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Original Research

Do cardiovascular disease comorbidities affect the cognitive function of Multiple Sclerosis patients?

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ABSTRACT

Introduction: Cognitive impairment is a core symptom of multiple sclerosis, leading to disability in 40–70% of patients. The most common cognitive domains affected by MS are information processing speed, complex attention, executive functions and less frequently, episodic declarative memory. Cardiovascular disease comorbidities have been shown to increase the decline rate in many neurological conditions. Our study aims to examine the possible impact of CVD risk factors in the cognitive decline rate of PwMS.

Methods: Over the course of a year, 248 PwMS with and without Cardiovascular comorbidity were cognitively evaluated using the written version of SDMT and the MoCA.

Results: Compared to control, MS patients with comorbid CVD had greater general cognitive decline and decreased processing speed. Patients with comorbid diabetes and dyslipidemia had the highest impairment, followed by those with hypertension, compared to the control group and those patients with a high BMI.

Conclusion: The presence of cardiovascular comorbidities and especially dyslipidemia increases the rate of cognitive decline in MS patients. In such cases, patients should be evaluated every 6 months instead of a year and the use of the SDMT is advised since it's time efficient,it requires minimal training and correlates with MRI findings.

1. Introduction

Cognitive impairment (CI) is considered a core symptom of Multiple Sclerosis (MS), leading to disability [1] in 40–70% of People with MS (PwMS) with either cortical or subcortical brain pathology [2]. The most frequent cognitive domains affected by MS are information processing speed, complex attention, executive functions and less frequently, episodic declarative memory [3]. Lower education level, longer disease duration, symptoms of initial clinical attack, relapse rate (rr), disease disability progression outside clinical relapses and immunomodulating therapies have been shown to affect the cognitive function of PwMS which in turn can be used as a predictor of disability progression [4,2].

It is well established that processing speed is a primary cognitive ability which is the basis of both lower level (such as attention) and higher level functions (memory and executive function). In addition, processing speed is one of the most impacted cognitive functions affecting approximately 70% pwMS [24,25].

The Symbol Digit Modalities Test (SDMT) constitutes a widely simple and practical measure of information processing speed (Drake et al., 2010). It is cost-efficient with no demand for academic skills and patient friendly. It is worth mentioning that the SDMT shows a stronger association with brain Magnetic Resonance Imaging findings than other neuropsychological instruments (such as Paced Auditory Serial Addition Test) [27,28,29].

Montreal Cognitive Assessment (MoCA) has been established as a sensitive tool for detecting general cognitive impairment in PwMS compared to healthy controls, and its use provides valid information on general cognitive function [17–18]. It is a brief tool that has been widely

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Table 1
Frequency Table Sample Characteristics.

Variable	*n*	%
Gender		
Male	123	49.60
Female	125	50.40
Missing	0	0.00
CVD		
None	53	21.37
Diabetes	48	19.35
Hypertension	45	18.15
BMI	50	20.16
Dyslipidemia	52	20.97

Table 2
Summary Statistics Table of Clinical Characteristics.

Variable	*M*	*SD*	*n*
Age	51.96	5.08	248
EDSS1	2.02	0.86	248
EDSS2	2.58	2.15	248
MoCA1	26.76	1.48	248
None	27.17	1.44	53
Diabetes	26.02	1.54	48
Hypertension	26.98	1.36	45
BMI	26.64	1.41	50
Dyslipidemia	26.94	1.41	52
MoCA2	26.12	1.81	248
None	26.87	1.83	53
Diabetes	25.48	1.89	48
Hypertension	25.91	1.92	45
BMI	26.42	1.70	50
Dyslipidemia	25.83	1.45	52
SDMT1	45.69	4.04	248
None	46.70	3.94	53
Diabetes	44.83	3.31	48
Hypertension	45.20	4.46	45
BMI	46.50	4.47	50
Dyslipidemia	45.08	3.71	52
SDMT2	42.60	4.74	248
None	44.55	4.48	53
Diabetes	41.52	3.82	48
Hypertension	41.78	5.08	45
BMI	43.78	4.72	50
Dyslipidemia	41.21	4.73	52

Table 3
Repeated Measures ANOVA (MOCA-Time).

Source	*df*	*SS*	*MS*	*F*	*p*	$\eta_p 2$
Between Groups						
CVD	4	82.35	20.59	5.37	<0.001	0.08
Within-Groups						
Time	1	52.07	52.07	39.55	<0.001	0.14
Time*CVD	4	17.64	4.41	3.35	0.011	0.05
Residuals	247	403.74	1.63			

considered superior compared to other short examination tests in the recognition of cognitive impairment [19–22].

Cardiovascular diseases (CVD) are the leading cause of death globally with approximately 17,9 million reported casualties in 2019 [5]. PwMS frequently adopt a more sedentary lifestyle [6], which is a result of the patient's impaired mobility, fatigue and bladder incontinence. CVD comorbidities, whose prevalence tends to increase with age, contribute and enhance the sedentary lifestyle already adapted [7]. In addition, vascular pathology affecting strategic areas of the brain may lead to executive, episodic and working memory, visuospatial or processing speed deficits [8].

The incidence of CVD increases to over 40% between the ages of 40 and 59, which appears to be the age range where it creates a considerable load on health-care facilities [9]. Consequently, the established financial burden due to MS related disability is increased exponentially as a result of the additional impact of CVD in the patients' cognition [10,30,31].

Based on the above-mentioned data, our study aims to examine the possible impact of CVD risk factors in the cognitive decline rate of PwMS.

2. Methods and materials

A total of 248 PwMS were recruited from the "MS and other autoimmune diseases outpatient clinic" within the 2nd Department of Neurology of Attikon University Hospital.

Inclusion criteria: *a) Definite MS diagnosis* [11]*, b) Age between 40 and 60 years, c) EDSS* $\leq$ *5, d) Presence of at most one CVD comorbidity, e) Disease duration* $>$ *13 years.*

Exclusion criteria*: a) Comorbid Neurological Condition b) Smoking, c) History of cardiovascular procedure, d) Clinical relapse in the last year*.

All participants were evaluated during the recruitment phase and one year later (2021–2022). The following parameters were collected: 1. Demographic characteristics (age, sex, education level), 2. somatometric characteristics (height (cm), weight(kg), Body Mass Index (BMI)), 3. CVD factors (confirmed diagnosis of diabetes mellitus type II, primary hypertension, dyslipidemia), 4. MS clinical features (EDSS, disease duration, relapse rate).

The presence of dyslipidemia was identified using the Adult Panel III criteria [12] or the prescription of statins in the last six months. High body mass index was calculated using the somatometric characteristics of each participant (BMI = w/h2) and hypertension was confirmed based on the WHO criteria [13] or the use of antihypertensive drugs. EDSS [14] score was determined by a certified neurologist, while the Montreal Cognitive Assessment (MoCA) [15] and the Symbol Digit Modalities Test - written version (SDMT) [16] were administered and evaluated by two separate psychologists.

Each participant was given an information sheet about the research and was asked to read and sign the consent form. In addition, all participants were anonymized prior to the analysis in compliance with the Helsinki Declaration (Ethics Committee Approval number: EBΔ185/15/03/22).

At the baseline the demographic, clinical and CVD characteristics, and somato-metric indexes of all patients were collected, the EDSS, the MoCA and the SDMT scores were measured. Weight was recorded in kilograms and height in centimeters respectively to calculate Body Mass Index (BMI). Systolic and diastolic pressure was measured (3 repetitions and median was chosen) and participants were asked if they had a diagnosis of type 2 diabetes and if they were taking anti-hypertensive therapy. At week 24, patients who met the study inclusion criteria were evaluated on the three previous scales and their scores were recorded.

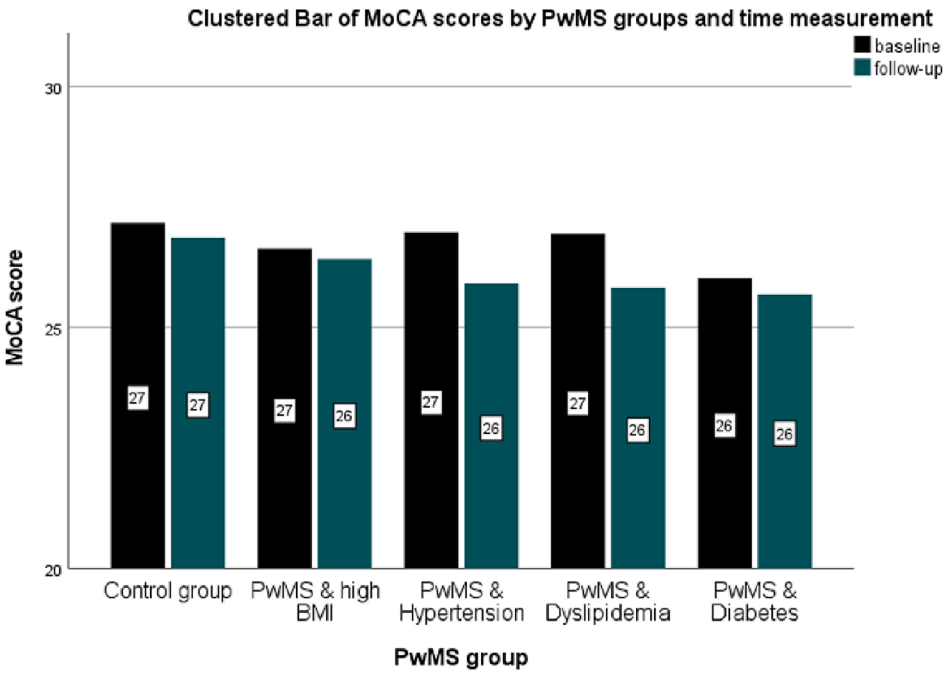
3. Results

Means ± standard deviations (SD) were calculated for each continuous variable and frequencies and percentages were obtained for nominal variables (Tables 1 and 2).

The mean age of the sample was 51.96 (SD = *5.06*), while the groups did not differ statistically significant in terms of this factor ($p > .05$).

The normality of the distributions of the SDMT and MoCA scores were assessed using the Q-Q plots, due to the relatively small groups sizes, while the homogeneity of variance was examined using the Levenes' test.

The first mixed design ANOVA showed a statistically significant interaction between MoCA score and the existence of CVD comorbidity between the two measurement points ($F\ (4,243) = 4.00,\ p = .011,\ \eta_p^2 = 0.05$), indicating a small to medium effect size. Post hoc pairwise comparisons, using a Bonferroni correction to adjust for multiple comparisons showed that at the baseline measurement there was a statistically



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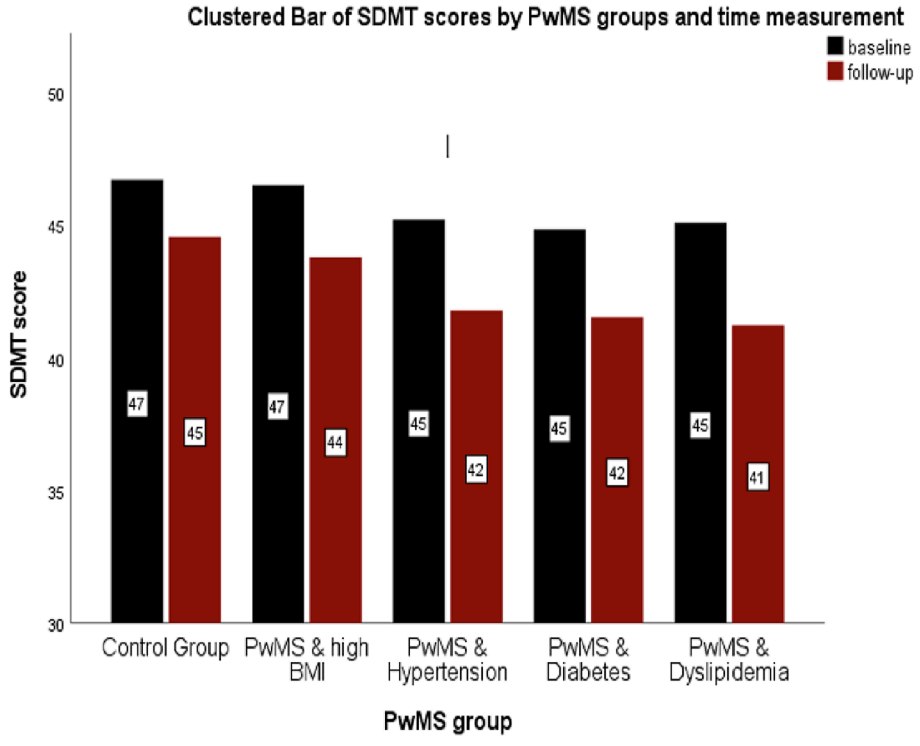

1b

Fig. 1. MoCA and SDMT scores changes.

significant difference between PwMS with diabetes, where their performance was lower compared to control group ($p < .001$) and those with hypertension ($p = .014$) and dyslipidemia ($p = .015$). At the follow-up evaluation (dt = 1 year) there was a statistically significant difference between PwMS without CVD comorbidity and those with diabetes ($p < .001$) and dyslipidemia ($p = .027$), indicating higher scores for the control group. It's worth noting that the MoCA scores of pwMS with comorbid diabetes showed a downward trend compared to PwMS with high BMI that did not pass the statistically significant level ($p = .087$). In addition, the post hoc pairwise comparison between the 5 groups in time showed that the MoCA scores of PwMS without CVD comorbidities remained stable ($p > .05$) while the diabetes, dyslipidemia and hypertension groups showed a moderate to high decline ($p = .022$, $p < .001$, $p < .001$) (Table 3, Fig. 1a).

Table 4
Repeated Measures ANOVA (SDMT-Time).

Source	*df*	*SS*	*MS*	*F*	*p*	$\eta_p 2$
Between Groups						
CVD	4	563,29	140,82	4,71	<0.001	0.072
Within-Groups						
Time	1	1183.11	1183.11	166.75	<0.001	0.41
Time*CVD	4	46,08	11,52	1,62	0.169	0.03
Residuals	243	1724.11	7.10			

The second mixed ANOVA regarding the progression of SDMT scores in time indicated no statistically significant interaction between PwMS with and without comorbidities in time (F (*4,243*) = *2.43, p =.169,* ηp^2 = *0.03*). A post hoc pairwise comparison, using a Bonferroni correction showed that PwMS without CVD comorbidities had higher scores at baseline than pwMS with either diabetes and dyslipidemia (*p =.020, p =.039*), while their scores were slightly higher compare to PwMS with hypertension (*p =.066*). PwMS with comorbid diabetes scored lower than those with high BMI (*p =.040*), while those with comorbid dyslipidemia scored marginally similar compared to PwMS with high BMI (*p* =.074). At the follow-up, the SDMT scores of PwMS with diabetes, dyslipidemia and hypertension showed greater decline compared to the control group (*p <.001, p <.001, p =.003*). PwMS with the aforementioned comorbidities showed greater decline not only compared to controls but compared to pwMS with high BMI (*p =.015, p =.005, p =.034*) (Table 4, Fig. 1b).

4. Discussion

Over the course of a year, 248 PwMS were cognitively evaluated using the written version of SDMT and the MoCA. Compared to controls, PwMS with comorbid CVD had greater general cognitive decline and decreased processing speed. Although all patients appeared more cognitively burdened over time, patients with comorbid diabetes and dyslipidemia had the highest impairment, followed by those with hypertension, compared to the control group and those patients with a high BMI. PwMS with high BMI did not appear to have a higher cognitive burden compared to controls.

The current findings are consistent with previous studies that examined the relationship between the cognitive burden with the lipid profile of pwMS. More specifically, a significant correlation between higher cholesterol levels and lower SDMT scores as well as a decline in cognitive function as assessed by MoCA, was found. without providing a comparison of patients with other CVD comorbidities (2 Πηγες). The elevated blood cholesterol levels and the lipid profile of pwMS with comorbid dyslipidemia have been linked to the severity of disability as well as higher pre-inflammatory markers [32,33].

Prolonged hyperglycemia and hyperinsulinemia due to diabetes may potentially cause neuron's molecular alterations and long-term increased inflammatory reactions in the brain [26] potentially leading to faster cognitive deterioration in pwMS [34].

Remarkably, even though hypertension is the third most prevalent comorbidity in MS [37] to the best of our knowledge there are no studies regarding the effect of hypertension in cognitive function of pwMS. In a sample of 353 healthy older people it was found that a cognitive impairment was associated with elevated blood pressure [35]. In addition, the risk of cognitive impairment increases 4.3 fold in patients who do not adhere to the anti-hypertensive medication [36].

To the best of our knowledge, this is the first study that attempted to divide PwMS into those without and those with a single CVD. Regarding the limitations of this study, the written form of SDMT was employed in this study, due to the fact that it is considered as being largely devoid of cultural bias and as the best screening method for those who are not native speakers and have a low motor impairment index [23]. Even though smoking is a well-established vascular risk factor since the study was conducted in the span of 1 year it was not taken into consideration since it's a lifestyle habit that cannot be accurately controlled. The relatively small sample size and the specific age range, as well as several other disease-related features that were not accurately documented (treatment, specific years of MS and CVD diagnosis), imply the need for more research toward this field. Nevertheless, it appears that in clinical practice, there is an increased need for heightened cognitive monitoring of PwMS and dyslipidemia, diabetes, or hypertension comorbidities, as well as preference of two very short and simple neuropsychological tools, MoCA and SDMT, that can separate the patients' mental load, according to their medical diagnoses.

5. Conclusion

Based on the results of our trial, physicians should take into consideration the presence of CVD factors when evaluating the progression of cognitive decline in patients with MS and should opt in using the SDMT as a primary indicator. Since dyslipidemia, diabetes and hypertension seem to contribute to a faster cognitive deterioration, physicians should shorten the evaluation period to 6 months instead of a year.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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