (90% vs 71%, $p > 0.05$). Comorbidity profiles were similar between groups ($p > 0.05$). Cerebellar involvement at disease onset was observed exclusively in the DN group (0/40 vs 3/21, $p = 0.037$). Follow-up duration was longer in AQP4+ patients (median 73.5 vs 31 months, $p = 0.001$). Despite differences in baseline severity, annualized relapse rates and EDSS worsening rates did not differ significantly between AQP4+ and DN groups ($p > 0.05$). Within the AQP4+ subgroup, younger age at onset and diagnosis, longer follow-up duration, and higher annualized relapse rate were associated with EDSS worsening ($p < 0.05$).

CONCLUSION AQP4-positive NMOSD is associated with higher baseline disability, while cerebellar onset appears more characteristic of double-negative disease. However, relapse activity and long-term disability progression are comparable between groups. These findings suggest that although NMOSD subtypes exhibit distinct baseline phenotypic features, their long-term clinical trajectories converge, indicating a dissociation between early biological heterogeneity and disease prognosis.

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Hormonal State at Disease Onset Shapes a Gradient of Disease Severity in Neuromyelitis Optica Spectrum Disorder

Yasemin Şimşek Aras, Said Alizada, Can Caliskan, Serkan Ozakbas

BACKGROUND Hormonal milieu is increasingly recognized as a modifier of immune-mediated neurological diseases. In neuromyelitis optica spectrum disorder (NMOSD), both sex and hormonal transitions may influence disease expression; however, the effect of hormonal status at disease onset on clinical phenotype, disability, and relapse activity remains unclear. Male patients may provide a relatively stable non-cycling hormonal reference group, enabling comparisons across distinct hormonal states.

OBJECTIVES To evaluate the impact of hormonal status at disease onset on clinical phenotype, comorbidity burden, disability outcomes, and relapse activity in NMOSD by comparing premenopausal-onset women, postmenopausal-onset women, and men.

METHODS We retrospectively analyzed 109 NMOSD patients: 43 premenopausal-onset women (39.4%), 35 postmenopausal-onset women (32.1%), and 31 men (28.4%). Groups were compared regarding onset phenotype, comorbidity burden, Expanded Disability Status Scale (EDSS) measures, and annualized relapse rate (ARR).

RESULTS Initial clinical phenotype distribution was similar across groups ($p = 0.901$). Optic neuritis was the most frequent onset manifestation in premenopausal-onset women and men, whereas myelitis predominated in postmenopausal-onset women. Comorbidity burden differed significantly ($p = 0.024$), showing a gradient across hormonal states: highest in postmenopausal-onset women (82.9%), intermediate in men (64.5%), and lowest in premenopausal-onset women (53.5%). Cardiovascular and metabolic comorbidities were enriched in postmenopausal-onset women, whereas psychiatric comorbidities were relatively more frequent in premenopausal-onset women. Disability outcomes demonstrated a similar gradient. Postmenopausal-onset women had significantly higher first, last, and maximum EDSS scores compared with both men and premenopausal-onset women (all $p < 0.001$). Men showed intermediate disability levels between the two female groups. Despite these differences, ARR did not differ significantly among groups ($p = 0.340$).

CONCLUSION Hormonal status at NMOSD onset was not associated with differences in onset phenotype or inflammatory relapse activity. However, a clear gradient in comorbidity burden and disability accumulation was observed across hormonal states, with the greatest burden in postmenopausal-onset women and intermediate values in men. These findings support the concept that NMOSD severity may be modulated along a hormonal continuum rather than determined solely by biological sex.

SECTION XII

Telemedicine and Digital Health

2 ABSTRACTS

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Digital Behavioral Signatures of Multiple Sclerosis Identified Through Telenursing-Based Telemedicine

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BACKGROUND Telemedicine systems may serve not only as communication platforms but also as remote indicators of disease activity, disability burden, and clinical phenotype in multiple sclerosis (MS).

OBJECTIVES To investigate whether telemedicine encounter patterns are associated with distinct MS phenotypes in a real-world telenursing cohort.

METHODS A total of 3145 telemedicine encounters were retrospectively analyzed. Demographic and clinical variables including age, age at onset, disease duration, EDSS, relapse count, annualized relapse rate (ARR), and treatment duration were compared according to encounter reason.

RESULTS Patients contacting the system for suspected relapse demonstrated an inflammatory phenotype characterized by lower age at onset (27.9 vs 29.1 years, $p=0.002$), lower disability (EDSS 1.24 vs 1.58, $p<0.001$), higher relapse burden (2.54 vs 2.14, $p<0.001$), and higher ARR (0.29 vs 0.26, $p=0.010$). In contrast, worsening-related encounters reflected a progressive disability phenotype, with older age (54.9 vs 39.2 years, $p<0.001$), substantially longer disease duration (21.0 vs 11.1 years, $p<0.001$), markedly higher disability levels (EDSS 5.72 vs 1.03, $p<0.001$), and lower inflammatory activity (ARR 0.10 vs 0.29, $p<0.001$). Information-seeking encounters were associated with younger age, shorter disease duration, and lower disability burden.

CONCLUSION Telemedicine encounter behavior may reflect biologically and clinically distinct MS phenotypes. Telenursing-based systems capture remote signatures of inflammatory activity and progressive disability, supporting their potential role as digital disease-monitoring and clinical prioritization tools in MS care.

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Most Suspected Relapses Are Not True Relapses: Real-World Impact of a Telenursing-Based Teletriage System in Multiple Sclerosis

Yasemin Şimşek Aras, Can Caliskan, Tuncay Basaran, Güvenç Arslan, Ela Zengin, Serkan Ozakbas

BACKGROUND The role of telemedicine-based relapse triage systems in distinguishing true relapses from pseudo-relapses and non-urgent neurological complaints in multiple sclerosis (MS) remains insufficiently characterized.

OBJECTIVES To evaluate the effectiveness of a telenursing-based teletriage system in identifying true relapses and reducing unnecessary acute evaluations in MS.

METHODS We retrospectively analyzed 3145 telemedicine encounters from an MS telenursing system. Reasons for contact, demographic and clinical characteristics, and encounter outcomes were assessed. Encounters triggered by suspected relapse were classified as confirmed relapse, pseudo-relapse, or non-urgent complaints managed without acute intervention.

RESULTS Among 1092 encounters for suspected relapse, only 276 (25.3%) resulted in confirmed relapse, whereas 204 (18.7%) were classified as pseudo-relapse and 612 (56.0%) were managed conservatively with routine follow-up recommendations. Patients with confirmed relapses had higher EDSS scores (2.01 vs 1.41, $p<0.001$), higher relapse counts (2.74 vs 2.23, $p=0.001$), higher annualized relapse rates (0.37 vs 0.27, $p<0.001$), and shorter treatment duration (1.62 vs 3.15 years, $p<0.001$) compared with non-relapse encounters. Pseudo-relapse encounters were associated with younger age, shorter disease duration, and lower disability levels.

CONCLUSION Most patient-reported suspected relapses were not confirmed as true relapses, highlighting the potential of telenursing-based teletriage to substantially reduce unnecessary acute visits, imaging, and corticosteroid exposure. At the same time, the system successfully prioritized patients with higher inflammatory disease activity who required urgent neurological evaluation.