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Research Article

Neurofilament and Brain Atrophy and Their Association with Cognition in Multiple Sclerosis: A 10-Year Follow-Up Study

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Introduction. Cognitive impairment is an important contributor to disability in multiple sclerosis (MS). Disconnection of neuronal circuits due to axonal injury is probably an important underlying mechanism for this disability. Neurofilament light chain (NfL) is a neuron-specific constituent of axons and has gained increasing attention as a biomarker of axonal injury. *Objective.* To assess the association between NfL in serum (sNfL) and cerebrospinal fluid (cNfL) and cognitive function over 10 years and compare these associations with volumetric brain magnetic resonance imaging (MRI) measurements. *Methods*. Newly diagnosed MS patients were followed prospectively with baseline NfL and MRI as well as with clinical and cognitive assessments for up to 10 years. *Results*. Forty-one patients were included. Baseline sNfL correlated negatively with symbol digit modalities test (SDMT) at baseline ($r = -0.45$, $p = 0.005$), year 5 ($r = -0.41$, $p = 0.017$), and at year 10 ($r = -0.52$, $p = 0.008$). Baseline cNfL correlated with baseline SDMT ($r = -0.34$, $p = 0.030$) and SDMT at year 10 ($r = -0.44$, $p = 0.037$). Baseline volumes of whole brain ($r = 0.476$, $p = 0.002$), gray matter ($r = 0.467$, $p = 0.002$), T1 ($r = -0.627$, $p < 0.001$), and T2 lesion volumes ($r = -0.475$, $p = 0.002$) correlated significantly with baseline SDMT. Longitudinal analyses showed that both MRI volumes and EDSS were associated with the rate of SDMT decline, whereas sNfL and cNfL were not. *Conclusion*. NfL levels measured in serum and cerebrospinal fluid were both associated with cognitive functioning in MS patients over a 10-year period from diagnosis. However, MRI volumes correlated strongly in addition to the rate of cognitive decline.

1. Introduction

The symptoms of multiple sclerosis (MS) vary considerably among individuals due to the widespread effects of the disease on the central nervous system. For the past decades, cognitive impairment has been recognized to be an important factor in disability due to MS, with a major negative influence on daily living [1, 2]. Reports from the early

1990s showed that cognitive impairment is evident already in the early phases of the disease and is independent of physical disability [3, 4]. More recent studies have detected cognitive impairment even before the first acknowledged symptoms of the disease [5].

The mechanisms responsible for cognitive impairment in MS are not fully understood, but the disconnection of neuronal circuits due to axonal injury plays an important role in the impairment of specific cognitive domains [6]. Neurofilament light chain (NfL) is a neuron-specific constitute of the axonal cytoskeleton that is a promising biomarker for neuroaxonal damage. Upon axonal damage, NfL is released into the extracellular space and is found increased in both CSF (cNfL) and serum (sNfL) in several neurological disorders, including MS. [7] Over the course of the last years, the literature on the correlation of NfL with both radiological and clinical parameters in MS has increased. Greater NfL levels are correlated with brain atrophy and spinal cord volume loss [8], with disability as measured by the expanded disability status scale (EDSS) [9], with disease activity [10, 11], and have been associated with conversion to secondary progressive MS (SPMS) [12]. The use of disease-modifying therapy (DMT) has also been shown to reduce the levels of NfL [13].

Studies on the relationship between NfL and cognitive impairment in MS have shown divergent results [14–17]. A study from 2020 failed to show any significant links between sNfL and cognition [18], whereas a later study showed that sNfL in combination with measurement of cortical thickness could explain the cognitive performance in relapsing-remitting MS (RRMS) [19]. Several studies have found MRI variables to be associated with cognitive impairment, notably thalamic atrophy correlates strongly with both global and selective cognitive impairment [20, 21].

In this prospective longitudinal cohort study, we aimed to assess the association between NfL and cognitive function over a 10-year period. Secondarily, we aimed to compare this with the association between MRI and clinical data at the time of diagnosis of MS with changes in cognitive function over the 10-year period.

2. Methods

2.1. Patients. One hundred and eight patients diagnosed with MS in southwestern parts of Norway at the Haukeland and Stavanger University Hospitals in the years 1998-2000 were invited to participate in the study. In total, 41 patients who agreed to participate with a lumbar puncture in addition to blood work-up were included at the time of diagnosis. Baseline clinical assessment comprised a full neurological examination including EDSS scoring and assessment of clinical phenotype, as well as cognitive evaluation by the symbol digit modalities test (SDMT) that was conducted by the same examiner throughout the study period. SDMT is widely regarded as the preferred psychometric measure available for assessing cognitive processing speed in MS patients [22]. We defined impaired cognitive information processing speed (IPS) as scoring below 55 on the SDMT, as previously suggested by others [23].

Patients were reexamined after 5 and 10 years with both clinical and cognitive examinations. At the 5-year follow-up, two patients had died, four patients were lost to follow-up, and thus, 35 patients remained in the study. At the 10-year follow-up, an additional two participants had died, and another seven were lost to follow-up, leaving 26 patients for the analyses. All evaluations were conducted in a remitting phase of the disease course, with baseline evaluations conducted with a median of 9 months after the last attack (Table 1).

The study was approved by the Regional Committee for Medical and Health Research Ethics of Western Norway. All patients signed an informed written consent in accordance with the Helsinki Convention at the time of inclusion.

2.2. MRI. MRI scans were performed at baseline, after 5 and 10 years of follow-up using the same standardized study protocol at both centers. Scans were performed using 1.5 T (Siemens, Symphony/Philips Medical Systems, Intera) units. The MRI protocol consisted of dual spin echo (SE) proton density (PD)/T2-weighted imaging (WI), a three-dimensional (3D) T1-W1, and an SE T1-WI. Further details on the MRI procedures are provided in a previous publication [24].

2.3. Neurofilament Acquisition. CSF was collected at the baseline visit, as previously described [25, 26]. To measure the levels of cNfL, CSF samples were aliquoted and kept frozen at -70°C. The samples had gone through one freeze-thaw cycle before the concentration of cNfL was measured with a sensitive sandwich ELISA method (NF-light Elisa kit; Uman-Diagnostics AB, Umeå, Sweden) according to the kit instructions [27]. Intra-assay coefficients of variation were below 15%, and interassay coefficients of variation were below 10%.

Serum NfL (sNfL) concentration was measured using the NF-Light assay on a single molecule array (Simoa) HD-X Analyzer according to kit instructions from the manufacturer (Quanterix, Billerica, MA). All measurements were performed by board-certified laboratory technicians who were blinded to clinical data. The samples were analyzed in one round of experiments using one batch of reagents with intra-assay coefficients of variation below 10%.

2.4. Statistical Analysis. Normally distributed continuous variables are presented as means with standard deviations (SD), whereas variables that are not normally distributed are presented with medians and interquartile ranges (IQR). We used the Pearson correlation to assess the linear relationship between continuous variables. Variables were log transformed due to skewness, as reported.

The associations between longitudinal SDMT and baseline levels of sNfL and cNfL were assessed in linear mixed regression models with SDMT as the dependent variable and log-transformed NfL as the independent variable. Time of measurement was included as a categorical variable, and the interaction between NfL and time was added to assess differences in changes between baseline and 5 years, and between baseline and 10 years. Random intercepts and slopes were included in the model to allow for the correlation between repeated measurements on the same patients.

Table 1: Demographic and clinical characteristics at baseline and follow-up visits of multiple sclerosis patients.

	Baseline ($N = 41$)	5 years ($N = 35$)	10 years ($N = 26$)
Age in years at baseline, mean (SD)	41.6 (9.8)	41.0 (9.7)	41.0 (9.2)
Female, *n* (%)	30 (68)	24 (69)	19 (73)
cNfL at baseline in ng/mL	310 (102, 1144)	302 (103, 1086)	284 (91, 1115)
sNfL at baseline in pg/mL	11.8 (8.1, 17.3)[a]	11.7 (8.1, 17.5)[b]	11.2 (7.8, 17.1)[b]
Disease duration in months at baseline	60 (42, 174)	60 (36, 108)	60 (48, 108)
Months since the last attack at baseline	9 (1, 18)[b]	10 (1, 18)	10 (1, 22)
EDSS	3.5 (2.0, 4.0)	3.5 (2.0, 4.0)	3.0 (2.0, 5.0)
SDMT, mean (SD)	41.0 (12.3)[b]	41.5 (15.3)	45.5 (17.8)
Cognitive impairment, *n* (%)	33 (83)[b]	28 (80)	19 (73)
Highest education level, *n* (%)			
(i) Primary school	3 (7)	2 (6)	2 (8)
(ii) High school	22 (54)	20 (57)	13 (50)
(iii) College/university	16 (39)	13 (37)	11 (42)
Disease course, *n* (%)			
(i) RRMS	34 (83)	26 (74)	14 (54)
(ii) SPMS	7 (17)	9 (26)	8 (31)
(iii) PPMS*	0 (0)	0 (0)	4 (15)*
Patients on DMT, *n* (%)	6 (15)	17 (49)	17 (68)
(i) Interferons	5	11	7
(ii) Glatiramer acetate	1	5	3
(iii) Mitoxantrone		1	1
(iv) Natalizumab			3
(v) Fingolimod			1

Descriptives are presented as median (IQR) unless otherwise specified. [a]2 missing; [b]1 missing. *Reclassified at 10 years examination. Abbreviation: SD: standard deviation; IQR: interquartile range; sNfL: serum neurofilament light chain; cNfL: cerebrospinal neurofilament light chain; EDSS: expanded disability status scale; SDMT: symbol digit modalities test; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; DMT: disease modifying therapy.

Adjusted models included sex, age at baseline, higher education as a proxy for socioeconomic status (more than 9 years of primary school yes/no), and (log-transformed) disease duration assessed at baseline. Parameter estimates related to NfL are reported with 95% confidence intervals (CI) and tested with Wald tests.

Similar models were estimated for other baseline variables (i.e., selected MRI volumes and EDSS). The models were compared on the basis of Akaike's information criterion (AIC).

Predicted means of SDMT were plotted for selected percentile values of sNfL, T1 lesion volume, and EDSS.

We used $p < 0.05$ as cutoff for statistical significance.

All analyses were performed in Stata (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC), applying mixed functions, estat ic, margins and marginsplot, and SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

3. Results

3.1. Demographics and Clinical Characteristics. Baseline characteristics for the included 41 patients are presented in Table 1. Their mean age at baseline was 41.6 years (SD 9.8), and 30 (73%) patients were female. Thirty-four (83%) of the patients were regarded as RRMS and seven (17%) as SPMS at the time of diagnosis. At the 10-year follow-up, 4 of the SPMS patients were recategorized as primary progressive MS (PPMS). The median disease duration was 60 months at the time of diagnosis (IQR 42 to 174), and the median EDSS was 3.5 (IQR 2.0 to 4.0). The median time since the last attack at baseline was 9 months (IQR 1, 18). In total, six (15%) patients had initiated a DMT at baseline, and this proportion rose to 17 (49%) patients at the 5-year visit and 17 patients (68%) at the 10-year visit.

The median cNfL was 310 ng/mL (IQR 102 to 1144), and the median sNfL was 11.8 pg/mL (IQR 8.1 to 17.3) at baseline. Log-transformed cNfL and sNFL correlated strongly with $r = 0.71$ ($p < 0.001$) (Figure 1(a)).

Mean baseline SDMT was 41.0 (SD 12.3). The mean change in SDMT was -0.5 (SD 10.9) between the baseline and the 5-year follow-up and -0.7 (SD 9.5) between the baseline and the 10-year follow-up. Individual trajectories are plotted in Supplementary Figure S1.

At baseline, 16 (39%) patients had higher education, and 33 (83%) patients were considered as with impaired IPS as

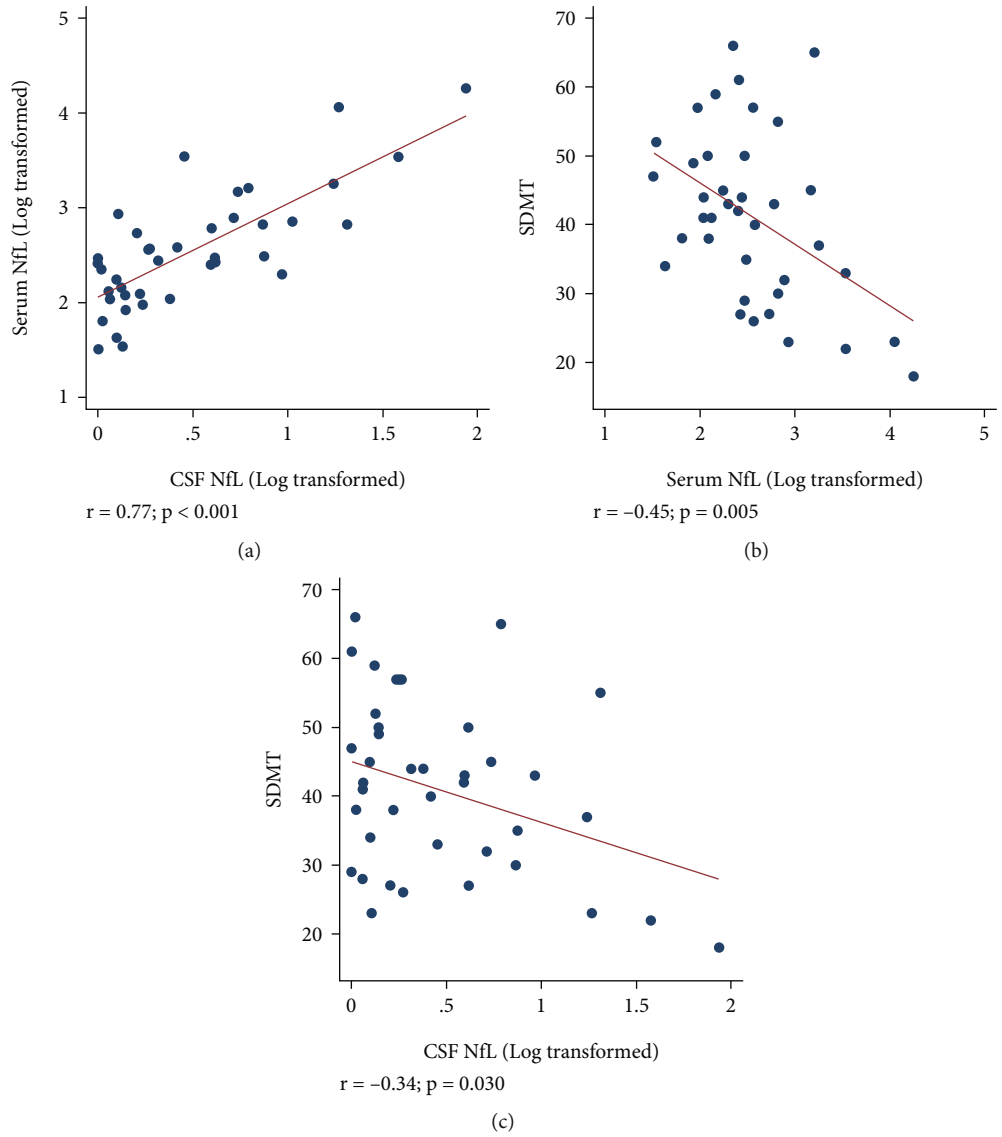


Figure 1: Scatter plots of baseline analyses (a) sNfL vs. cNfL ($n = 39$), (b) SDMT vs. sNfL ($n = 38$), and (c) SDMT vs. cNfL ($n = 40$) for patients with MS. Pearson's correlation coefficients indicated. Abbreviations: NfL: neurofilament light chain; CSF: cerebrospinal fluid; cNfL: CSF NfL; sNfL: serum NfL; SDMT: symbol digit modalities test.

per the SDMT. There were no statistically significant differences between cognitively impaired and cognitively preserved patients at baseline with regard to their level of sNfL, cNfL, age, sex, education level, disease duration, or EDSS at baseline.

3.2. Associations between NfL Levels and SDMT. A significant cross-sectional correlation was found between SDMT and log-transformed sNfL ($r = -0.45$, $p = 0.005$, Figure 1(b)), and a slightly lower correlation was found between SDMT and log-transformed cNfL ($r = -0.34$, $p = 0.030$, Figure 1(c)) at baseline. Significant cross-sectional correlations were also found between log-transformed baseline sNfL and SDMT at year 5 ($r = -0.41$, $p = 0.015$) and year 10 ($r = -0.51$, $p = 0.009$) and between log-transformed baseline cNfL and SDMT at year 10 ($r = -0.42$, $p = 0.023$), but not at year 5 ($r = -0.24$, $p = 0.187$).

In the longitudinal analyses, baseline sNfL was associated with SDMT during the 10-year observation period ($p < 0.001$, Table 2). For each one-unit higher log sNfL, expected baseline SDMT decreased by 9.5 points (β -9.5, 95% CI -15.5 to -3.4, $p = 0.002$), after adjustment for age, sex, higher education, and disease duration. Higher levels of sNfL were also associated with an increased rate of reduction in SDMT from baseline to 5 years and from baseline to 10 years, but none of these associations were statistically significant ($p = 0.249$ for a combined test). Baseline cNfL was also associated with longitudinal SDMT ($p = 0.005$) but provided a slightly poorer model fit (AIC 746 vs. 741). Predicted values of SDMT for the 10^{th}, 50^{th}, and 90^{th} percentile of sNfL are given in Figure 2(a).

3.3. Associations between MRI Volumes and SDMT. Cross-sectional analyses found that baseline T1 and T2 lesion

Table 2: Associations between longitudinal SDMT and baseline measures of NfL, MRI volumes, and EDSS in multiple sclerosis patients.

	Main effect		Effect on decline BL-5 years		Effect on decline BL-10 years		Overall	Interactions	Model fit
BL variable	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	p	p	AIC
sNfL	-9.5 (-15.5, -3.4)	.002	-2.7 (-8.4, 3.1)	.368	-4.9 (-10.6, 0.9)	.100	<.001	.249	741
cNfL	-14.3 (-22.9, -5.7)	.001	0.8 (-7.0, 8.5)	.847	-1.2 (-9.1, 6.8)	.775	.005	.902	746
WBV	0.053 (0.006, 0.099)	.027	0.051 (0.018, 0.085)	.002	0.040 (0.004, 0.077)	.031	<.001	.005	738
GMV	0.086 (0.011, 0.162)	.025	0.074 (0.023, 0.126)	.005	0.071 (0.022, 0.119)	.005	<.001	.003	737
T1 LV	-5.1 (-7.5, -2.6)	<.001	-1.6 (-4.1, 0.8)	.186	-3.6 (-5.9, -1.4)	.002	<.001	.007	726
T2 LV	-3.1 (-5.0, -1.2)	.001	-1.1 (-2.9, 0.7)	.224	-2.5 (-4.1, -0.9)	.003	<.001	.011	733
EDSS	-2.3 (-5.4, 0.8)	.150	-4.4 (-6.7, -2.2)	<.001	-1.1 (-3.8, 1.6)	.436	<.001	<.001	735

Results of linear mixed regression model. sNfL and cNfL values were log-transformed, and T1 and T2 lesion volumes were square root transformed. Models incorporated fixed effects of the baseline variable, time as a factor (comparing 5 years vs. baseline and 10 years vs. baseline), and the interaction between the baseline variable and time, as well as random intercepts and random effects of time. Main effects are estimated effects on SDMT at baseline. Adjusted for sex, age at baseline, higher education (yes/no), and log disease duration. Results based on 97 observations of 38 patients. Corresponding unadjusted estimates provided in Supplementary Table S1. Abbreviation: SDMT: symbol digit modalities test; NfL: neurofilament light chain; MRI: magnetic resonance imaging; EDSS: expanded disability status scale; BL: baseline; CI: confidence interval; AIC: Akaike information criterion; sNfL: serum NfL; cNfL: cerebrospinal NfL; WBV: whole brain volume; GMV: gray matter volume; LV: lesion volume.

volumes correlated significantly with baseline SDMT ($r = -0.627$, $p < 0.001$ and $r = -0.520$, $p < 0.001$, respectively), as did whole brain volume ($r = 0.476$, $p = 0.002$) and gray matter volume at baseline ($r = 0.467$, $p = 0.002$) with baseline SDMT. Similar cross-sectional correlations were found for later SDMT measurements. Baseline T1 lesion volume ($r = -0.551$, $p = 0.001$), T2 lesion volume ($r = -0.475$, $p = 0.004$), gray matter volume ($r = 0.572$, $p < 0.001$), and whole brain volume ($r = 0.605$, $p < 0.001$) all correlated significantly with SDMT at year 5. Baseline T1 lesion volume (-0.627, $p < 0.001$), T2 lesion volume (-0.520, $p = 0.001$), whole brain volume ($r = 0.476$, $p = 0.002$), and gray matter volume ($r = 0.467$, $p = 0.002$) correlated with SDMT at year 10.

In the longitudinal analyses, after adjusting for age, sex, education, and disease duration, a one-unit higher square root T1 lesion volume was statistically significantly associated with a decrease in expected baseline SDMT of 5.1 points (β -5.1, 95% CI -7.5 to -2.6, $p < 0.001$) and an increased rate of decline in SDMT from baseline to 10 years (difference in changes -3.6, 95% CI -5.9 to -1.4, $p = 0.002$).

3.4. Associations between EDSS and SDMT. Baseline EDSS correlated significantly with baseline SDMT ($r = -0.432$, $p = 0.005$) and 5-year SDMT ($r = -0.597$, $p < 0.001$), but not with 10-year SDMT ($r = -0.297$, $p = 0.141$). In the longitudinal analysis, there was a significant association between EDSS and SDMT ($p < 0.001$), but only a significant association between baseline EDSS and a decrease in SDMT between baseline and year 5 ($p < 0.001$, Table 2).

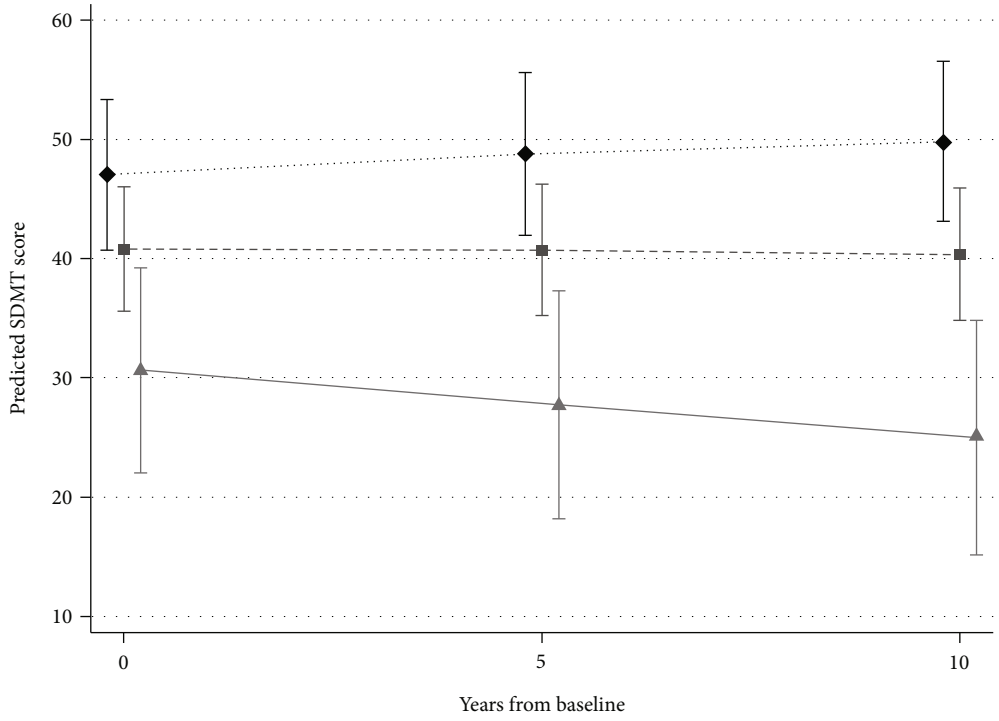
3.5. Compared Associations of NfL, MRI, and EDSS with Cognitive Performance. All baseline MRI volumes, including volumes of the whole brain, gray matter structures, T1 and T2 lesion volumes, and EDSS showed stronger associations with longitudinal SDMT than did baseline cNfL and sNfL, as evaluated by the model fit statistics. (Table 2) The model with baseline T1 lesion volume had the lowest AIC (726) and, thus, showed the strongest association with SDMT. Baseline EDSS was also associated with longitudinal SDMT ($p < 0.001$) in a model with AIC of 735, where higher baseline EDSS was statistically significantly associated with an increased rate of decline in SDMT from baseline to 5 years (β -4.4, 95% CI -6.7 to -2.2, $p < 0.001$). Predicted mean SDMT for percentiles of baseline T1 lesion volume and EDSS are given in Figures 2(b) and 2(c).

4. Discussion

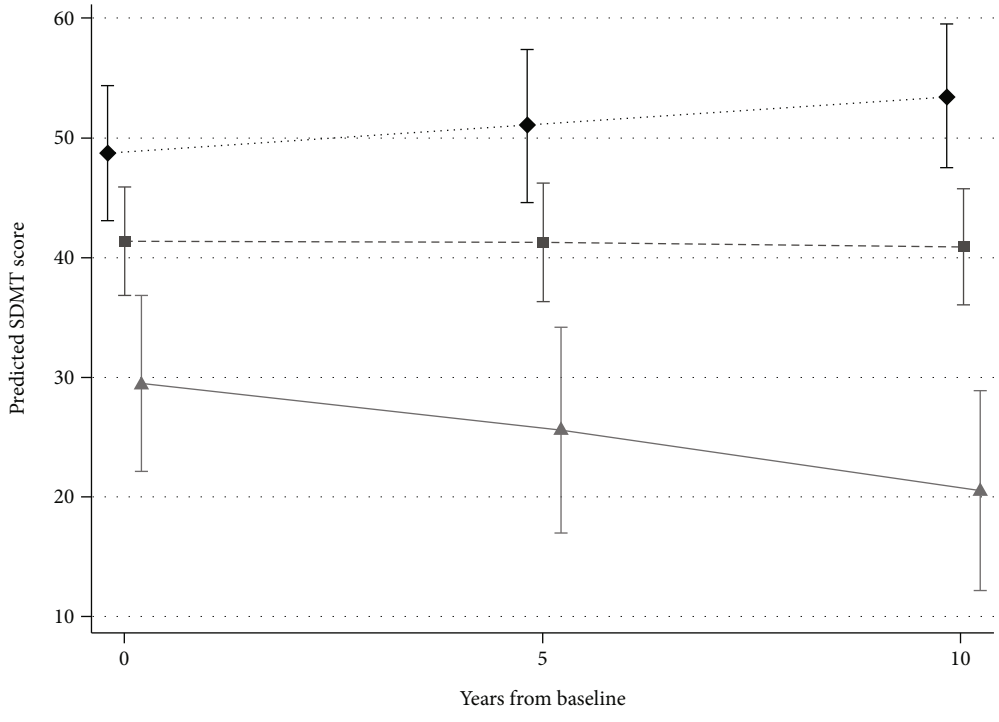
In this study, we show significant cross-sectional inverse correlations between baseline levels of NfL and SDMT scores at baseline and after 5 and 10 years in an unselected cohort of newly diagnosed MS patients, after adjusting for age, sex, higher education, and disease duration. However, based on the longitudinal analyses, although an association was seen between NfL and SDMT over the study period of 10 years, neither sNfL nor cNfL showed an association with longitudinal change in SDMT.

Previous reports on the association between NfL and cognition, as evaluated by SDMT, have been diverging, possibly due to the small sample size that accounts for most of the studies. One study demonstrated significant associations between SDMT and sNfL among MS patients followed for 5 years [28]. Similarly, others have also found NfL to be associated with cognitive processing speed in MS by measuring NfL in plasma [29], CSF [14], or by using different test protocols for cognitive processing speed than in our study [14, 30]. Conversely, a study from 2018 did not find any significant association between neither annual nor 10-year SDMT and sNfL [31], and yet another study showed no significant association between early measurement of sNfL and cNfL and cross-sectional baseline cognitive impairment, nor cognitive impairment after 9 years [15]. Several recent studies report a similar lack of association [15, 17, 18].

We found the association between the change in SDMT scores and baseline MRI volumes to be superior to that between NfL and SDMT. In particular, T1 and T2 lesion volumes at baseline showed the strongest associations with

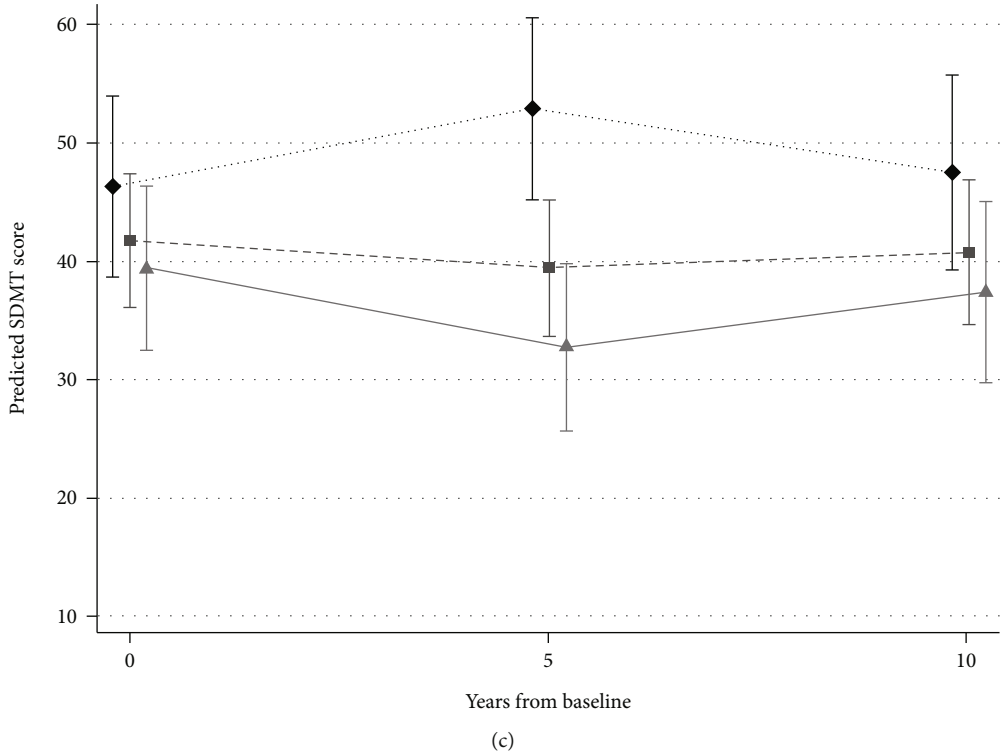


(a)



(b)

Figure 2: Continued.



(c)

Figure 2: Predicted values of SDMT for the 10th (diamonds, black dotted line), 50th (squares, dark gray dashed line), and 90th (triangles, light gray solid line) percentile values at baseline of (a) log-transformed sNfL, (b) square-rooted T1 lesion volume, and (c) EDSS. Percentile values for log-transformed sNfL were 1.81, 2.47, and 3.54, corresponding to concentrations of 6.1, 11.8, and 34.5 pg/mL. Percentile values for square-rooted T1 lesion volumes were 0.41, 1.86, and 4.21, corresponding to volumes of 0.2, 3.5, and 17.7 mL. Percentile values for EDSS were 1.5, 3.5, and 4.5. Results from linear mixed modelling with time (baseline, five years, 10 years) as a categorical variable. Covariate values fixed at female sex, age at baseline 41 years, no higher education, disease duration 60 months. Abbreviation: SDMT: symbol digit modalities test; sNfL: serum neurofilament light chain; CI: confidence interval.

subsequent SDMT changes. A previous study on a group of 45 stable patients with MS did not find a significant correlation between SDMT and sNfL but found that several cognitive test scores correlated with MRI volumes [18]. The biological process of NfL release into CSF and blood is related to acute injury, and although the observed half-life of NfL is several months, NfL release must be considered a temporal process, whereas MRI measures such as lesion load and atrophy reflect accumulated damage and, thereby, better predict outcomes such as cognitive impairment [32]. The relationship between cognitive impairment and MRI measures of lesion load and atrophy has been investigated in several studies, supporting our results [20, 33]. However, assessment of brain atrophy on clinical routine imaging is challenging and not commonly used in real-world settings [34]. The low cost and methodological advantages of obtaining serum samples, on the other hand, indicate the implementation of sNfL for routine use to be more feasible. Ongoing projects are underway to develop a routine analyzer platform, which will further increase the availability of sNfL for widespread use [35].

Interestingly, baseline EDSS showed a stronger association with SDMT than did NfL. Although EDSS is heavily focused on motor impairment in MS, previous reports have also linked EDSS progression to cognitive decline [36]. In our cohort, the association between EDSS and SDMT was probably influenced by both the long disease duration at inclusion and the low treatment rate at baseline.

The study strengths include the long follow-up time of 10 years of an unselected group of patients with newly diagnosed MS, who underwent volumetric MRI examinations and clinical and cognitive exams. The relatively low proportion of only 15% of patients on DMTs at baseline can also be regarded as a strength as this further allows for a better understanding of the relationship between NfL and clinical parameters, unbiased by treatment. Higher use of DMTs early in a longitudinally followed cohort should be expected to decrease both disease progression and NfL concentration [37]. Consequently, one would assume our cohort to display stronger associations with NfL than more recently collected cohorts with higher treatment rates and more effective therapies.

However, this study has several limitations. Firstly, the limited sample size, which unfortunately is also the case for most of the studies on this subject, renders the possibility of errors in the estimated associations between the evaluated measures, even if appropriate statistical tests are used. Additionally, there was a high dropout rate as 37% of the patients at baseline were lost at the 10-year follow-up. Furthermore, the study was initiated at a time when different criteria for

MS were used, effectively meaning an increased time before establishing a diagnosis, compared to the current McDonald criteria [38]. The median disease duration at baseline was 60 months, which might explain why 83% of the patients were defined as cognitively impaired already at baseline. This was a higher incidence of cognitive impairment among newly diagnosed patients compared with previous studies [14, 31]. Another trait of our cohort was the correspondingly low progression of the score at the 10-year follow-up, where the mean SDMT score had progressed from 41.0 at baseline to 45.5 after 10 years. In other words, our cohort consists of patients with a long disease duration, where they already, at the time of baseline, have suffered a substantial cognitive decline. In fact, seven patients had a progressive subtype at the time of diagnosis.

The lack of longitudinally collected samples of NfL further limits the interpretation of the relationship with cognition.

Another weakness is the limited cognitive testing performed on the participants and the lack of control for psychiatric comorbidities in the analyses. SDMT is regarded as the best method for assessing IPS in MS patients [22]. IPS is an important element of cognitive function, and its deficits influence several areas of cognition, such as working memory, executive functions, learning, and memory [39]. Deficits in IPS have been established as negative predictors of outcomes, including employment [40], car driving [41], and quality of life [42]. However, despite the sound validation of SDMT and the test being the most commonly recommended for cognitive screening among patients with MS [2], it is too narrow to be treated as a complete measure of cognition [43].

5. Conclusion

MRI volumetric measurements seem to predict cognitive performance better than NfL. NfL might thereby not be an optimal prognostic biomarker for cognitive impairment in MS, although methodical issues may interfere with our results. However, MRI volumetric measurements are currently not available for use in routine clinical settings, and sNfL measurements seem more feasible for clinical implementation. Studies with larger sample sizes and long-term follow-up, as well as the development of a more accessible analyzing platform, are called for.

Data Availability

Data is available by contacting the corresponding author.

Conflicts of Interest

Alok Bhan, Cecilie Jacobsen, Ingvild Dalen, Guido Alves, and Niels Bergsland have nothing to disclose. Kjell-Morten Myhr has received scientific advisory board or speaker honoraria from Biogen, Novartis, and Roche and has participated in clinical trials organised by Biogen, Merck, Novartis, Roche, and Sanofi. Henrik Zetterberg (HZ) is a Wallenberg Scholar supported by grants from the Swedish Research Council (#2018-02532), the European Research Council (#681712 and #101053962), the Swedish State Support for Clinical Research (#ALFGBG-71320), the Alzheimer Drug Discovery Foundation (ADDF), USA (#201809-2016862), the AD Strategic Fund and the Alzheimer's Association (#ADSF-21-831376-C, #ADSF-21-831381-C, and #ADSF-21-831377-C), the Bluefield Project, the Olav Thon Foundation, the Erling-Persson Family Foundation, Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (#FO2022-0270), the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 860197 (MIRIADE), the European Union Joint Programme – Neurodegenerative Disease Research (JPND2021-00694), and the UK Dementia Research Institute at UCL (UKDRI-1003). He has served on scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, ALZ-Path, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Passage Bio, Pinteon Therapeutics, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche; and is a cofounder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). Robert Zivadinov has received personal compensation from Bristol Myers Squibb, EMD Serono, Sanofi, Keystone Heart, Protembis, and Novartis for speaking and consultant fees. He has received financial support for research activities from Sanofi, Novartis, Bristol Myers Squibb, Octave, Mapi Pharma, Keystone Heart, Protembis, and V-WAVE Medical. Elisabeth Farbu has received scientific advisory board honoraria from Biogen, Sanofi Genzyme, Novartis, and Roche and has received an unrestricted grant from Novartis.

Supplementary Materials

Supplementary Figure S1: individual trajectories of SDMT scores over the study period of multiple sclerosis patients. Abbreviation: SDMT: symbol digit modalities test. Supplementary Table S1: unadjusted associations between longitudinal SDMT and baseline measures of NfL, MRI volumes, and EDSS in multiple sclerosis patients. *(Supplementary Materials)*

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