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Neurofilament Light Chain and Disability Measures as Predictors of Cognitive Decline in Early Multiple Sclerosis

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Background: This study investigated whether cerebrospinal fluid (CSF) and serum neurofilament light chain (NfL), a biomarker of axonal degeneration, combined with manual dexterity and ambulation measures, can serve as reliable predictors of MS-related cognitive impairment (CI).

Material/Methods: A total of 99 newly diagnosed patients with MS (PwMS) and 37 healthy controls (control group [CG]) were included in the study. Serum NfL levels were measured in both groups, whereas PwMS also underwent CSF NfL analysis. Cognition was assessed using the Brief International Cognitive Assessment for MS (BICAMS) test battery. Disability was evaluated using the Expanded Disability Status Scale (EDSS), Nine-Hole Peg Test (NHPT), and Timed 25-Foot Walk Test (T25FWT). PwMS were classified as cognitively impaired if Z-scores of 1 or more BICAMS tests were below -1.5 standard deviations from the mean of the CG scores.

Results: PwMS had significantly lower median scores in the Brief Visuospatial Memory and Learning Revised (BVMT-R) and California Verbal Learning Test II (CVLT) (p=0.003 and p<0.001, respectively). They had significantly longer NHPT and T25FWT times (p<0.001) and higher serum NfL concentrations (11.8 vs 5.8 pg/mL, p<0.001). CI was identified in 32.3% of PwMS. Linear regression showed that lower CSF NfL levels significantly predicted higher BVMT-R scores. Logistic regression analysis demonstrated that NHPT and T25FWT times significantly predicted impairment in SDMT and BVMT-R. Serum NfL concentration showed a tendency toward predicting SDMT impairment (p=0.051), whereas CSF NfL levels significantly predicted abnormal BVMT-R scores and overall CI.

Conclusions: In early-stage MS, CSF and serum NfL concentrations, along with ambulation and manual dexterity measurements, can be valuable tools for predicting cognitive impairment.

Keywords: Multiple Sclerosis • Neurofilament Proteins • Cognitive Dysfunction

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Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) that usually manifests in young adults. Characteristic demyelinating lesions appear in CNS white matter, leading to relapses accompanied by various neurological symptoms. Up to 65% of patients with MS (PwMS) experience both physical disability during relapses and progressive impairment over time, along with cognitive dysfunction [1-3]. Cognitive impairment (CI) can be detected even at diagnosis and does not necessarily correlate with physical disability or Expanded Disability Status Scale (EDSS) scores [4]. Although multiple cognitive domains may be affected, the most commonly impaired functions are information processing speed, visuospatial ability, anterograde episodic memory, attention, and executive functions [2,5-7]. Despite significantly contributing to reduced quality of life and unemployment, CI remains under-assessed in clinical practice [4]. Early cognitive evaluation could play a crucial role in guiding treatment initiation and modification. Identifying an accessible and quantifiable biomarker that reflects neurodegenerative processes underlying CI in MS remains an unmet need.

Neurofilaments, essential components of the axonal cytoskeletal, maintain structural integrity and facilitate proper function [8]. Axonal degeneration, observed in various neurological diseases and normal aging [9,10], leads to increased neurofilament concentrations in cerebrospinal fluid (CSF) and subsequently in blood. Among neurofilament subunits, the neurofilament light chain (NfL) is the most abundant, lightest, and highly soluble [11], making it the most frequently investigated biomarker for neurodegeneration [12]. Changes in NfL concentration have been linked to MS-related disability, disease activity, relapse timing, and responses to disease-modifying therapies [12,13]. However, the relationship between CI and NfL levels remains unclear in the scientific literature [14-17].

This study investigated the association between NfL concentrations, physical disability parameters, and CI in newly diagnosed PwMS. Moreover, serum NfL (sNfL) and CSF NfL were analyzed to determine their potential role in addressing this clinical challenge.

Material and Methods

Participants

This study was approved by the Ethics Committee for Scientific Research of the Faculty of Medicine of Vilnius University (2020/2-1200-685; 2023-LP-91). This single-center, prospective study included PwMS without relapse who underwent diagnostic workup for MS at Vilnius University Hospital Santaros Clinics between February 2020 and August 2024, along with a group of healthy controls. The inclusion criteria were age 18-65 years, MS diagnosed according to the revised 2017 McDonald's criteria, no other known CNS or psychiatric diseases that could produce physical disability or impair cognitive functions, no sight or hearing disability, no known history of substance abuse, and agreement to participate in the study by signing a written informed consent form. None of the PwMS had received prior disease-modifying therapies. Exclusion criteria included unwillingness to participate and technical difficulties in obtaining CSF or serum for analysis.

Inclusion criteria for the CG were as follows: age 18-65 years; absence of MS diagnosis; no other known CNS, psychiatric, or clinical conditions affecting cognitive function or causing disability; no hearing or visual impairments; no known history of substance abuse; and willingness to participate by signing an informed consent form.

An a priori power analysis, conducted using G*Power version 3.1.9.7 [18], determined that the minimum sample size of N=134 would be adequate (80% power for detecting a medium effect and a significance criterion of α=.05 were used).

Cognitive Testing

Cognitive testing was performed using the Brief International Cognitive Assessment for MS (BICAMS) battery, a rapid and easily performed set of tests designed to evaluate information processing speed (IPS), visual and verbal learning, and memory (immediate recall) [19].

IPS was examined using the Symbol Digit Modalities Test (SDMT) [20]. In this test, participants were given a worksheet containing a key that paired 9 symbols with single digits. The remainder of the worksheet consisted of a pseudo-random sequence of symbols. The participants had to indicate as quickly as possible which digit corresponded to the symbol. The result was then presented as the total number of correct arrangements during the 90 s of testing.

The Brief Visuospatial Memory Test-Revised (BVMT-R) [21] evaluated immediate visual recall and learning. The test included 6 abstract geometric figures (arranged as 2 figures in 3 rows) displayed on a single sheet. Participants were shown the figures for 10 s during 3 learning trials. Afterward, the figures were removed, and participants had to reproduce them from memory on an empty sheet of paper. Each figure was awarded 0, 1, or 2 points based on the correct shape and location. The final score was the sum of points from each trial, with a maximum possible score of 36.

The California Verbal Learning Test 2nd Edition (CVLT-II) [22] assessed immediate verbal recall and learning. The investigator

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read aloud a 16-word list composed of 4 semantic categories, each containing 4 items arranged in random order. Participants attempted to recall as many items as possible after each reading. The score was the sum of items recalled across all 5 learning trials, with a maximum score of 80.

All cognitive tests were performed by the same investigator in a quiet room. Z-scores for individual tests were calculated based on median scores and interquartile ranges (IQRs) of the CG. CI was defined as a Z-score below -1.5 for any of the tests (SDMT, BVMT-R, and CVLT-II). Overall cognitive performance was considered impaired if the participant had 1 or more abnormal individual test results.

Physical Disability Assessment

Physical disability in PwMS was assessed by the same investigator using the Expanded Disability Status Scale (EDSS) [23]. Two additional tests were used to evaluate physical disability: the Nine-Hole Peg Test (NHPT) and the 25-Foot Walk Test (T25FWT).

The NHPT [24] evaluated upper-limb fine motor control (manual dexterity). The testing set comprised a rectangular board with 9 pegs in a shallow container on one side and 9 holes on the other side. Participants were required to arrange the pegs into the holes in any order and then put the pegs back into the container as quickly as possible. The test was performed twice using both hands, starting with the dominant hand. The mean time was calculated for all the trials.

The T25FWT [25] is the most commonly used test for evaluating walking problems and lower-extremity function. Participants were asked to walk 25 feet as quickly as possible while ensuring safety. Two trials were conducted, and the final score was the mean time from both trials.

Laboratory Testing

CSF NfL levels were measured using enzyme immunoassay (ELISA) for the quantitative determination of human neurofilament light protein in CSF (NF-light®, UmanDiagnostics, Umea, Sweden; distributed by IBL International GMBH, Germany). Serum NfL (sNfL) levels were measured using the SiMoA assay. Samples were coded and blinded to participants' group and clinical data.

Statistical Analysis

Data are presented as mean±standard deviation or median (IQR). The normality of distributions was assessed using the Shapiro-Wilk test. Pearson's correlation coefficient (r) and Spearman's rank correlation coefficient (rho) were used for simple correlations. Differences between the CG and PwMS were assessed using the *t* test for normally distributed variables and the Mann-Whitney U test for non-normally distributed data. Linear and logistic regressions were performed to identify associations of CI (overall and in each individual test) with NfL levels, disability measures, and clinical and demographic data. Dependent variables were individual scores of BICAMS tests in linear regressions and the categorical outcome of cognitive testing – eg, normal or impaired, reported as SDMT(+) or (-) – in logistic regression. CSF or serum NfL were included as independent variables. Age, sex, and education were included in all models as possible covariates that could influence cognitive performance and NfL levels. All statistical analyses were performed using IBM SPSS Statistics v. 30. Statistical significance was set at $P<0.05$.

Results

A total of 99 PwMS and 37 controls were included in the study. PwMS and CG did not differ in the proportion of females to males, age, or education (**Table 1**). The median CSF NfL concentration in PwMS was 1062.80 ng/mL. The median sNfL level in PwMS was almost twice as high as in controls (11.8 pg/mL vs 5.8 pg/mL). A moderately strong correlation was found between the concentrations of NfL in the CSF and serum of PwMS (Spearman's rho=0.607, $P<0.001$).

The results of BVMT-R and CVLT-II scores were significantly higher in the CG (31.0 vs 27.0 and 64.0 vs 54.0, respectively). The CG also performed better on SDMT (55.6 vs 48.6), although this difference did not reach statistical significance. NHPT and T25FWT scores were significantly lower in the CG than in the PwMS (**Table 1**). Moreover, sNfL concentration had a weak positive correlation with EDSS scores (Spearman's rho=0.254, $P=0.011$) and NHPT speed (Spearman's rho=0.292, $P=0.004$).

All 3 tests (SDMT, BVMT-R, and CVLT-II) exhibited statistically significant moderate negative correlations with NHPT (Spearman's rho=-0.564, -0.564, and -0.396, respectively, $P<0.001$) and T25FWT speed (Spearman's rho=-0.548, -0.548 and -0.282, respectively, $P<0.001$). SDMT showed a weak negative correlation with EDSS scores (Spearman's rho=-0.273, $P=0.006$).

NHPT was positively correlated with EDSS (Spearman's rho=0.359, $P<0.001$) and T25FWT (Spearman's rho=0.548, $P<0.001$). Similarly, T25FWT exhibited positive correlations with EDSS (Spearman's rho=0.310, $P<0.004$).

In the CG, 1 (2.7%) participant had an abnormal score in 1 BICAMS test (BVMT-R). Conversely, the PwMS group showed larger proportions of abnormal individual test results: 10 (10.1%) for SDMT and BVMT-R and 25 (25.3%) for CVLT-II.

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Table 1. Demographic and clinical characteristics of study participants.

Variable	PwMS	CG	*P*
Sex, n (%)	Women 63 (63.6%) Men 36 (36.4%)	Women 29 (78.4%) Men 8 (21.6%)	0.102
Age, years	32.0 [19.0]	31.0 [10.0]	0.308
Education, years	16.0 [3.0]	16.0 [2.0]	0.135
EDSS	2.0 [1.5]	–	–
NHPT, s	22.9 [6.9]	18.6 [2.9]	<0.001
T25FWT, s	4.1 [1.4]	3.5 [0.7]	<0.001
SDMT	48.6±12.2	55.6±10.3	0.110
BVMT-R	27.0 [8.0]	31.0 [6.0]	0.003
CVLT-II	54.0 [19.0]	64.0 [10.0]	<0.001
CSF NfL, ng/mL	1062.8 [2083.3]	–	–
Serum NfL, pg/mL	11.8 [13.8]	5.8 [4.3]	<0.001

BVMT-R – Brief Visuospatial Memory Test-Revised; CG – control group; CSF – cerebrospinal fluid; CVLT-II – California Verbal Learning Test II; EDSS – Expanded Disability Status Scale; MS – multiple sclerosis; NfL – neurofilament light chain; NHPT – Nine-Hole Peg Test; SDMT – Symbol Digit Modalities Test; PwMS – patients with MS; T25FWT – Timed 25-Foot Walk Test.

Overall, 33 (32.3%) of PwMS had impairment in 1 or more cognitive domains. Participants were divided into groups according to the result of each test and overall CI. Group characteristics are presented in **Table 2**. No significant differences were observed in NfL concentrations between the groups. Patients with intact IPS (SDMT[+] group) had significantly shorter NHPT and T25FWT times. The BVMT-R intact group (BVMT-R[+]) performed significantly faster on NHPT.

Multiple linear regression models were used to identify variables predicting BICAMS battery scores. All models included age, sex, and education, followed by the inclusion of 1 disability marker (EDSS, NHPT, or T25FWT) to avoid collinearity. Additionally, NfL concentration in either CSF or serum were included as independent variables. Statistically significant linear regression models, which explained the largest proportions of the variances in BICAMS test scores and included NfL or disability parameters as significant predictors, are shown in **Table 3**.

Regarding demographic characteristics, higher education levels emerged as a significant predictor of better SDMT and BVMT-R scores, whereas older age was a significant predictor of lower SDMT and CVLT-II scores. Female sex was also identified as a significant predictor of better CVLT-II results.

All disability parameters – higher EDSS, higher NHPT, and higher T25FWT scores – significantly predicted lower SDMT scores. The BVMT-R score was similarly associated only with T25FWT performance.

Lower CSF NfL level was a significant independent variable for higher BVMT-R scores.

Logistic regression was used to determine which variables significantly predicted the allocation of PwMS to a cognitively impaired group, considering each test individually and overall. All models included demographic characteristics (age, sex, and education), 1 of the disability parameters (EDSS, NHPT, or T25FWT), and/or NfL concentrations (in the CSF or serum). For the SDMT(-), BVMT-R(-), and COG(-) (overall CI) groups, all analyzed models were significant. Only 2 models were significant for the CVLT-II(-) group. The best models are listed in **Table 4**.

Regression analysis showed that, among demographic characteristics, older age was a significant independent variable for the SDMT(-) group, fewer years of education for the SDMT(-) and BVMT-R(-) groups, and male sex for the CVLT-II(-) group. Both older age and male sex significantly predicted overall CI. Slower NHPT and T25FWT times were significant independent variables for the SDMT(-) and BVMT-R(-) groups.

sNfL concentration tended to be a significant predictor of the SDMT(-) group: for each 10 pg/mL increase, the odds ratio (OR) was 1.403, *P*=0.051. CSF NfL was a significant predictor of the BVMT-R(-) group: the OR was 1.033 for every 100 ng/mL increase of CSF NfL in a model with EDSS and 1.031 for every 100 ng/mL increase in a model with NHPT. CVLT(-) models with demographic characteristics and CSF NfL/sNfL were statistically significant; however, the only significant independent

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Table 2. Comparison of characteristics between cognitively impaired (-) and intact (+) groups.

Variable/test	SDMT(+) n=89	SDMT(-) n=10	*p*	BVMT-R(+) n=89	BVMT-R(-) n=10	*p*
Age, years	33.0 [16.0]	52.0 [31.0]	0.301	33.0 [17.0]	45.0 [22.0]	0.764
Education, years	16.0 [3.0]	15.3 [4.1]	0.283	16.0 [2.0]	13.0 [4.0]	0.096
EDSS	2.0 [1.5]	3.8 [4.8]	0.196	2.0 [1.5]	4.0 [4.0]	0.925
NHPT, s	22.5 [6.6]	30.6 [7.0]	**0.019**	22.5 [6.6]	26.9 [8.4]	**0.035**
T25FWT, s	4.0 [1.1]	6.6 [2.4]	**0.031**	4.0 [1.2]	5.0 [3.3]	0.250
CSF NfL, ng/mL	1078.1 [1923.1]	965.9 [4800.7]	0.713	952.5 [1799.0]	4479.5 [4202.1]	0.301
sNfL, pg/mL	11.6 [13.9]	15.6 [34.5]	0.089	11.5 [13.1]	20.8 [21.6]	0.301
Test	**CVLT-II(+) n=74**	**CVLT-II(-) n=25**	***p***	**COG(+) n=67**	**COG(–) n=32**	***p***
Age, years	32.5 [17.0]	35.0 [22.0]	0.602	32.0 [13]	36.0 [25]	0.475
Education, years	16.0 [2.0]	15.0 [4.0]	0.870	16.0 [2]	15.0 [4.0	0.647
EDSS	2.0 [1.5]	2.0 [2.0]	0.844	2.0 [1.5]	2.0 [2.5]	0.951
NHPT, s	22.2 [6.7]	25.3 [5.5]	0.350	21.9 [6.5]	25.3 [6.6]	0.079
T25FWT, s	4.0 [1.2]	4.5 [1.3]	0.203	4.0 [1.2]	4.5 [1.5]	0.147
CSF NfL, ng/mL	966.2 [1766.1]	1078.1 [3984.4]	0.148	938.4 [1484.7]	1078.1 [3984.4]	0.116
sNfL, pg/mL	13.0 [13.6]	11.1 [17.8]	0.953	12.3 [13.7]	11.6 [17.5]	0.776

(+) – cognitive domain intact; (-) – cognitive domain impaired; BVMT-R – Brief Visuospatial Memory Test-Revised; CG – control group; COG – overall cognitive impairment; CSF – cerebrospinal fluid; CVLT-II – California Verbal Learning Test II; MS – multiple sclerosis; NHPT – Nine-Hole Peg Test; SDMT – Symbol Digit Modalities Test; PwMS – patients with MS; sNfL – serum neurofilament light chain; T25FWT – Timed 25-Foot Walk Test; s – seconds; EDSS – Expanded Disability Status Scale.

Table 3. Linear regression models predicting BICAMS battery test scores.

Dependent variable	Regression models	R^2	P (R^2)
SDMT	50.99-0.51 × **age** +1.14 × **education** +3.23 × sex -1.40 × **EDSS**	0.393	<0.001
	67.82-0.37 × **age** +1.14 × **education** +1.33 × sex -1.01 × **NHPT**	0.490	<0.001
	65.86-0.36 × **age** +0.69 × education +4.86 × sex -3.89 × **T25FWT**	0.478	<0.001
BVMT-R	16.75-0.06 × age +0.93 × **education** -2.16 × sex -0.07 × EDSS -0.06 × **CSF NfL**	0.193	<0.001
	19.71-0.03 × age +0.97 × **education** -2.49 × sex -0.19 × NHPT -0.05 × **CSF NfL**	0.211	0.001
	18.97+0.4 x age +0.89 × **education** -2.30 × sex -1.43 × **T25FWT** -0.002 × sNfL	0.147	0.006
CVLT-II	60.35-0.26 × **age** +0.52 × education +7.15 × **sex** -0.47 × NHPT	0.235	<0.001

BVMT-R – Brief Visuospatial Memory Test-Revised; CSF – cerebrospinal fluid; CVLT-II – California Verbal Learning Test II; EDSS – Expanded Disability Status Scale; NfL – neurofilament light chain; NHPT – Nine-Hole Peg Test; SDMT – Symbol Digit Modalities Test; T25FWT – Timed 25-Foot Walk Test; R^2 – proportion of variance in the dependent variable that can be explained by the independent variables. **Bold** font indicates significant independent variables.

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Table 4. Logistic regression models predicting cognitive impairment.

Dependent variable	Regression models $Ln(p/(1-p)) = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3$	F^2	p (F^2)	Significant independent variables		
				Variable	Exp(B), 95% CI	p
SDMT(-)	-5.14 + 0.08 × age - 0.58 × **education** - 0.84 × sex + 0.33 × **NHPT**	0.507	<0.001	Education NHPT	0.56 (0.343-0.914) 1.39 (1.080-1.810)	0.02 0.012
	-3.89 + 0.05 × age - 0.48 × education - 2.61 × sex + 1.33 × T25FWT + 0.143 × sNfL	0.591	<0.001	T25FWT	3.94 (1.547-10.038)	0.006
	-1.75 + 0.09 × **age** - 0.30 × education - 1.48 × sex + 0.34 × **sNfL***	0.422	<0.001	Age sNfL	1.089 (1.017-1.167) 1.403	0.014 0.051
BVMT-R(-)	2.77 + 0.04 × age - 0.59 × **education** - 0.87 × sex + 0.48 × EDSS + 0.03 × CSF **NfL**	0.466	<0.001	Education CSF NfL	0.544 (0.340-0.901) 1.033 (1.004-1.064)	0.017 0.024
	-0.05 + 0.02 × age - 0.66 × **education** - 0.37 × sex + 0.21 × NHPT + 0.03 × **CSF NfL**	0.478	<0.001	Education CSF NfL	0.518 (0.303-0.885) 1.031 (1.001-1.061)	0.016 0.045
	1.22 – 0.003 × age – 0.56 × **education** - 1.13 × sex + 0.86 × T25FWT + 0.03 × CSF-NfL	0.448	0.003	Education T25FWT	0.572 (0.342-0.956) 2.368 (1.107-5.063)	0.033 0.026
	-0.31 + 0.02 × age - 0.64 × **education** + 0.245 × **NHPT** + 0.03 × sNfL	0.391	0.004	Education NHPT	0.523 (0.332-0.843) 1.278 (1.010-1.616)	0.007 0.043
CVLT-II(-)	-1.247 + 0.034 × age - 0.031 × education - 1.39 × **sex** + 0.01 × CSF-NfL	0.163	0.032	Sex	0.249 (0.087-0.711)	0.009
	-1.112 + 0.031 × age - 0.04 × education - 1.38 × **sex** + 0.12 × sNfL	0.160	0.034	Sex	0.252 (0.089-0.717)	0.010
COG(-)	-0.837 + 0.07 × **age** – 0.11 × education – 1.56 × **sex** - 0.16 × EDSS + 0.03 × CSF NfL	0.312	<0.001	Age Sex CSF NfL	1.068 (1.018-1.120) 0.210 (0.069-0.644) 1.027 (1.003-1.052)	0.007 0.006 0.027
	-0.849 + 0.06 × **age** - 0.12 × education - 1.46 × **sex** - 0.01 × NHPT + 0.02 × ΧΣΦ ΝφΛ	0.297	<0.001	Age Sex CSF NfL	1.061 (1.010-1.114) 0.232 (0.075-0.719) 1.024 (1.000-1.048)	0.019 0.011 0.048

BVMT-R – Brief Visuospatial Memory Test-Revised; CI – confidence interval; CSF – cerebrospinal fluid; CVLT-II – California Verbal Learning Test II; EDSS – Expanded Disability Status Scale; Exp(B) – Odd's ratio; F^2 – effect size; NfL – neurofilament light chain; NHPT – Nine-Hole Peg Test; SDMT – Symbol Digit Modalities Test; T25FWT – Timed 25-Foot Walk Test. **Bold** – significant independent variables.

variable was male sex. CSF NfL was a statistically significant predictor of overall CI, with an OR of 1.027 in a model with EDSS and 1.005 in a model with NHPT for every 100 pg/mL increase in CSF NfL

Discussion

This study presents our single-center assessment of the association between CI and NfL concentrations in PwMS. At diagnosis, PwMS already exhibited differences in cognitive parameters, physical disability, and sNfL levels when compared to the CG.

PwMS had lower scores on the BVMT-R and CVLT-II tests, while SDMT scores did not significantly differ between the groups. This finding is inconsistent with previous studies, were all cognitive domains tested by the BICAMS battery were found to be worse in PwMS compared to healthy controls [26-28]. IPS is regarded as one of the most sensitive cognitive domains to damage in MS [1,26,29]. In a validation study of the Lithuanian version of the BICAMS [27], the mean SDMT score was 15 points higher in the CG, whereas our mean difference was approximately 7 points, without statistical significance. However, that study analyzed PwMS with a mean disease duration of 11.7±9.2 years, whereas our cohort consisted of participants assessed at the time of diagnosis. A longer disease duration allows for more time for axonal neurodegeneration and general brain atrophy, which could explain IPS impairment in MS. Normal IPS at the time of diagnosis could indicate a window of opportunity for interventions to prevent future decline. Interventions such as rehabilitation (both on site and online) [30] or dietary changes for overweight PwMS [31] might improve not only IPS, but also disability parameters and general quality of life.

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The literature reports overall CI rates in PwMS of 20-65% [3,32]. Our study found an overall CI prevalence of 32.3%, which aligns with most recent studies, albeit on the lower end of the spectrum. This difference may stem from the fact that our patient cohort was assessed at the time of diagnosis rather than later in the disease course. However, differences between CI rates in early and late disease stages remain unclear. Studies involving patients with established MS have reported CI rates between 27.2% and 59.5% [14,16,33], whereas those assessing newly diagnosed patients have found rates ranging from 20% to 49% [15,32,34-36]. This overlap may be related to variations in cognitive test batteries and CI definitions used across studies. For example, some studies define CI as a Z-score below -1.5 [16,34,35] or below 5th percentile [37] in at least 1 cognitive test, whereas others require impairment in at least 2 [15,33,36] or even 3 [32] tests. Aktas et al included patients with SDMT Z-scores ≤-0.5 but >-3.0 [14]. Differences in cognitive testing methodologies may further contribute to the variability in reported CI rates. Although many studies now use the BICAMS battery [16,34,36], others employ a combination of BICAMS and other tests, such as PASAT [37], COWAT [33], and partial BICAMS battery (SDMT and BVMT) with other tests [14] or only SDMT with other tests [35]. One study used Trail-Making Test A and Word List Generation [15].

Another factor influencing CI prevalence is the use of disease-modifying therapies (DMTs), which are frequently administered to patients with longer disease durations. Evidence suggests that DMTs can improve cognitive parameters to some extent [38]. To mitigate this, 1 study exclusively included patients who were not receiving natalizumab [37].

The median CSF NfL concentration in this study was consistent with values reported in published studies evaluated in a meta-analysis [34]. Although we did not measure CSF NfL levels in the CG, according to Yilmaz et al, our median was more than twice the upper normal range for individuals around age 30 (similar to our PwMS), but it falls within the normal range for individuals aged 60-70 years [9].

In line with previous studies, PwMS had significantly higher sNfL concentrations than the CG [8]. The CSF and sNfL concentrations showed a strong correlation, which is consistent with published findings [34]. Many studies have found that CSF and/or serum NfL correlates with various domains of cognitive impairment [39-43]. A recent meta-analysis has demonstrated that both CSF and serum NfL levels were associated with IPS outcomes [44]. However, we did not find a correlation between NfL levels and BICAMS test scores and found only a weak association between NfL and walking speed. In contrast, cognitive test results were inversely correlated with walking and manual dexterity scores.

Regression analysis showed that male sex was a significant predictor of worse CVLT-II results, a finding consistent with previous research from our center [45]. The NHPT and T25FWT scores were independent predictors of IPS, visual learning, and memory, but not for verbal learning or general CI. However, CSF NfL was significantly associated only with BVMT-R(-) and overall CI. These findings align with prior studies that reported weak correlations between higher sNfL [13] or CSF NfL levels [30] and impaired visuospatial memory and learning. However, in 1 of these studies, this trend was mainly observed in patients with secondary progressive MS.

Higher sNfL levels in regression models showed a tendency to predict allocation to the SDMT(-) group, although this association did not reach statistical significance. Aktas et al did not find an association between SDMT and sNfL levels [13], but Jakimovski et al did [15]. The lack of statistical significance in our study may be due to the relatively small sample size. However, the observed trend suggests that this relationship warrants further investigation.

One limitation of this study was the lack of control for neuropsychological parameters such as depression or fatigue, which are known to affect all cognitive domains assessed by the BICAMS [36,46]. Moreover, radiological measures, such as brain atrophy and lesion burden, were not included despite their established correlation with cognitive status [47,48]. A more detailed analysis of the association between NfL and SDMT or BVMT-R scores would require larger sample sizes. Longitudinal studies could help determine whether baseline NfL predicts future cognitive or disability parameters.

Conclusions

CSF NfL concentration, along with walking and manual dexterity measurements, may contribute to identifying early cognitive impairment in patients with MS, especially in the visual domain. In addition, the association of sNfL and IPS impairment also warrants further exploration. Larger-cohort studies are needed to confirm the predictive value of neurofilament light chain biomarkers in early MS.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

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