Neuroendocrinology Letters Volume 45 No. 7-8 2024
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

ORIGINAL PAPER

Disease characteristics and cognitive impairment in multiple sclerosis: A short-term observation is not enough

Bianka Suchá[1], Pavel Šiarnik[1], Stela Biathová[1], Stanislava Klobucká[2,3], Žofia Rádiková[4,5], Katarína Klobučníková[1], Peter Turčáni[1], Branislav Kollár[1]

1 1st Department of Neurology, Faculty of Medicine, Comenius University, Bratislava, Slovakia
2 Rehabilitation Centre Harmony, Bratislava, Slovakia
3 Department of Physical and Rehabilitation Medicine, Faculty of Medicine, Slovak Medical University, Bratislava, Slovakia
4 Institute of Clinical and Translational Research, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovakia
5 Faculty of Health Sciences, University of Ss. Cyril and Methodius, Trnava, Slovakia

Correspondence to: Assoc. prof. Pavel Šiarnik, MD, PhD, MPH
1st Department of Neurology, Faculty of Medicine, Comenius University,
Mickiewiczova 13, 813 69, Bratislava, Slovakia
TEL: +421903116499, E-MAIL: palo.siarnik@gmail.com

Submitted: 2024-09-28 Accepted: 2024-11-02 Published online: 2024-12-22

Key words: **Multiple sclerosis; Cognition; Depression; Disease-modifying therapy; Neurofilament light chain; Disability**

Neuroendocrinol Lett 2024; **45**(7-8):419–426 **PMID:** 39737492 45072401 • **www.nel.edu**

Abstract

BACKGROUND: Multiple sclerosis (MS) is a disease that affects the central nervous system. One of its manifestations is cognitive impairment (CI), which can negatively affect the quality of life in people with MS (pwMS). This study aimed to investigate the nature of CI in MS and its associations with various disease characteristics.

METHODS: Symbol Digit Modalities Test and cognitive tests adapted for the Slovak population as part of the NEUROPSY battery were used. For the assessment of depression, the Patient Health Questionnaire-9 was used. To assess the degree of functional disability, the Expanded Disability Status Scale, Timed 25-Foot Walk, and 9-Hole Peg Test were used. Plasma neurofilament light chain level (pNfL, a promising marker of neurodegeneration) was assessed. Variables in the CI vs. non-CI group were compared.

RESULTS: In cognition, we observed statistically significant differences between the CI and the non-CI group in multiple measures. In the degree of functional disability, we found statistically significant differences between the groups in all measures. However, we found no statistically significant differences in depression, pNfL, type of disease-modifying therapy, or education. The Digit Span Forward (longest line) (OR: 0.375, 95%CI: 0.156-0.901, $p = 0.028$) and Trail Making Test-B (OR: 0.066, 95%CI: 0.013-0.339, $p = 0.001$) were the only independent variables in a model that predicted CI in binary logistic regression analysis.

CONCLUSION: Our cross-sectional study design failed to reveal the association of CI with various disease characteristics, or markers of neurodegeneration. For this purpose, longitudinal observation of pwMS, and future prospective studies are highly warranted.

Abbreviations:

9-HPT	- 9-Hole Peg Test
CVF	- Category Verbal Fluency
CI	- Cognitive Impairment
CNS	- Central Nervous System
CR	- Cognitive Reserve
CSF	- Cerebrospinal Fluid
DMT	- Disease-Modifying Therapy
DSB	- Digit Span Backward
DSF	- Digit Span Forward
EDSS	- Expanded Disability Status Scale
EF	- Executive Functions
IPS	- Information Processing Speed
LVF	- Letter Verbal Fluency
MS	- Multiple Sclerosis
pNfL	- Plasma Neurofilament Light chain
pwMS	- People with Multiple Sclerosis
RAVLT	- Rey Auditory Verbal Learning Test
ROCFT	- Rey-Osterrieth Complex Figure Test
RRMS	- Relapse-Remitting Multiple Sclerosis
SDMT	- Symbol Digit Modalities Test
SIMOA®	- Single-Molecule Array
T25FW	- Timed 25-Foot Walk
TMT	- Trail Making Test

INTRODUCTION

Multiple sclerosis (MS) is a chronic, progressive, immune-mediated, neurodegenerative disorder of the central nervous system (CNS); its pathogenesis includes inflammation, axonal loss, and demyelination (Merritt, 2010). MS causes brain atrophy and widespread lesions in the CNS (Kutzelnigg *et al.* 2005). This process may result in disability in various areas, including motor, sensory, visual, balance-coordination, and cognitive impairment (CI) (Chiaravalloti & DeLuca, 2008).

Various studies have reported that the prevalence of CI in people with MS (pwMS) is 32,5–73% (Wallin *et al.* 2006; Wu *et al.* 2024). CI can be related to MS subtype, disease duration, and cognitive reserve (CR) (Buchanan *et al.* 2010). PwMS with higher CR are less likely to develop CI (Benedict *et al.* 2009; Elshebawy *et al.* 2021). The development of CI in MS mirrors the high interindividual variability that also characterizes the presence of physical disability and is a result of neurodegeneration (Geurts *et al.* 2012), disconnection of various regions (Dineen *et al.* 2009) and functional reorganization (Schoonheim *et al.* 2015). Attention, information processing speed (IPS), learning and memory, and executive functions (EF) appear to be the most affected cognitive domains (Grzegorski & Losy, 2017; Chiaravalloti & DeLuca, 2008).

Depression is common in pwMS and can affect many aspects of cognition in MS, including working memory, IPS, learning and memory, abstract reasoning, and EF (Altieri *et al.* 2024). Successful treatment of depression could also lead to improvement in cognition in pwMS (Demaree *et al.* 2003).

One of the most studied biomarkers reflecting the entity of subcortical axonal damage in various neurological diseases, including MS, is the plasma level of the neurofilament light chain (pNfL) in peripheral blood (Gaetani *et al.* 2019). The great applicability of pNfL in MS is based on the fact that its concentration in cerebrospinal fluid (CSF) and plasma increases proportionally to the damage to the CNS (Yuan, Nixon, 2021). A link between pNfL levels and cognition in pwMS has been reported, with higher pNfL levels associated with more severe CI (Jakimovski *et al.* 2020; Mattioli *et al.* 2020).

Several studies examined the effect of MS disease-modifying therapies (DMTs) on neuropsychological tests (Mattioli *et al.* 2011; Patti *et al.* 2010; Weinstock-Guttman *et al.* 2012). DMTs have the potential to positively influence cognition in pwMS. In particular, all approved DMTs reduce the accumulation of irreversible CNS damage, as shown by the positive effects on the lesion load of T2 and T1, and some of them potentially slow the progression of brain atrophy (Gold *et al.* 2010). DMTs might mitigate CI in pwMS (Gudesblatt *et al.* 2018). In some studies, CI has not been observed in pwMS on DMT, even with longer disease duration (Harel *et al.* 2019). However, the number of studies specifically addressing this effect remains insufficient (Chen *et al.* 2020), likely because DMTs primarily target other MS symptoms, such as functional disability.

This study aims to investigate the relationships between CI and various disease characteristics, including disease duration, degree of functional disability, and DMT. Additionally, our objective is to explore affected cognitive domains and the most sensitive diagnostic tests assessing cognition. As for pNfL and depression, we plan to explore the association with cognition.

METHODS

Research design and participants

The research sample consisted of 55 pwMS, who met inclusion and exclusion criteria. These pwMS are managed and treated at the 1st Department of Neurology, Faculty of Medicine, Comenius University, University Hospital, Bratislava, Slovakia.

This research is a part of the longitudinal examination of pwMS, which ran from January 2022 to August 2024 and was composed into 3 rounds of examinations – first in 2022, second in 2023, and third in 2024. The inclusion criteria for pwMS were as follows: 1) pwMS with confirmed clinically definitive relapse-remitting MS (RRMS) according to the revised McDonald's criteria (Thompson *et al.* 2018) aged ≥ 18 years, 2) pwMS treated with DMT, such as: glatiramer acetate, interferon beta-1a, teriflunomide, dimethyl fumarate, cladribine, fingolimod, natalizumab, ofatumumab (2 pwMS started DMT treatment later in the research – since they completed all other clinical examinations, for example, cognitive assessment, they were included in this study). Exclusion criteria were: 1) presence of relapse 12 weeks or less prior to enrollment in the study; usage of corticosteroids 4 weeks or less prior to enrollment in the study; 2) presence of

neurodegenerative diseases other than RRMS, developmental disorder (e.g. ADHD), severe depression symptomatology (identified during cognitive assessment); 3) patient underwent a complex psychological examination of cognition 6 months or less prior to the enrollment to the study; 4) presence of severe motor and sensory disability, which could potentially complicate the application of the examination methods used; 5) patient does not actively use the Slovak language.

For the purposes of this study, the data were selected from the first round of examinations, which ran from January 2022 to August 2022 and included an initial anamnestic interview; Timed 25-Foot Walk (T25FW), and 9-Hole Peg Test (9-HPT); Rey auditory verbal learning test (RAVLT), Rey-Osterrieth Complex Figure Test (ROCFT), Symbol Digit Modalities test (SDMT), Digit span: forward (DSF) and backward (DSB), Verbal fluencies: letter (LVF) and category (CVF), Trail Making Test (TMT); and Patient Health Questionnaire-9 (PHQ-9). Neurological examination (with Expanded Disability Status Scale [EDSS] score assessment) and the collection of peripheral blood for the pNfL analysis were performed on different day, but no more than 12 weeks apart from cognitive assessment.

Clinical assessment

To assess cognition, we used the following:

1. **SDMT** (Smith, 1982), assesses information processing speed (Van Schependom *et al.* 2014), but some sources (Leavitt, 2021) state that in MS it is rather a general cognitive screener. In our study, we used an oral version of SDMT. A total test score is the sum of all correct answers given during 90 seconds.

We used standardized cognitive tests adapted for the Slovak population that are involved in the NEUROPSY battery (Hajdúk *et al.* 2021). Namely:

2. **RAVLT**, assesses verbal learning and memory. The total score consists of the sum of correctly reproduced words in: the first list of words (A) – first 5 learning trials, reproduction after interference list, reproduction after 30 minutes; second list of words (interference list, follows after 5 learning trials of list A).
3. **ROCFT**, assesses visuospatial skills, non-verbal learning, and memory. The total score consists of: a copy of the figure; reproduction after 3 minutes; reproduction after 30 minutes.
4. **DSF and DSB**, assess immediate memory, attention (DSF) and cognitive flexibility, working memory (DSB). The total score (in both parts) consists of the sum of correctly reproduced sequences and the length of the last reproduced sequence (in numbers).
5. **LVF and CVF**, assess word retrieval from memory, either starting on a specific letter or belonging to a specific category. For the LVF, the letter K was used. For the CVF, the category Animals was used. The total score consists of the number of correct words said within 60 seconds.
6. **TMT**, assessing information processing speed, attention (TMT-A), and cognitive flexibility (TMT-B). The total score consists of the time needed to complete the task (TMT-A and TMT-B), but a person can be stopped after 300 seconds. Also, the difference between TMT-A and TMT-B time is considered as an index of EF (Lezak, 2012).

To assess the degree of functional disability, we used the following:

1. **EDSS**, a method of rating overall neurological impairment in pwMS (Kurtzke, 1983).
2. **9-HPT**, assesses the upper limb function (Feys *et al.* 2017), consisting of 2 trials with the dominant hand and 2 with the non-dominant hand.
3. **T25FW**, assesses walking ability by tracking the walking speed (Kalinowski *et al.* 2021). The task is to walk a 25-foot-long distance (approximately 8 meters; 2 trials must be completed).

To assess depression, the PHQ-9 was given to pwMS. This was part of the cognitive assessment.

To assess pNfL level, 3ml of peripheral blood was collected into an EDTA tube in the Centre of demyelinating diseases, then centrifuged for 10 minutes at the speed of 4000 rpm and stored at –70°C until analyzed.

Data analysis

The raw scores of the cognitive tests were converted into z-scores. Population-based norms were used for the SDMT (Strober *et al.* 2020) and for RAVLT, ROCFT, Digit span, Verbal fluencies, and TMT (Hajdúk *et al.* 2021). CI in specific cognitive domains was confirmed when one of these criteria was met:

1. Two or more tests assessing one cognitive domain (e.g. EF) had a score of 1.5 standard deviation (SD) or more below the population mean.
2. The difference between two or more tests assessing one cognitive domain and two or more tests assessing different cognitive domain was at least 1.5 SD (e.g. if in one pwMS, two tests assessing verbal memory have scores of 2.0 SD, two tests assessing EF have scores 0.5 SD, then this pwMS had CI in EF).

When assessing depression (PHQ-9), we used the raw test score. A score ranging from 10 to 14 points equals mild depression, from 15 to 19 equals moderate depression, and from 20 to 27 equals severe depression. Participants scoring from 0 to 9 were considered as pwMS with no self-reported depression (Hajdúk *et al.* 2021).

In methods assessing *the degree of functional disability*, the scores were used as follows. In 9-HPT, the average time of 2 trials (in seconds) for the dominant hand and the average time of 2 trials (in seconds) for the non-dominant hand. In T25FW, the average time of 2 trials (in seconds) was analyzed.

Tab. 1. Demographic and clinical characteristics of the study population

	All pwMS	No CI	CI	*p*-value
N	55	35	20	
Age (years)	42.4±10.3	40.4±9.9	45.9±10.5	0.061
Females/males	33/22	21/14	12/8	1.0
Education (years)	15.3±3.3	15.9±3.0	14.3±3.7	0.071
Sleep (hours)	6.6±1.7	6.5±1.7	6.0±1.5	0.287
Age at disease onset	32.9±10.2	31.6±10.0	35.1±10.6	0.232
Disease duration (years)	10.0, 10.0 (1.0-21.0)	10.0, 9.0 (1.0-19.0)	11.0, 9.0 (1.0-21.0)	0.247
DMT: 1st line/ 2nd line/ none	32/21/2	19/14/2	13/7/0	0.478

DMT – Disease-Modifying Therapy, **: $p < 0.01$, *: $p < 0.05$

The pNfL analysis was performed by a Single-Molecule Array (SIMOA®) technique, with the NF-Light Advantage Kit on the Simoa-HD1 analyzer, according to the manufacturer's protocol (Quanterix, Lexington, MA, USA) (www.quanterix.com) (Disanto *et al.* 2017; Kuhle *et al.* 2015).

Statistics

Continuous variables were expressed as means ± SD or median, interquartile range (IQR), minimal, and maximal values, depending on the normality of the data distribution. Categorical variables were expressed as numbers and proportions (%). To compare variables in the CI vs. non-CI population, the Student *t-test*, Mann–Whitney test, and $\chi 2$ test were used for particular variables. In multivariate binary logistic regression analysis, odds ratios (OR) with 95% confidence interval (CI) were reported to declare the statistical significance and the strength of association between CI and the independent variables. The dependent variable was CI and the independent variables were sociodemographic factors (age, sex, laterality, the duration of education, length of sleep), MS characteristics (EDSS, disease duration, age at disease onset, type of DMT), pNfL level, and results of particular tests (SDMT, RAVLT, ROCFT, Digit span, Verbal fluencies, TMT, PHQ-9). *P* values < 0.05 were considered statistically significant. SPSS (version 18, SPSS Inc., Chicago, USA) was used for statistical analysis.

RESULTS

We compared 1) the demographic and clinical characteristics of the study population, 2) the degree of functional disability, 3) depression, and 4) pNfL in CI (n = 20) and non-CI (n = 35) groups.

The main demographic and clinical characteristics of the study population in relation to cognition are stated in Tab. 1. In our study, we did not find statistically significant differences between the CI and non-CI groups in these variables.

We observed statistically higher results in the functional disability in the CI group, compared to the non-CI group, except for the laterality (we included laterality in this results section, due to its association with hand dexterity, measured by 9HPT) (Tab. 2).

The prevalence of depression (measured by PHQ-9) in our study group was 29.1% (16 out of 55 pwMS). We did not observe any statistically significant differences between the CI and non-CI groups ($p = 0.109$). Furthermore, we did not observe any significant difference in pNfL between the CI and non-CI groups ($p = 0.828$).

Tab. 2. The degree of functional disability in association with cognition

	All pwMS	No CI	CI	*p*-value
Laterality: amb/ L / R	1/3/51	0/2/33	1/1/18	0.409
EDSS	2.5, 2.5 (0-5.5)	2.0, 2.0 (1.0-5.0)	4.0, 2.0 (0-5.5)	**0.011****
9-HPT DH (seconds)	23.9±7.4	21.4±4.2	28.3±9.6	**0.001****
9-HPT N-DH (seconds)	24.7±6.8	22.2±3.9	29.0±8.6	**<0.001****
T25FW (mean)	5.3±1.8	4.7±1.0	6.4±2.5	**0.001****
9-HPT: DH z-score	1.9, 3.0 (-0.8-19.1)	1.5, 2.3 (-0.8-6.9)	2.9, 6,3 (-0.1-19.1)	**0.004****
9-HPT: N-DH z-score	1.6, 3.3 (-1.1-10.8)	1.3, 2.4 (-1.14-4.8)	3.6, 6.1 (0.2-10.8)	**0.01****

EDSS: Expanded Disability Status Scale, T25FW: Timed 25-Foot Walk, 9-HPT DH: The 9-Hole Peg Test Dominant Hand, 9-HPT N-DH: The 9-Hole Peg Test Non-dominant Hand, **: $p < 0.01$, *: $p < 0.05$

Tab. 3. Difference between CI and non-CI group in various cognitive tests

	All pwMS	No CI	CI	*p*-value
RAVLT (A1)	0.8, 1.5 (-1.94-3.73)	0.9, 1.3 (-0.3-3.7)	0.2, 2.6 (-1.9-2.9)	0.083
RAVLT (A2)	0.7, 1.8 (-1.1-3.1)	0.9, 1.5 (-1.1-3.0)	0.4, 1.8 (-0.9-3.1)	0.159
RAVLT (A3)	0.8, 1.5 (-1.0-2.6)	0.9, 1.4 (-1.0-2.1)	0.3, 1.7 (-0.8-2.6)	0.319
RAVLT (A4)	0.7, 1.3 (-1.0-2.7)	0.8, 1.1 (-0.9-2.4)	0.4, 1.7 (-1.0-2.7)	0.267
RAVLT (A5)	0.5, 1.4 (-1.3-2.3)	0.5, 1.0 (-0.8-1.8)	-0.2, 1.3 (-1.3-2.3)	0.065
RAVLT (A6)	0.5,1.8 (-1.5-2.5)	0.6, 1.3 (-0.9-2.1)	-0.4, 1.9 (-1.5-2.5)	0.065
RAVLT (B)	0.3, 1.6 (-3.0-2.9)	0.4, 1.5 (-1.1-2.9)	0.1, 1.9 (-3.0-2.7)	0.149
RAVLT (A30)	0.5, 1.6 (-1.3-2.4)	0.8, 0.8 (-0.7-2.1)	-0.4, 2.2 (-1.3-2.4)	**0.025***
RAVLT(A1-A5)	0.7, 1.3 (-1.1-3.1)	1.0, 1.0 (-0.9-3.1)	0.4, 1.5 (-1.1-2.8)	**0.042***
DSF	-0.6, 1.4 (-2.0-1.9)	-0.1, 1.6 (-1.8-1.9)	-1.0, 1.3 (-2.0-0.6)	**0.003****
DSF (longest line)	-0.4, 1.7 (-2.1-2.0)	-0.2, 1.7 (-1.5-2.0)	-1.1, 1.7 (-2.1-1.4)	**0.007****
DSB	-0.1, 1.0 (-2.0-3.1)	-0.3, 1.2 (-1.3-3.1)	-0.3, 1.3 (-2.0-0.5)	**0.015***
DSB (longest line)	-0.1, 1.6 (-1.9-2.8)	0.2, 1.5 (-1.3-2.8)	-0.8, 1.4 (-1.9-1.5)	**0.005****
TMT-A	-0.2, 1.6 (-5.8-1.2)	0.1, 0.7 (-2.4-1.2)	-1.7, 2.4 (-5.8-0.8)	**<0.001****
TMT-B	-0.4, 1.5 (-5.3-1.0)	0.1, 0.7 (-1.1-1.0)	-1.2, 2.0 (-5.3-0.7)	**<0.001****
EF index (TMT: B-A)	0.01, 0.9 (-4.4-1.0)	0.2, 0.7 (-0.9-1.0)	-0.5, 1.9 (-4.4-0.5)	**<0.001****
SDMT	-1.2, 1.6 (-3.8-2.5)	-1.0, 1.3 (-2.9-2.5)	-2.3, 1.7 (-3.8-0.5)	**<0.001****
ROCFT (copy)	0.1, 0.9 (-3.4-1.1)	0.1, 0.8 (-1.5-1.1)	-0.1, 1.5 (-3.4-0.7)	0.146
ROCFT (3 minutes)	-0.01, 1.2 (-2.1-1.7)	0.2, 1.4 (-2.1-1.7)	-0.2, 0.7 (-2.1-0.9)	0.085
ROCFT (30 minutes)	-0.02, 1.0 (-2.1-1.8)	0.1, 1.2 (-1.8-1.8)	-0.2, 0.7 (-2.1-1.2)	0.135
LVF	-0.3, 1.3 (-2.8-2.0)	0.1, 1.1 (-1.4-2.0)	-1.1, 1.5 (-2.8-1.4)	**0.002****
CVF	-0.1, 1.6 (-3.2-2.9)	0.1, 1.7 (-3.2-2.8)	-0.1, 1.8 (-1.8-2.9)	0.267

RAVLT: Rey Auditory Verbal Learning Test, DSF: Digit Span Forward, DSB: Digit Span Backwards, TMT: Trail Making Test, EF index: Index of executive functions, SDMT: Symbol Digit Modalities Test, ROCFT: Rey-Osterrieth Complex Figure Test, LVF: Letter Verbal Fluency, CVF: Category Verbal Fluency, **: $p < 0.01$, *: $p < 0.05$

When comparing the results of the particular cognitive tests (Tab. 3), we observed significantly lower z-scores in the CI group when compared to the non-CI group in these tests: RAVLT (A30), RAVLT (A1-A5), DSF, DSF (longest line), DSB, DSB (longest line), TMT-A, TMT-B, TMT: B-A, SDMT, and LVF.

For the identification of the most sensitive cognitive test as a predictive parameter for CI, forward binary logistic regression analysis was used. The DSF longest line (OR: 0.375, 95%CI: 0.156-0.901, $p = 0.028$) and TMT-B (OR: 0.066, 95%CI: 0.013-0.339, $p = 0.001$) were the only independent variables in a model predicting CI.

DISCUSSION

In our study, we focused on the association of cognition with various disease characteristics. We also tried to identify affected cognitive domains. Of the 55 pwMS, 20 had CI (36.4%), which corresponds to the results of a meta-analysis published recently, where the prevalence of CI in pwMS was 32.5 % (Wu *et al.* 2024). The research studies involved in this meta-analysis used complex neuropsychological examination to determine the presence/absence of CI.

We observed an association of CI with the degree of functional disability (except laterality). Regarding the main demographic and clinical characteristics of our study population, did not find statistically significant differences between the CI and the non-CI group. We also did not find any significant difference in the prevalence of depression or in pNfL between the CI and the non-CI group.

CR and its protective effect on cognition in pwMS are well known (Sumowski & Leavitt, 2013). A more severe CI may develop after a longer duration of RRMS, therefore, it is important to study the effect of CR on cognition in pwMS longitudinally (Rocca *et al.* 2019). In our study, we did not find differences in the disease duration between groups with the presence/absence of CI. The reason is probably a heterogeneous study group with a disease duration ranging from 1 year to 21 years. There are many factors contributing to the increased CR, including premorbid intelligence, education level, leisure activities, engaging in cognitively stimulating activities, exercise, or employment

(Stern, 2009). Out of these factors, we investigated only the duration of education and found no statistically significant difference between the CI and the non-CI group. Other factors contributing to CR should definitely be addressed in future studies. Not addressing them in our research is probably one of the biggest limitations of this study.

Depression is prevalent in MS (Feinstein, 2011) and can negatively affect cognition (Anderson *et al.* 2023). Some sources state that the presence of depression can exacerbate already existing CI, but not directly cause it (Patel *et al.* 2018). In our study, we were unable to find any association between depression and cognition. We assume that the reason might be our choice of a self-report rating scale of depressive symptoms. Some of our patients were treated for depression or had a plan to consult a psychiatrist, but, according to PHQ-9, they did not meet the criteria for self-reported depression and, therefore, were not considered depressed. However, some of the pwMS who met the criteria for mild or moderate depression (according to PHQ-9) reported significant fatigue, sleep disturbances, difficulties with concentration etc., which, in some cases, may not be present due to depression, but due to MS itself (Feinstein *et al.* 2014). In the future, an instrument that differentiates between these aspects should be chosen.

Early use of DMT soon after confirming the MS may be beneficial for cognition since it has the potential to stop or slow the development of lesions or brain atrophy (Noyes & Weinstock-Guttman, 2013). Both first and second-line DMT can stabilize the disease. Recent findings propose an early use of high-efficacy DMTs as more beneficial (Filippi *et al.* 2022). In our study, the type of DMT was not found to be a factor differentiating in pwMS with/without CI. We must admit that the cross-sectional design may not be appropriate to investigate this association and is in accordance with the limitations of the current study. Many pwMS and their cognition may be protected by higher CR for some time, even with the significant brain pathology present. Therefore, a longitudinal design with follow-up after more years may be more suitable, when CR alone cannot compensate for the negative effect of neurodegeneration (Kania *et al.* 2023). For example, a study by Harel *et al.* (2019) with follow-up for at least 10 years after the disease onset pointed out a positive effect of DMT on cognition.

Some studies found an association of pNfL levels with cognition (Quintana *et al.* 2018), and some did not (Sayed *et al.* 2024). The concentration of pNfL increases with a more significant neuronal loss (Gaetani *et al.* 2019). The results of some studies indicate that higher pNfL may be associated with faster cognitive decline (Williams *et al.* 2022) and a decrease in score in one cognitive test after 1 year (Friedova *et al.* 2020). The pNfL is certainly a promising biomarker in MS, but its association with cognition needs to be studied more thoroughly in future prospective studies.

We observed a statistically significant association of CI with the tests measuring verbal learning and reproduction from long-term verbal memory (RAVLT: A30, A1-A5), cognitive flexibility, information processing speed, and word retrieval from memory (TMT-A, TMT-B, TMT: B-A, SDMT and LVF), attention and working memory (all DS measures) – DSF also measures immediate memory (Lezak, 2012). However, we did not observe any difference in RAVLT A1 and B. We suppose that immediate memory is not among the most affected domains. For the identification of the most sensitive cognitive test as a predictive parameter for CI, forward binary logistic regression analysis was used. The DSF longest line and TMT-B were the only independent variables in a model that predicted CI.

Our results indicate that CI can be present in various cognitive domains (as mentioned above), which is consistent with the results of other research studies (Benedict *et al.* 2017). These findings underscore the importance of a neuropsychological examination consisting of more tests. Batteries of tests like Brief International Cognitive Assessment in MS (BICAMS) or (MACFIMS) were not yet adapted for the Slovak population. The use of similar cognitive tests is more than appropriate, as cognition needs to be examined routinely and longitudinally in pwMS.

We proposed a criterium for CI in our study stating: *"The difference between two or more tests assessing one cognitive domain and two or more tests assessing different cognitive domain was at least 1.5 standard deviation (e.g. if in one pwMS, two tests assessing verbal memory have z-scores 2.0 SD, two tests assessing EF have z-scores 0.5 SD, then this pwMS had CI in EF)"*. As stated by Sumowski *et al.* (2018), a patient may report a decrease in cognition compared to the previous above average level of functioning, which might have been present in some pwMS with high CR. This change may be significant (a decline by 1.5 SD), but still not detected in one cognitive assessment and the patient might be characterized as a person without CI. Since this study is part of a larger research, we plan to examine whether these pwMS will continue to impair cognition or not.

In conclusion, a cross-sectional study design seems to be less appropriate for the investigation of the relationship of CI and various disease characteristics or DMT. For this purpose, longitudinal observation of cognition in pwMS is needed and future prospective studies are highly warranted. A battery consisting of more cognitive tests is more suitable for this purpose.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

ETHICAL APPROVAL

This research was carried out as part of the dissertation thesis of Bianka Suchá conducted at the Center of demyelinating diseases at the 1st Department of Neurology, Faculty of Medicine, Comenius University, University Hospital, Bratislava, Slovakia.

The study was approved by the Ethical Committee of the University Hospital Bratislava (Decision number 136/2021).

INFORMED CONSENT

All participants agreed with the participation in the study and signed the informed consent.

FINANCIAL SUPPORT

This research was supported by the grants APVV-15-0228, and APVV-21-0261.

REFERENCES

1 Altieri M, Cerciello F, Gallo A, Santangelo G. (2024). The relationship between depression and cognitive performance in multiple sclerosis: A meta-analysis. Clin Neuropsychol. **38**(1): 21–41.
2 Anderson JR, Fitzgerald KC, Murrough JW, et al. (2023). Depression symptoms and cognition in multiple sclerosis: Longitudinal evidence of a specific link to executive control. Mult Scler. **29**(13): 1632–1645.
3 Benedict RHB, DeLuca J, Enzinger C, Geurts JJG, Krupp LB, Rao SM. (2017). Neuropsychology of Multiple Sclerosis: Looking Back and Moving Forward. J Int Neuropsychol Soc. **23**(9–10): 832–842.
4 Benedict RH, Ramasamy D, Munschauer F, Weinstock-Guttman B, Zivadinov R. (2009). Memory impairment in multiple sclerosis: correlation with deep grey matter and mesial temporal atrophy. J Neurol Neurosurg Psychiatry. **80**(2): 201–206.
5 Buchanan R, Radin D, Chakravorty BJ, Tyry T. (2010). Perceptions of informal care givers: health and support services provided to people with multiple sclerosis. Disabil Rehabil. **32**(6): 500–510.
6 Demaree H, Gaudino E, DeLuca J. (2003). The relationship between depressive symptoms and cognitive dysfunction in multiple sclerosis. Cognitive Neuropsychiatry. **8**(3): 161–171.
7 Dineen RA, Vilisaar J, Hlinka J, et al. (2009). Disconnection as a mechanism for cognitive dysfunction in multiple sclerosis. Brain. **132**(Pt 1): 239–249.
8 Disanto G, Barro C, Benkert P, et al. (2017). Serum Neurofilament light: A biomarker of neuronal damage in multiple sclerosis. Ann Neurol. **81**(6): 857–870.
9 Elshebawy H, Fahmy EM, Elfayoumy NM, Abdelalim AM, Ismail RS. (2021). Clinical predictors to cognitive impairment in multiple sclerosis patients. The Egyptian Journal of Neurology, Psychiatry and Neurosurgery. **57**(1): 38.
10 Feinstein A. (2011). Multiple sclerosis and depression. Mult Scler. **17**(11): 1276–1281.
11 Feinstein A, Magalhaes S, Richard JF, Audet B, Moore C. (2014). The link between multiple sclerosis and depression. Nat Rev Neurol. **10**(9): 507–517.
12 Feys P, Lamers I, Francis G, et al. (2017). The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis. Mult Scler. **23**(5): 711–720.
13 Filippi M, Amato MP, Centonze D, et al. (2022). Early use of high-efficacy disease modifying therapies makes the difference in people with multiple sclerosis: an expert opinion. J Neurol. **269**(10): 5382–5394.
14 Friedova L, Motyl J, Srpova B, et al. (2020). The weak association between neurofilament levels at multiple sclerosis onset and cognitive performance after 9 years. Multiple Sclerosis and Related Disorders. **46**: 102534.
15 Gaetani L, Blennow K, Calabresi P, Di Filippo M, Parnetti L, Zetterberg H. (2019). Neurofilament light chain as a biomarker in neurological disorders. J Neurol Neurosurg Psychiatry. **90**(8): 870–881.
16 Geurts JJG, Calabrese M, Fisher E, Rudick RA. (2012). Measurement and clinical effect of grey matter pathology in multiple sclerosis. Lancet Neurol. **11**(12): 1082–1092.
17 Gold R, Wolinsky JS, Amato MP, Comi G. (2010). Evolving expectations around early management of multiple sclerosis. Ther Adv Neurol Disord. **3**(6): 351–367.
18 Grzegorski T, Losy J. (2017). Cognitive impairment in multiple sclerosis - a review of current knowledge and recent research. Rev Neurosci. **28**(8): 845–860.
19 Gudesblatt M, Wissemann K, Zarif M, et al. (2018). Improvement in Cognitive Function as Measured by NeuroTrax in Patients with Relapsing Multiple Sclerosis Treated with Natalizumab: A 2-Year Retrospective Analysis. CNS Drugs. **32**(12): 1173–1181.
20 Hajdúk M, Brandoburová P, Pribišová K, Abrahámová M, Cviková V, Dančík D et al. (2021). NEUROPSY štandardizácia neuropsychologickej testovej batérie na dospelej slovenskej populácii. [(NEUROPSY: standardization of the neuropsychological test battery on slovak adult population.) Bratislava: Comenius University in Bratislava) (In Slovak)]
21 Harel Y, Kalron A, Menascu S, et al. (2019). Cognitive function in multiple sclerosis: A long-term look on the bright side. PLoS One. **14**(8): e0221784.
22 Chen MH, Goverover Y, Genova HM, DeLuca J. (2020). Cognitive Efficacy of Pharmacologic Treatments in Multiple Sclerosis: A Systematic Review. CNS Drugs. **34**(6): 599–628.
23 Chiaravalloti ND, DeLuca J. (2008). Cognitive impairment in multiple sclerosis. Lancet Neurol. **7**(12): 1139–1151.
24 Jakimovski D, Zivadinov R, Ramanthan M, et al. (2020). Serum neurofilament light chain level associations with clinical and cognitive performance in multiple sclerosis: A longitudinal retrospective 5-year study. Mult Scler. **26**(13): 1670–1681.
25 Kalinowski A, Cutter G, Bozinov N, et al. (2021). The timed 25-foot walk in a large cohort of multiple sclerosis patients. Mult Scler. **28**(2): 289.
26 Kania K, Ambrosius W, Kozubski W, Kalinowska-Łyszczarz A. (2023). The impact of disease modifying therapies on cognitive functions typically impaired in multiple sclerosis patients: a clinician's review. Front Neurol. **14**: 1222574.
27 Kuhle J, Disanto G, Lorscheider J, et al. (2015). Fingolimod and CSF neurofilament light chain levels in relapsing-remitting multiple sclerosis. Neurology. **84**(16): 1639–1643.
28 Kurtzke JF. (1983). Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology. **33**(11): 1444–1444.
29 Kutzelnigg A, Lucchinetti CF, Stadelmann C, et al. (2005). Cortical demyelination and diffuse white matter injury in multiple sclerosis. Brain. **128**(Pt 11): 2705–2712.
30 Leavitt VM. (2021). The SDMT is not information processing speed. Mult Scler. **27**(11): 1806–1807.
31 Lezak MD, Howieson DB, Bigler ED, Tranel D, eds. (2012). Neuropsychological assessment (5th ed.). Oxford University Press.
32 Mattioli F, Bellomi F, Stampatori C, et al. (2020). Longitudinal serum neurofilament light chain (sNfL) concentration relates to cognitive function in multiple sclerosis patients. J Neurol. **267**(8): 2245–2251.
33 Mattioli F, Stampatori C, Capra R. (2011). The effect of natalizumab on cognitive function in patients with relapsing-remitting multiple sclerosis: preliminary results of a 1-year follow-up study. Neurol Sci. **32**(1): 83–88.
34 Noyes K, Weinstock-Guttman B. (2013). Impact of diagnosis and early treatment on the course of multiple sclerosis. Am J Manag Care. **19**(17 Suppl): s321–331.
35 Patel VP, Walker LA, Feinstein A. (2018). Revisiting cognitive reserve and cognition in multiple sclerosis: A closer look at depression. Mult Scler. **24**(2): 186–195.

36 Patti F, Amato MP, Bastianello S, et al. (2010). Effects of immunomodulatory treatment with subcutaneous interferon beta-1a on cognitive decline in mildly disabled patients with relapsing-remitting multiple sclerosis. Mult Scler. **16**(1): 68–77.

37 Quintana E, Coll C, Salavedra-Pont J, et al. (2018). Cognitive impairment in early stages of multiple sclerosis is associated with high cerebrospinal fluid levels of chitinase 3-like 1 and neurofilament light chain. Eur J Neurol. **25**(9): 1189–1191.

38 Rocca MA, Riccitelli GC, Meani A, et al. (2019). Cognitive reserve, cognition, and regional brain damage in MS: A 2 -year longitudinal study. Mult Scler. **25**(3): 372–381.

39 Sayed A, Ashmawy GA, Ramadan I, Galeel AA, Hamed M. (2024). Cognitive profile in Egyptian multiple sclerosis patients has no correlation with serum neurofilament level. Egypt J Neurol Psychiatry Neurosurg. **60**(1): 68.

40 Schoonheim MM, Meijer KA, Geurts JJG. (2015). Network Collapse and Cognitive Impairment in Multiple Sclerosis. Frontiers in Neurology. **6**: 82.

41 Smith A. (1982). Symbol Digit Modalities Test (SDMT). Manual (Revised).

42 Stern Y. (2009). Cognitive reserve. Neuropsychologia. **47**(10): 2015–2028.

43 Strober LB, Bruce JM, Arnett PA, et al. (2020). A new look at an old test: Normative data of the symbol digit modalities test –Oral version. Mult Scler Relat Disord. **43**: 102154.

44 Sumowski JF, Leavitt VM. (2013). Cognitive reserve in multiple sclerosis. Mult Scler. **19**(9): 1122–1127.

45 Sumowski JF, Benedict R, Enzinger C, et al. (2018). Cognition in multiple sclerosis. Neurology. **90**(6): 278–288.

46 Van Schependom J, D'hooghe MB, Cleynhens K, et al. (2014). The Symbol Digit Modalities Test as sentinel test for cognitive impairment in multiple sclerosis. Eur J Neurol. **21**(9): 1219–1225, e71–72.

47 Wallin MT, Wilken JA, Kane R. (2006). Cognitive dysfunction in multiple sclerosis: Assessment, imaging, and risk factors. J Rehabil Res Dev. **43**(1): 63–72.

48 Weinstock-Guttman B, Galetta SL, Giovannoni G, et al. (2012). Additional efficacy endpoints from pivotal natalizumab trials in relapsing-remitting MS. J Neurol. **259**(5): 898–905.

49 Williams T, Tur C, Eshaghi A, et al. (2022). Serum neurofilament light and MRI predictors of cognitive decline in patients with secondary progressive multiple sclerosis: Analysis from the MS-STAT randomised controlled trial. Mult Scler. **28**(12): 1913–1926.

50 Wu W, Francis H, Lucien A, Wheeler TA, Gandy M. (2024). The Prevalence of Cognitive Impairment in Relapsing-Remitting Multiple Sclerosis: A Systematic Review and Meta-analysis. Neuropsychol Rev. Published online.

51 Yuan A, Nixon RA. (2021). Neurofilament Proteins as Biomarkers to Monitor Neurological Diseases and the Efficacy of Therapies. Front Neurosci. **15**: 689938.