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RESEARCH

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Cognitive profile in Egyptian multiple sclerosis patients has no correlation with serum neurofilament level

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Abstract

Background Grey matter loss is thought to be the primary reason of cognitive disability in MS, with trans-synaptic axonal degeneration acting a supportive role. This research sought to evaluate cognitive profile of Egyptian multiple sclerosis patients and find out if it has a correlation with serum neurofilament or not.

Methods This was a cross-sectional research performed on a total of 60 patients with MS and 30 healthy controls. BICAMS battery of neuropsychological tests was used which includes SDMT, CVLT and BVMT. Serum NFLs using ELISA technique.

Results Mean ± SD of NFL in RRMS was 82.25 ± 170.9, in PPMS was 22.08 ± 7.26, in SPMS was 95.82 ± 187.5, and in control group was 56.65 ± 125.4, there was high statistical substantial variations among the different groups while there was non-statistical variation between RRMS and PPMS groups, also there was no variation between PPMS and SPMS with regard to serum level of NFL. There is no significant correlation between the NFL and different cognitive tests.

Conclusion Since sNfL did not strongly connect with cognitive function in MS patients, it is possible that it cannot be used as a substitute indicator for neuropsychological state in these groups.

Keywords Multiple sclerosis, Cognition, Neurofilament, NFL

Introduction

Multiple sclerosis (MS) is one of autoimmune diseases common in females more than males. It is a multifocal disease with various symptoms that may be motor, cerebellar, sensory, visual, and sphincter and many other rare symptoms [1].

One of the most important symptoms that gain attention nowadays is cognitive impairment. It may occur separately as cognitive relapse which needs attention and treatment by corticosteroids. Cognitive impairment affects all types of multiple sclerosis either in remitting relapsing type (RRMS), primary progressive and secondary progressive. It may occur early and start with the early pathogenic process of MS or it may occur lately with progression of the disease [2].

Some MS patients do not report any cognitive symptoms along their disease course which means that its pathogenesis remains elusive and not related to the course of the disease [3].

Multiple biomarkers are now available for activity and progression of the disease and associated cognitive affection. Neurofilament light chain (NFL) is considered one of the novel biomarkers for assessment of activity of the disease. It also increases in progressive stages of the disease [4].

Cognitive problems in patients with multiple sclerosis have not received much attention up to this point due to

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potential difficulties in identification in the usual clinical setting. Between 40 and 70 percent of MS patients experience cognitive impairment (CI) even in the early stages of the disease [5].

Cognitive abnormality in MS has been associated with both white matter (demyelinated lesions and white matter that appears normal) and grey matter (cerebral cortex, deep nuclei), with white matter loss being associated with deficits in working memory and mental speed of processing and grey matter atrophy being associated with deficits in verbal memory [6].

In this research, we sought to evaluate cognitive profile in Egyptian multiple sclerosis patients and find out if it has correlation with serum neurofilament or not.

Methods

60 multiple sclerosis patients are diagnosed clinically and radiologically according to McDonald's criteria [7] and 30 healthy controls. MS patients were being split in to two groups; 30 patients with PMS and 30 with RRMS, then the PMS group was further subdivided in to PPMS (15 patients) and SPMS (15 patients).

Complete history taking, including educational level, disease duration, age of onset, number of relapse, the current DMT used, compliance with the drug, switching or not. Disability assessment using expanded disability status scale (EDSS) [8]. Timed 25 walk test (25WT) and 9 peg hole test (9PHT). Self-report of cognitive complains using perceived deficit questionnaire (PDQ) [9].

Neuropsychological tests were done for assessment of cognition using Arabic version brief international cognitive assessment for MS (BICAMS). Symbol digit modality test is part of the BICAMS battery, reversed visuospatial memory (BVMTR) exam and the California verbal learning test (CVLT) [10].

Depression anxiety and stress scale 21 (DASS) score for evaluation of depression, stress and anxiety. Fatigue scale for motor and cognitive functions (FSMC) with its mental and physical subscale [11].

The amount of neurofilament light chain (NFL) in human serum was measured using the sandwich-ELISA method. The micro-ELISA plate that comes with this kit has been pre-coated with a human NEFL-specific antibody. The micro-ELISA plate wells are filled with benchmarks, specimens, and a particular antibody. After that, an avidin-horseradish peroxidase (HRP) mixture and a biotinylated detecting antibody specific for Human NEFL are added to each microplate well. Free pieces are removed from the wash. Into each well, the substrate solution is poured. The only wells that will be blue in color include human NEFL, biotinylated detect antibody, and avidin-HRP conjugated. When stop solution is added, the enzyme–substrate process is halted, and the color becomes yellow. The optical density (OD) is determined spectrophotometrically at a wavelength of 450 nm ± 2 nm. The degree of human NEFL directly correlates with the variation in OD value. The amount of human NFL in the samples is determined by comparing the OD of the samples to the reference curve.

Statistical analysis of the data

Data have been fed to the laptop and analyzed the use of IBM SPSS software program package deal model 20.0. (Armonk, NY: IBM Corp) Qualitative information have been defined the use of quantity and percent. The Shapiro–Wilk was used to confirm the normality of distribution of variables. Significance of the acquired consequences changed into judged on the 5% level.

The used checks were Chi-square test for categorical variables, to examine among specific groups, Fisher's Exact or Monte Carlo correction for Chi-square while extra than 20% of the cells have predicted much less than 5, one-way ANOVA test for generally disbursed quantitative variables, to examine among extra than groups, and post hoc test (Tukey) for pairwise comparisons, Kruskal–Wallis test for no longer generally disbursed quantitative variables, to examine among extra than studied groups and post hoc test (Dunn's) for pairwise comparisons, Mann–Whitney test for no longer generally disbursed quantitative variables, to examine among studied groups, Student's *t*-test for generally disbursed quantitative variables, to examine among studied groups, Spearman coefficient to correlate among disbursed no longer generally quantitative variables and linear regression analysis to hit upon the maximum independent/ affecting element for affecting different cognitive tests.

Results

Demographic data and clinical features

The mean age of RRMS patients was 33.33 ± 6.84 years old, compared to 41.43 ± 8.89 years for PMS and 35.50 ± 8.70 years for the control group. There were non-statistically substantial variations between the three groups with regard to each of the education level and there was a statistical variation between the three groups with regard to gender, with the majority of RRMS patients being females (Table 1).

There were great statistically substantial variations between the RRMS group and subdivided groups of PMS regarding the age of onset of disease, where it was at a lower age among the RRMS group, followed by the SPMS group, while it was at an older age in the PPMS group, furthermore, as regards disease duration; there was high statistically substantial variations between the three groups where it was of longest

Table 1 Comparison of the three analyzed groups based on demographic information

	RRMS (*n* = 30)		PMS (*n* = 30)		Control (*n* = 30)		Test of Sig	*p*
	No.	%	No.	%	No.	%		
Gender								
Males	5	16.7	14	46.7	7	23.3	$\chi^2 = 7.248^*$	0.027*
Females	25	83.3	16	53.3	23	76.7		
Age (/years)								
Min.–Max	25.0–51.0		22.0–60.0		18.0–50.0		$F = 7.857^*$	0.001*
Mean ± SD	$33.33^b \pm 6.84$		$41.43^a \pm 8.89$		$35.50^b \pm 8.70$			
Median (IQR)	33.0 (27.0–36.0)		43.0 (36.0–48.0)		32.0 (28.0–44.0)			
Sig. bet. grps	$p_1 = 0.001^*$, $p_2 = 0.564$, $p_3 = 0.017^*$							
Education								
Low	3	10.0	6	20.0	6	20.0	$\chi^2 = 2.059$	0.725
Medium	14	46.7	15	50.0	14	46.7		
High	13	43.3	9	30.0	10	33.3		

Means with common letters are not significant (i.e., means with different letters are significant)

IQR inter-quartile range, *SD* standard deviation, χ^2 Chi-square test

F F for one-way ANOVA test, pairwise comparison bet. each 2 groups was done using Post Hoc Test (Tukey)

p: *p* value for comparing between the three studied groups

p_1: *p* value for comparing between RRMS and PMS

p_2: *p* value for comparing between RRMS and control

p_3: *p* value for comparing between PMS and control

* Statistically significant at $p \leq 0.05$

duration among SPMS patients, also as regards EDSS; there were high statistically substantial variations between groups where it was lower in the RRMS group and higher mean in SPMS (Table 2).

Table 3 shows that there were high statistically substantial variations between the RRMS group and PMS as regards each of 25 FWT, right 9PHT, and Left 9PHT which were higher among patients with PMS than in RRMS patients.

Regarding DASS score, it was noticed that the total score was significantly high in the RRMS group with a median 27.5 (p value = 0.013), including its subscales, anxiety, stress and depression (Table 4).

The same for FSMC which showed a statistically significant increase in both RRMS and PMS in comparison to the control group (p values = 0.001, 0.001, respectively) (Table 5).

Cognitive assessment results and its correlation

Table 6 describes mean ± SD. Of SDMT was 35.07 ± 13.42, 25.53 ± 9.10 and 53.43 ± 8.68 among patients with RRMS, PMS and control, respectively, and there was high statistical substantial variations between different groups which was higher among patients with RRMS and lower level among PMS group.

Furthermore, there were high statistical substantial variations between three groups with regard to each of immediate recall, short term tall, short term cued, long term cued and long term total which were of higher level in RRMS group, and with regard to total BVMT; mean ± SD. Was 17.27 ± 9.05, 13.07 ± 7.54 and 24.30 ± 3.64 in RRMS, PMS and control groups, respectively, with high statistical substantial variations between three groups.

Correlation between SDMT and EDSS in each groups

Group I (RRMS) showed high substantial negative connection between SDMT and age, BMI, EDSS and relapses number, and in group II (PMS); there were non-significant correlation between SDMT and other variables of patients except as regards EDSS, there was negative significant correlation between SDMT and EDSS (Fig. 1).

Regression analysis for cognitive tests

Univariate analysis (Table 7) showed a significant effect of several parameters on SDMT such as type of MS, age and age of onset, educational level and EDSS. On multivariate it was found that EDSS has significant and independent effect on SDMT.

Table 2 Comparison of the three study groups based on several clinical data

	RRMS ($n=30$)		PPMS ($n=15$)		SPMS ($n=15$)		Test of Sig.	*p*
	No.	%	No.	%	No.	%		
Age at onset (/years)								
Min.–Max	18.0–43.0		19.0–50.0		18.0–40.0		$F=9.765^{*}$	$<0.001^{*}$
Mean ± SD	$24.93^{b} \pm 6.71$		$36.13^{a} \pm 10.03$		$28.60^{b} \pm 8.24$			
Median (IQR)	23.0 (20.0–29.0)		35.0 (28.50–45.50)		27.0 (21.0–36.0)			
Sig. bet. grps	$p_1<0.001^{*}, p_2=0.324, p_3=0.033^{*}$							
Disease duration (/years)								
Min.–Max	3.0–21.0		3.0–14.0		4.0–21.0		$H=10.521^{*}$	0.005^{*}
Mean ± SD	8.40 ± 4.52		6.07 ± 3.92		12.07 ± 5.96			
Median (IQR)	7.0^{ab} (5.0–11.0)		4.0^{b} (3.0–8.0)		10.0^{a} (7.0–16.5)			
Sig. bet. grps	$p_1=0.065, p_2=0.057, p_3=0.001^{*}$							
EDSS								
Min.–Max	1.50–6.0		5.0–7.0		5.50–6.50		$H=42.250^{*}$	$<0.001^{*}$
Mean ± SD	3.18 ± 1.28		5.87 ± 0.44		6.07 ± 0.32			
Median (IQR)	2.75^{b} (2.0–4.0)		6.0^{a} (5.50–6.0)		6.0^{a} (6.0–6.25)			
Sig. bet. grps	$p_1<0.001^{*}, p_2<0.001^{*}, p_3=0.412$							

Means/medians with common letters are not significant (i.e., means/ medians with different letters are significant)

IQR inter-quartile range, *SD* standard deviation, χ^2: Chi-square test

F: *F* for one-way ANOVA test, pairwise comparison bet. each 2 groups was done using post hoc test (Tukey)

H: *H* for Kruskal–Wallis test, pairwise comparison bet. each 2 groups was done using post hoc test (Dunn's for multiple comparisons test)

p: *p* value for comparing between the three studied groups

p_1: *p* value for comparing between RRMS and PPMS

p_2: *p* value for comparing between RRMS and SPMS

p_3: *p* value for comparing between PPMS and SPMS

* Statistically significant at $p \leq 0.05$

The same different parameters affecting total recall immediate and total BVMT test; type of MS especially RRMS, age of patients, female and male gender, and EDSS are factors affect total immediate recall (Fig. 2)

Age of patients and EDSS only parameters that affect total BVMT significantly and EDSS is the only factor affecting it independently (Fig. 3).

Neurofilament levels and its correlations with different parameters

Figure 4 shows that mean ± SD. Of NFL in RRMS was 82.25 ± 170.9, in PPMS was 22.08 ± 7.26, in SPMS was 95.82 ± 187.5, and in control group was 56.65 ± 125.4, there was high statistical substantial variations between the different groups while there were non- statistical variations between RRMS and PMS groups. There were variations between PPMS and SPMS as regards serum level of NFL.

Table 3 Comparison of the two groups under investigation regarding 25 WT and 9PHT

	RRMS (*n* = 30)	PMS (*n* = 30)	*U*	*p*
25 FWT				
Min.–Max	6.0–26.50	11.0–190.0	69.0*	< 0.001*
Mean ± SD	10.98 ± 5.24	41.38 ± 40.98		
Median (IQR)	9.50 (7.0–12.50)	25.50 (19.0–44.0)		
Right 9PHT				
Min.–Max	18.50–55.0	22.0–148.0	181.50*	< 0.001*
Mean ± SD	28.08 ± 7.98	44.45 ± 25.30		
Median (IQR)	24.75 (22.50–33.0)	36.50 (29.50–55.0)		
Left 9PHT				
Min.–Max	16.50–116.0	26.0–162.0	118.0*	< 0.001*
Mean ± SD	32.73 ± 17.02	56.32 ± 31.28		
Median (IQR)	28.75 (25.50–33.0)	47.0 (37.0–60.0)		

IQR inter-quartile range, *SD* standard deviation, *U* Mann–Whitney test

p: *p* value for comparing between the two studied groups

* Statistically significant at $p \leq 0.05$

Also there were no any significant correlation between serum neurofilament level and any cognitive tests used (Table 8).

There were non-statistical substantial variations between both switched or ongoing DMT and the serum level of NFL in both MS groups (Table 9).

Discussion

MS is common in middle-aged females as in the current study with statistical variations between three groups as regards gender where most patients with RRMS were females, the median age of RRMS patients was higher than the mean age in PMS in agreement with literatures [3, 12].

Furthermore, in our study, there was high statistical substantial variations between RRMS group and subdivided groups of PMS as regards age of onset of disease where it was lower among RRMS patients and the oldest age in PPMS group. Furthermore, with regard to disease duration; it was of longest duration among SPMS patients, also with regard to EDSS, it was lower in RRMS group and highest in PPMS.

In consistence with our findings, the study of Hussein et al. 12 there were 400 confirmed cases of multiple sclerosis, including two-thirds women and one-third men. The average age at illness start was 28.42 ± 8.48. The patients' average age was 32.59 ± 9.41 years, while the average age of illness start was 28.42 ± 8.48 years.

Egyptian research by Hashim et al. [13] which was conducted at Cairo University revealed that the average age of illness beginning in females was 27.7 ± 7.99 years old, whereas it was 29.02 ± 2.63 years old in males.

As opposed to that, the research of Filippatou et al. [14] reported that age differences between RRMS patients and controls were not statistically substantial, although PMS patients were older than the other groups.

In the present investigation, the mean NFL in RRMS was higher than PMS but not statistically significant. There were significant statistical variations between MS groups and control group. There were variations between PPMS and SPMS as regards serum level of NFL but not statistically significant. In comparison with the study of Aktas et al. [15] which reported that the median NFLs value was 16.02 pg/mL, whereas those with SPMS had greater significant values ($U = 67.0$, $p = 0.038$, $r = -0.308$; RRMS: median = 12.00 pg/mL, SPMS: median = 20.00 pg/mL).

Another research by Bridel et al. [16] revealed that the mean ± SD. of NFL in healthy control was 7.1 (2.9), the mean ± SD. of NFL in RRMS was 14.4 (9.8), in PPMS was 14.5 (5.8), in SPMS was 13.1 (7.6). At baseline, NFLs was comparable among MS subtypes but greater in all MS subtypes compared to HC.

In the current study, there were non-statistical substantial variations between both switched and ongoing disease-modifying therapy and the serum level of NFL in both MS groups. Early research suggests that sNfL levels may be able to distinguish between various therapies at the level of patient groups [17] In one analysis of Novakova et al. [18] after an average follow-up of 12 months, patients who switched between disease-modifying medicines with equivalent effectiveness had stable NFLs levels, compared to patients who advanced to therapies with greater efficacies.

Patients beginning highly active immunotherapies had greater NFLs levels at treatment onset than those starting on mild/moderate treatments, confirming, and extending these results. This causes a bigger relative reduction once therapy starts [19, 20] so, baseline sNfL levels were able to predict the number of future therapy changes as well as therapy intensifications.

Table 4 Comparison between the three studied groups according to DASS score

	Group I ($n=30$)	Group II ($n=30$)	Group III ($n=30$)	*H*	*p*
DASS total score					
Min.–Max	4.0–63.0	2.0–67.0	4.0–49.0	6.746*	0.034*
Mean ± SD	31.17 ± 15.82	24.33 ± 16.11	20.87 ± 12.57		
Median (IQR)	27.50[a](16.0–43.0)	22.0[ab] (11.0–32.0)	19.50[b](11.0–28.0)		
Sig. bet. grps	$p_1=0.059$, $p_2=0.013^*$, $p_3=0.546$				
Anxiety					
Min.–Max	2.0–24.0	2.0–16.0	0.0–30.0	5.581	0.061
Mean ± SD	10.43 ± 5.93	7.07 ± 4.43	8.30 ± 8.38		
Median (IQR)	10.0[a] (6.0–13.0)	6.0[a] (4.0–9.0)	7.50[a] (1.0–11.0)		
Stress					
Min.–Max	1.0–32.0	0.0–19.0	1.0–40.0	8.426*	0.015*
Mean ± SD	14.23 ± 8.45	8.77 ± 5.01	9.90 ± 8.58		
Median (IQR)	12.0[a] (8.0–19.0)	8.0[b] (5.0–12.0)	7.0[b] (4.0–15.0)		
Sig. bet. grps	$p_1=0.015^*$, $p_2=0.010^*$, $p_3=0.882$				
Depression					
Min.–Max	1.0–36.0	0.0–21.0	1.0–28.0	6.629*	0.036*
Mean ± SD	12.83 ± 9.70	7.97 ± 5.14	7.83 ± 6.93		
Median (IQR)	11.50[a] (5.0–15.0)	6.50[ab] (4.0–11.0)	5.50[b] (4.0–4.0)		
Sig. bet. grps	$p_1=0.070$, $p_2=0.013^*$, $p_3=0.496$				

Medians with common letters are not significant (i.e., medians with different letters are significant)

IQR inter-quartile range, *SD* standard deviation

H: *H* for Kruskal–Wallis test, pairwise comparison bet. each 2 groups was done using post hoc Test (Dunn's for multiple comparisons test)

p: *p* value for comparing between the three studied groups

p_1: *p* value for comparing between Group I and Group II

p_2: *p* value for comparing between Group I and Group III

p_3: *p* value for comparing between Group II and Group III

* Statistically significant at $p \leq 0.05$

Group I: RRMS

Group II: PMS

Group III: Control

These results are also consistent with the research of Bridel et al. [16] which revealed that mean NFLs was higher in all MS subtypes when compared to HC ($p<0.0001$) and was more favorably correlated with age in HC ($r=0.70$, $p<0.001$). Median NFLs was reduced in untreated RRMS and treated RRMS ($p=0.036$) and higher in HC (p 0.001) at follow-up compared to baseline. HC (50.0%), untreated RRMS (51.4%), treated RRMS (33.3%), SPMS (45.0%), and PPMS (46.2%) all showed differences in NFLs levels at follow-up that were more than 20% from baseline values.

In the present research, there was no statistically substantial relationship between the serum concentration of NFL and any of the following variables in either group of MS patients: age, BMI, duration of illness, EDSS, or age of disease onset; however, there was a substantial inverse relationship between the serum level of NFL and the number of relapses in the PMS group of patients.

In compliance with our results, the investigation of Aktas et al. [15] found no association between NFLs either the RRMS or SPMS subsamples, nor with age, sex, educational level, EDSS score, age at illness start, subtype of MS, immunotherapy categorization, time since last relapse, time since last changes in immunomodulatory medication. They found also no correlation between serum neurofilaments and different cognitive tests as our results. Other results found a correlation between CI and neurofilament level in CSF sample mainly which may be

Table 5 Comparison between the three studied groups according to FSMC

	Group I ($n=30$)	Group II ($n=30$)	Group III ($n=30$)	*F*	*p*
FSMC total score					
Min.–Max	39.0–100.0	35.0–95.0	28.0–78.0	18.827*	< 0.001*
Mean ± SD	72.03[a] ± 14.60	70.50[a] ± 15.91	49.93[b] ± 16.17		
Median (IQR)	74.5(66.0–82.0)	72.0 (64.0–81.0)	48.5(33.0–61.0)		
Sig. bet. grps	$p_1=0.923$, $p_2<0.001^*$, $p_3<0.001^*$				
Mental subscale					
Min.–Max	13.0–58.0	13.0–45.0	14.0–45.0	8.622*	< 0.001*
Mean ± SD	32.07[a] ± 8.94	29.67[a] ± 8.45	23.37[b] ± 7.71		
Median (IQR)	32.0 (27.0–36.0)	29.0 (25.0–35.0)	20.0 (18.0–30.0)		
Sig. bet. grps	$p_1=0.511$, $p_2<0.001^*$, $p_3=0.013^*$				
Physical subscale					
Min.–Max	23.0–55.0	15.0–56.0	10.0–46.0	19.482*	< 0.001*
Mean ± SD	39.97[a] ± 8.79	40.83[a] ± 10.12	26.57[b] ± 10.76		
Median (IQR)	40.0 (34.0–48.0)	42.50 (36.0–48.0)	25.50 (18.0–33.0)		
Sig. bet. grps	$p_1=0.939$, $p_2<0.001^*$, $p_3<0.001^*$				

Means with common letters are not significant (i.e., means with different letters are significant)

IQR: inter-quartile range, SD: standard deviation

F: *F* for one-way ANOVA test, pairwise comparison bet. each 2 groups was done using post hoc test (Tukey)

p: *p* value for comparing between the three studied groups

p_1: *p* value for comparing between Group I and Group II

p_2: *p* value for comparing between Group I and Group III

p_3: *p* value for comparing between Group II and Group III

* Statistically significant at $p \leq 0.05$

Group I: RRMS

Group II: PMS

Group III: Control

more accurate than serum samples [21, 22]. Other studies proved that neurofilament level were elevated in MS patients and correlated with CI in MS patients [23, 24]. Different cognitive tests used, and different sample sizes may be the factor behind this controversies.

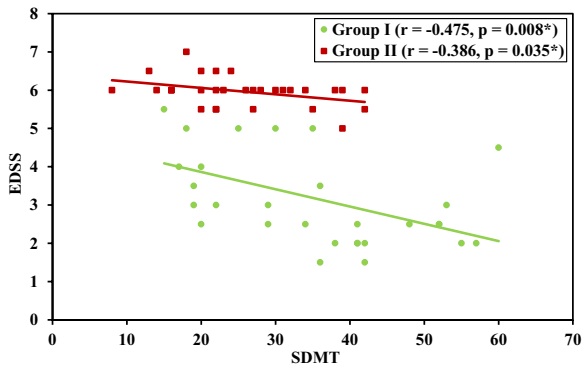

Fig. 1 Correlation between SDMT and EDSS in each group. Group I: RRMS, Group II: PMS

Most of studies used different method for detection neurofilament which is single-molecule array (Simoa) assay and quantified in picograms per milliliter in contrary to ours using ELISA methods which may affect results so, still questionable if NFL is a marker for axonal damage or degeneration and progression [25].

In line with our results of cognitive tests, Montaser et al. [17] found a very substantial variation between the subgroups of MS patients and the control group with respect to SDMT, with SPMS being more impacted than RRMS. In the present study, in group I (RRMS); there was high substantial negative relationship between SDMT and age, BMI, EDSS and number of relapses, and in group II (PMS); there were non-significant correlation between SDMT and other variables of patients except as regards EDSS, there was negative substantial connection between SDMT and EDSS.

Vázquez-Marrufo et al. [26] in which a statistical investigation revealed that several factors had meaningful connections. The moderate connection between SDMT and EDSS ($r=-0.679$, $p=0.0009$) was noteworthy.

Table 6 Comparison between the studied groups with subdivisions regarding BICAMs battery

	RRMS ($n=30$)	PPMS ($n=15$)	SPMS ($n=15$)	Control ($n=30$)	Test of Sig.	p
SDMT						
Min.–Max	15.0–60.0	14.0–42.0	8.0–39.0	33.0–69.0	$F=37.090^{*}$	$<0.001^{*}$
Mean ± SD	$35.07^{b} \pm 13.42$	$28.53^{bc} \pm 9.32$	$22.53^{c} \pm 8.09$	$53.43^{a} \pm 8.68$		
Median (IQR)	35.50 (22.0–42.0)	27.0 (21.0–36.0)	22.0 (18.0–26.0)	52.0 (49.0–60.0)		
Sig. bet. Grps	$p_1=0.210$, $p_2=0.002^{*}$, $p_3<0.001^{*}$, $p_4=0.406$, $p_5<0.001^{*}$, $p_6<0.001^{*}$					
Immediate recall (CVLT)						
Total						
Min.–Max	37.0–72.0	35.0–65.0	30.0–63.0	50.0–74.0	$F=12.449^{*}$	$<0.001^{*}$
Mean ± SD	$56.17^{b} \pm 9.43$	$50.27^{bc} \pm 8.66$	$47.27^{c} \pm 11.50$	$62.40^{a} \pm 6.20$		
Median (IQR)	55.5 (49.0–63.0)	50.0 (44.0—58.50)	48.0 (36.0–58.0)	62.5 (59.0–67.0)		
Sig. bet. Grps	$p_1=0.152$, $p_2=0.010^{*}$, $p_3=0.035^{*}$, $p_4=0.784$, $p_5<0.001^{*}$, $p_6<0.001^{*}$					
Short term recall						
Short term total recall						
Min.–Max	7.0–16.0	4.0–16.0	5.0–13.0	12.0–16.0	$F=16.037^{*}$	$<0.001^{*}$
Mean ± SD	$12.10^{a} \pm 2.56$	$10.0^{b} \pm 3.30$	$8.80^{b} \pm 3.32$	$13.73^{a} \pm 1.11$		
Median (IQR)	13.0 (10.0–14.0)	10.0 (9.0–12.0)	7.0 (6.0–12.50)	14.0 (13.0–14.0)		
Sig. bet. Grps	$p_1=0.044^{*}$, $p_2<0.001^{*}$, $p_3=0.061$, $p_4=0.553$, $p_5<0.001^{*}$, $p_6<0.001^{*}$					
Short term cued Recall						
Min.–Max	9.0–16.0	10.0–16.0	7.0–16.0	14.0–16.0	$F=10.235^{*}$	$<0.001^{*}$
Mean ± SD	$13.70^{b} \pm 2.09$	$13.40^{b} \pm 1.88$	$12.33^{b} \pm 2.74$	$15.37^{a} \pm 0.72$		
Median (IQR)	14.0 (13.0–16.0)	13.0 (12.50–14.50)	13.0 (10.0–14.0)	15.50(15.0–16.0)		
Sig. bet. Grps	$p_1=0.956$, $p_2=0.099$, $p_3=0.004^{*}$, $p_4=0.399$, $p_5=0.006^{*}$, $p_6<0.001^{*}$					
Long term recall						
Long term total recall						
Min.–Max	4.0–16.0	4.0–16.0	3.0–16.0	12.0–16.0	$F=7.117^{*}$	$<0.001^{*}$
Mean ± SD	$12.43^{ab} \pm 3.34$	$11.13^{bc} \pm 3.46$	$9.87^{c} \pm 4.17$	$13.97^{a} \pm 1.22$		
Median (IQR)	12.50 (10.0–16.0)	12.0 (9.50–13.0)	11.0 (6.0–13.0)	14.0 (13.0–15.0)		
Sig. bet. Grps	$p_1=0.523$, $p_2=0.041^{*}$, $p_3=0.206$, $p_4=0.658$, $p_5=0.019^{*}$, $p_6<0.001^{*}$					
Long term cued recall						
Min.–Max	9.0–16.0	11.0–16.0	8.0–16.0	14.0–16.0	$F=6.537^{*}$	$<0.001^{*}$
Mean ± SD	$14.60^{ab} \pm 1.79$	$13.67^{bc} \pm 1.84$	$13.0^{c} \pm 2.85$	$15.27^{a} \pm 0.69$		
Median (IQR)	15.0 (14.0–16.0)	14.0 (12.50—15.0)	14.0 (11.50–15.50)	15.0 (15.0–16.0)		
Sig. bet. Grps	$p_1=0.345$, $p_2=0.026^{*}$, $p_3=0.465$, $p_4=0.730$, $p_5=0.026^{*}$, $p_6=0.001^{*}$					
Total BVMT						
Min.–Max	2.0–33.0	1.0–27.0	1.0–27.0	18.0–29.0	$H=29.403^{*}$	$<0.001^{*}$
Mean ± SD	17.27 ± 9.05	15.60 ± 7.94	10.53 ± 6.39	24.30 ± 3.64		
Median (IQR)	17.50^{b}(10.0–26.0)	17.0^{bc} (9.50–20.0)	9.0^{c} (6.50–13.0)	24.0^{a} (21.0–28.0)		
Sig. bet. Grps	$p_1=0.481$, $p_2=0.015^{*}$, $p_3=0.001^{*}$, $p_4=0.137$, $p_5=0.001^{*}$, $p_6<0.001^{*}$					

Means with common letters(a-a)(b-bc) are not significant (i.e., means with different letters(a-b) are significant

BVMT brief visuospatial memory test, *SDMT* symbol digit modality test, *CVLT* California verbal learning test, *IQR* inter-quartile range, *SD* standard deviation

F: *F* for one-way ANOVA test, pairwise comparison bet. Each 2 groups was done using post hoc test (Tukey)

H: *H* for Kruskal–Wallis test, pairwise comparison bet. Each 2 groups was done using post hoc test (Dunn's for multiple comparisons test)

p: p value for comparing between the four studied groups, p_1: p value for comparing between RRMS and PPMS

p_2: p value for comparing between RRMS and SPMS, p_3: p value for comparing between RRMS and control

p_4: p value for comparing between PPMS and SPMS, p_5: p value for comparing between PPMS and control

p_6: p value for comparing between SPMS and control

*Statistically significant at $p \leq 0.05$

Table 7 Univariate and multivariate linear regression analysis for the parameters affecting SDMT ($n=60$) for total patients

	Univariate		#Multivariate	
	p	B (LL–UL 95%C.I)	*p*	B (LL–UL 95%C.I)
Type of MS [RRMS]	0.002*	9.533 (3.609 to 15.458)	0.268	– 5.552 (– 15.488 to 4.384)
Age (/years)	0.012*	– 0.450 (– 0.796 to – 0.103)	0.459	– 0.224 (– 0.828 to 0.379)
Female	0.364	3.135 (– 3.730 to 10.00)		
Male	0.364	– 3.135 (– 10.00 to –3.730)		
Increasing in Education level	0.020*	5.361 (0.885 to 9.838)	0.113	3.351 (– 0.823 to 7.525)
Age at onset (/years)	0.048*	– 0.347 (– 0.691 to – 0.004)	0.863	0.049 (– 0.514 to 0.612)
Disease duration (/years)	0.447	– 0.239 (– 0.862 to 0.385)		
EDSS	< 0.001*	– 4.013 (– 5.621 to – 2.406)	0.004*	– 4.616 (– 7.659 to – 1.573)
Presence of ongoing DMT	0.364	0.364 (– 13.035 to 4.852)		
No. of relapses	0.079	– 1.117 (– 2.367 to 0.133)		
Interval bet. 1st and 2nd relapse (/months)	0.887	– 0.016 (– 0.237 to 0.206)		
DASS total score	0.335	0.097 (– 0.102 to 0.295)		
FSMC total score	0.984	– 0.002 (– 0.216 to 0.212)		
Mental subscale	0.576	0.104 (– 0.267 to 0.476)		
Physical subscale	0.582	– 0.095 (– 0.439 to 0.249)		

DASS depression, anxiety and stress score, *FSMC* fatigue score for motor and cognitive functions, *B* unstandardized coefficients, *C.I* confidence interval, *LL* lower limit, *UL* upper limit

All variables with $p<0.05$ was included in the multivariate

* Statistically significant at $p \leq 0.05$

In addition to above findings, we found that as regards parameters affecting total recall immediate; type of MS especially RRMS, age of patients, female and male gender, and EDSS are factors affect total recall immediate, while as regards parameters affecting total BVMT among MS patients; we found that age of patients and EDSS only parameters that affect total BVMT.

In a cross-sectional study of Hassanshahi et al. [27] which sought to assess spatial perception, visual processing speed, memory, and visual learning in MS patients according to age, gender, and educational attainment, no substantial variation was found in the mean scores of the dependent variables (JLO, SDMT, and BVMR-T scores) according to the classes of independent factors (sex, education status) ($P>0.05$). Age was a confounding variable, but it had no effect ($P>0.05$). Additionally, there was no substantial connection between gender and education level ($P>0.05$). Age, gender, and

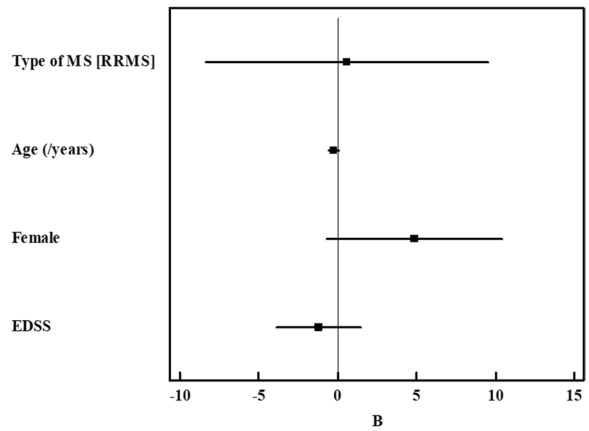

Fig. 2 Multivariate linear regression analysis for the parameters affecting total recall immediate ($n=60$) for total patients

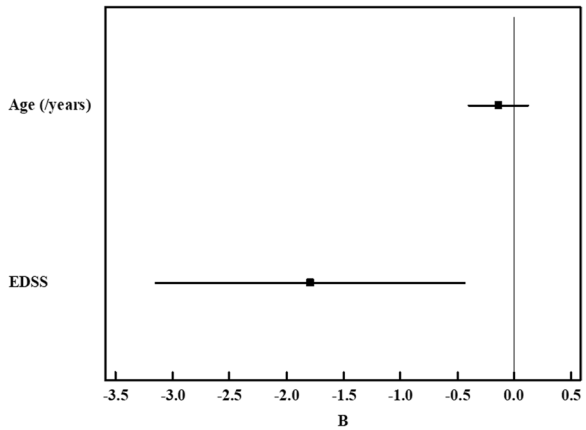

Fig. 3 Multivariate linear regression analysis for the parameters affecting total BVMT ($n=60$) for total patients

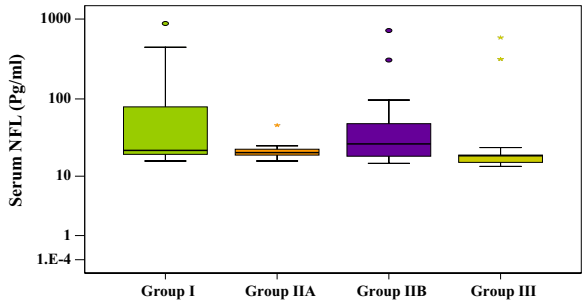

Fig. 4 Comparison of the four investigated groups based on serum NFL. Group I: RRMS, Group IIA: PPMS, Group IIB: SPMS, Group III: Control

Table 8 Correlation between serum NFL with different clinical variables in each group

Serum NFL (Pg/ml) vs	RRMS ($n=30$)		PMS ($n=30$)	
	r_s	p	r_s	p
Total BVMT	0.041	0.830	− 0.107	0.574
Total recall immediate	− 0.272	0.146	− 0.014	0.940
SDMT	0.237	0.207	− 0.035	0.855

r_s: Spearman coefficient

education level had no discernible impact on memory, visual learning, visual processing speed, or spatial perception, according to the study's findings.

In agreement with the outcomes produced by CaparelliDáquer et al. [28] who revealed that Men and higher education groups had the greatest marks on the judgement of line orientation (JLO) test's right response. The findings may not be consistent because of the various sample populations and sizes.

A tiny sample size was one of the research's drawbacks. The length of the condition, cultural circumstances, and lifestyle may also have had an impact on the cognitive test findings. Also this research is defective at determining the exact duration of drugs received for treatment.

Conclusions

Considering all of the aforementioned factors, our findings imply that serum NFLs concentrations do not seem to be a surrogate biomarker for cognitive function and neuropsychiatric symptoms in persons with relatively mild clinical manifestations and no acute disease activity. In light of its potential use in clinical settings, the sensitivity of NFLs as a single metric for such complex functional results is called into doubt, particularly in small samples outside of large scientific studies.

Table 9 Relation between serum NFL with different clinical variables in each group

	No.	Serum NFL (Pg/ml)		Test of Sig.	p
		Mean ± SD	Median (Min.–Max.)		
Group 2 (n = 30) Group 1 (n = 30)					
Switched					
No	26	83.81 ± 182.88	21.96 (16.0–879.80)	$U=34.0$	0.298
Yes	4	72.08 ± 58.51	71.14 (19.37–126.67)		
Ongoing DMT					
Naeive	9	119.18 ± 285.37	21.96 (17.45–879.80)	$H=3.415$	0.181
First line	15	84.86 ± 106.89	74.87 (16.0–444.32)		
Second line	6	20.30 ± 2.49	20.06 (16.48–23.66)		
Switched					
No	19	25.42 ± 18.08	20.64 (16.0–96.88)	$U=72.00$	0.171
Yes	11	116.87 ± 216.69	29.70 (14.89–718.38)		
Ongoing DMT					
Second line	14	22.28 ± 7.49	20.75 (16.0–46.44)	$U=86.00$	0.294
Others	16	91.04 ± 182.15	24.53 (14.89–718.38)		

SD standard deviation, *H H* for Kruskal–Wallis test, *U*: Mann–Whitney test

p: *p* value for relation between serum NFL and different clinical variables

Abbreviations

MS	Multiple sclerosis
sNFL	Serum neurofilament level
BICAMS	Brief international cognitive assessment for multiple sclerosis
25WT	25 Walk test
9PHT	9 Peg hole test
SDMT	Symbol digit modality test
RBVMT	Reversed visuospatial memory test
CVLT	California verbal learning test
RRMS	Remitting relapsing multiple sclerosis
PPMS	Primary progressive multiple sclerosis
SPMS	Secondary progressive multiple sclerosis
EDSS	Expanded disability status scale
PMS	Progressive multiple sclerosis
JLO	Judgement of line orientation
DASS	Depression anxiety and stress scale
CI	Cognitive impairment
FSMC	Fatigue scale for motor and cognitive functions

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Author contributions
AS is the corresponding author, GA participated in creating the idea and principle of the conducted research. AA was the radiologist who revised radiological findings for all patients, supervised, and revised the written material of radiology. MH, IR supervised and revised the written material, methodology, and revised the writing process. The authors read and approved the final manuscript.

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Available with manuscript.

Declarations

Ethics approval and consent to participate
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Consent for publication
All participants had signed an informed consent to participate and for the data to be published without names.

Competing interests
The authors declare no competing interests.

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