RESEARCH ARTICLE

The impact of athrosclerosis on cognition and disability in multiple sclerosis patients: the ATHUS score

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Abstract

Aim: Atherosclerosis of the large arteries of the neck could be related to the cognitive and motor deficit. We investigated if the atherosclerosis of common carotid and femoral arteries in patients with multiple sclerosis (MS) is directly linked with a disability and has an inverse relationship with cognitive performance.

Methods: We enrolled, in this prospective study, a random sample of 105 patients with MS and 22 healthy controls. All participants received a comprehensive neuropsychological assessment. The physical disability was quantified with the Expanded Disability Status Scale (EDSS). We utilized ultrasound of the carotid and femoral arteries to evaluate the degree of stenosis and intima-media thickness (IMT). We created a novice ultrasound index of atherosclerosis (ATHUS score) based on the arterial stenosis and the IMT of the carotid and femoral arteries. We then compared the results of the psychometric assessment and EDSS with the ATHUS score.

Results: The analysis demonstrated that higher cognitive function is correlated with lower values of ATHUS score ($p = 0.01$). Also, there was a direct correlation between the ATHUS score and EDSS ($p = 0.001$).

Conclusion: Our results suggest that the degree of atherosclerosis, as calculated by the ATHUS score, is directly related to low cognitive score and higher sensory and motor disability. HIPPOKRATIA 2019, 23(2): 81-86.

Keywords: Multiple sclerosis, atherosclerosis, cognition, ATHUS score

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Introduction

Cognitive decline in multiple sclerosis (MS) has been recognized since the late nineteenth century[1]. The areas of cognition predominantly affected are the processing speed, episodic memory, executive function, verbal fluency, and visuospatial analysis[2,3]. The duration of MS is considered a poor indicator of the presence of cognitive impairment[4]. A moderate correlation exists between the imaging quantification of brain white matter lesions and the performance of patients with MS in the Expanded Disability Status Scale (EDSS). The association between neuroradiological markers and clinical disability is not strong, known as clinic-radiological paradox[5]. Several studies demonstrated that MS is probably related to endothelial dysfunction[6]. In addition, the relationship between vascular risk factors and cognitive dysfunctions is well established[6-8]. Studies of carotid and femoral arteries demonstrated a direct correlation between subclinical carotid atherosclerosis and cognitive decline[9-14]. We tried to demonstrate whether atherosclerosis in the common carotid and femoral arteries in patients with multiple sclerosis has an additional impact on disability and cognitive impairment.

Materials and Methods

A random sample of 105 patients with MS (male: 39, female: 66) that agreed to participate and 22 healthy controls (male: 8, female: 14) were enrolled in this prospective study. The controls were individuals who presented to the outpatient department of Neurology from March 2012 until April of 2012 with somatic complaints attributed finally to anxiety neurosis. In the design of the study, we selected random and consecutive sampling with simple randomization. The patients were recruited from the outpatient and inpatient services of the 1st Neurology Department of AHEPA University Hospital from March 2012 until April of 2012 (Table 1). The random sample of the 105 MS patients is considered to be representative of the MS patients who attend our department, which is a tertiary referral center for Northern Greece. The diagnosis of MS was made based on the revised McDonald Criteria[15] by a board-certified Neurologist. All the patients

Table 1: Demographic and clinical characteristics of the 105 patients with multiple sclerosis and the 22 healthy controls who were enrolled in this prospective study.

	MS (n =105)	HC (n =22)	p
Male / Female (n)	39 / 66	8 / 14	
Age (mean ± SD; years)	46.06 ± 11.052	37.85 ± 11.66	
Disease Phenotype (n; RR/SP/PP)	51/43/11	NA	
EDSS (mean ± SD : median/IQR)	4.41 ± 2.4 : 5/3.5	0 ± 0 : 0/0	0.001
Diabetes Mellitus (%)	9.2	12.5	
Hyperlipidemia (%)	45.3	50	
Thrombophilia (%)	20.2	0	
Hypertension (%)	17.1	25	
Cognition			
MMSE (mean ± SD : median/IQR)	27.37 ± 3.02 : 28/4	30/0/30/0	0.001
Verbal Fluency Test (n, % abnormal)	44 (41.9 %)	3 (13.6 %)	0.013
Osterreith Complex Figures (n, % abnormal)	32 (30.5 %)	1 (4.5 %)	0.012
Greek Verbal Learning Test (n, % abnormal)	36 (34.3 %)	2 (9.1 %)	0.019
Trail Making (n, % abnormal)	32 (30.5 %)	2 (9.1 %)	0.039
Hamilton (mean ± SD : median/IQR)	0.44 ± 1.055 : 0/0	0 ± 0.612 : 0/0	0.506
ATHUS score (mean ± SD : median/IQR)	0.57 ± 1.35 : 0/0	0.77 ± 2.34 : 0/0	0.518

A p-value <0.05 was considered significant, n: number, MS: multiple sclerosis, HC: Controls, RR: relapsing remitting MS, SP: secondary progressive MS, PP: primary progressive MS, EDSS: Expanded Disability Status Scale, MMSE: Mini Mental State Examination, ATHUS: atherosclerotic ultrasonic score, SD: standard deviation, IQR: interquartile range.

with MS had a diagnosis of relapsing-remitting (RR), or secondary progressive (SP), or primary progressive (PP) MS. All the patients were above 18 years of age, fluent in Greek, and provided their verbal and written consent. The study was approved by the Medical Ethics Committee of the Aristotle University of Thessaloniki (No 31, 18/2/2013).

None of the patients at the time of the study was receiving any MS disease-modifying treatment, which could potentially lead to analysis bias. Patients with a clinical diagnosis of dementia, psychosis, metabolic, cardiological or infectious diseases, alcoholism, history of stroke, sickle cell disease, and cardiovascular disease were excluded from the study. Patients with depression, as this was demonstrated by Hamilton Depression Rating Scale[16], were also excluded from the study. All participants (patents and controls) who were recruited concluded the study.

The physical disability was quantified with EDSS by a single Neurologist (AV). All patients underwent a detailed physical examination. We applied a comprehensive neuropsychological assessment addressing all major cognitive domains performed by two independent examiners (ET and AV). The ultrasonographer (TT) was blinded to the results of the other investigators within practical constraints. All the tests used were validated and standardized for the Greek population.

We evaluated verbal memory, episodic memory, visuospatial perception, executive function, processing speed, visual memory, and mood. More specifically, we performed the Mini-Mental State Examination (MMSE)[17]; for verbal fluency, the Greek Verbal Learning Test (the standardized version of the California verbal test)[13,14,18,19], the Trail Making Test Part A (as a test for the evaluation of information processing speed), the Trail Making Test Part B (as a test for the evaluation of executive function)[20] and the Osterreith Complex Figures[21]. The diagnoses of dementia and mild cognitive impairment (MCI) were reached through diagnostic consensus meetings of all the researchers and principal investigators, both neurologists and neuropsychologists, involved in the project, according to the international criteria[22]. The selection of neuropsychological tests was based on prior neuropsychological knowledge of particular cognitive functions that each test evaluates. The Psychometric tests used were standardized for the Greek population.

We used ultrasound to evaluate the degree of stenosis and intima-media thickness (IMT) in the common carotid and femoral arteries. A total of 127 participants underwent an ultrasound examination by a board-certified ultrasonographer, who was blinded to the results of the other investigators and *vice versa*. The ultrasound equipment used was VIVID 3 (GE Healthcare Life Sciences, Marlborough, MA, USA). Each patient was placed in the supine position for the ultrasonographic examination of the common carotid and femoral arteries. Carotid and femoral IMT and plaques were measured on both sides using high-resolution B-mode ultrasound with an electric linear transducer. To avoid inter-observer variability, all measurements were performed by the same examiner and equipment. All images were digitally recorded. The measurements were made in real-time manually from digitalized still images taken during scanning by high-resolution ultrasonography. The IMT was measured in the far wall of the common carotid and femoral arteries at sites of greatest arterial thickness[23]. For the evaluation of IMT, the greatest distance between the lumen–intima interface and the media–adventitia interface in areas without atherosclerotic plaques was determined. Measurements of IMT were made three times and then averaged to produce a mean IMT for each side for the carotids, and femoral arteries[24-28]. We accept as the cut-off value for the IMT the 0.8 mm based on a previous study and taking into account the age range of our population[29]. Vessels with IMT above 0.8mm were classified as abnormal. A plaque was defined as a distinct protrusion greater than 1.5 mm into the lumen of the vessel. We created an ultrasound index of atherosclerosis (ATHUS score) based on the arterial stenosis and the IMT of the four vessels (two carotids and two femoral arteries). Each artery was assigned a score (Plaque: presence =1, absence =0; IMT: >0.8 mm =1, <0.8 mm =0). Patients could receive a score in the range of 0-8, taking into account the four vessels (common carotid arteries, femoral arteries, both sides). We used the European Carotid Surgery Trial (ECST) criteria for stenosis grading[30]. We then compared the ATHUS score with MMSE and the EDSS (Table 2), and also with the other neuropsychometric tests (Table 3).

Then study analysis was performed with IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA). Statistical significance was considered at a p-value of less than 0.05 and was tested with the Mann-Whitney non-parametric test for continuous variables and with the chi-square for nominal variables. The assessment of the normality of the data was conducted with the Shapiro-Wilk test.

Results

Twenty-one of the MS patients and one individual from the control group have had ATHUS score ≥1 (Table 1). The normality of the distributions was evaluated utilizing the Shapiro-Wilk test. The distributions proved to be not normal, which indicated the use of non-parametric tests in our analysis. MS patients and healthy controls were separable on the basis of i) EDSS (p =0.001), ii) MMSE (p =0.001), iii) Verbal Fluency test (p =0.013), iv)

Table 2: Descriptive statistics of the ultrasound index of atherosclerosis (ATHUS) in relation to the Mini Mental State Examination (MMSE) and the Expanded Disability Status Scale (EDSS) in the 105 multiple sclerosis patients. ATHUS ≥1 is associated with lower values of MMSE and higher values of EDSS.

			MMSE	EDSS
p			**0.004**	**0.001**
ATHUS score	normal =0	Mean	28.05	3.98
		SD	2.33	2.39
		Median	29	4
		IQR	4	4
ATHUS score	abnormal ≥1	Mean	24.82	6.068
		SD	3.91	1.65
		Median	25	6
		IQR	5	2.5

SD: standard deviation, IQR: interquartile range, EDSS: Expanded Disability Status Scale, MMSE: Mini Mental State Examination, ATHUS: atherosclerotic ultrasonic score. Mann Whitney test show statistical significance between the groups with MMSE and EDSS variables. A p-value <0.05 was considered significant.

Table 3: Ultrasound index of atherosclerosis (ATHUS) score and other neuropsycological tests in the 105 multiple sclerosis patients. ATHUS ≥1 is associated with worse performance in all neuropsycological tests.

ATHUS Score	Verbal fluency		Osterreith Complex Figure		Greek Verbal Learning Test		Trail Making	
p	0.001		0.001		0.001		0.001	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Normal =0	55	28 (33.7 %)	64	19 (22.9 %)	61	22 (26.5 %)	65	18 (21.7 %)
Abnormal ≥1	6	16 (72.7 %)	9	3 (59.1 %)	8	14 (63.6 %)	8	14 (63.6 %)
	61	44	73	32	69	36	73	32

ATHUS: atherosclerotic ultrasonic score. Pearson Chi-Square show statistical significance for all nominal neuropsychological tests. A p-value <0.05 was considered significant.

Osterreith Complex Figures (p =0.012), v) Greek Verbal Learning test (p =0.019), vi) Trail Making test (p =0.039), indicating that MS might have an impact on disability and cognitive decline. On the other hand, the Hamilton test (p =0.506) and ATHUS (p =0.518) failed to separate the MS sufferers and healthy controls, indicating that depression and atherosclerosis are equally presented in both groups (Table 1). Overall, the distribution of ATHUS had the following characteristics in our population of MS sufferers and controls, mean: 0.6, standard deviation (SD): 1.56, median: 0, interquartile range (IQR): 0, maximum: 8, minimum: 0.

As to the impact of ATHUS score on MMSE and EDSS in the MS patients (Table 2), it was demonstrated that ATHUS ≥1 was associated with lower values of MMSE (p =0.004) and higher values of EDSS (p =0.001), as compared to ATHUS =0 (higher values of MMSE and lower values of EDSS). These results indicated that the atherosclerotic load, as expressed by ATHUS, is producing an additional intellectual decline and motor disability in MS patients.

Also, regarding the other neuropsychometric tests (Verbal Fluency test, Osterreith Compex Figures, Greek Verbal Learning test, and Trail Making test), it was demonstrated that ATHUS ≥1 was associated with worse performance in all these tests compared to ATHUS =0 in a statistically significant manner (p =0.001 for all tests performed). These results indicated that atherosclerotic load in MS patients has an additional impact on the intellectual decline (Table 3). The Mann-Whitney and chi-square tests showed a significant correlation between EDSS and neuropsychometric tests (p =0.001). However, further analysis of this correlation is beyond the scope of the current paper.

An effort was also made to correlate EDSS and cognitive scores in MS patients. More specifically: i) a significant correlation was demonstrated between EDSS and MMSE (Pearson correlation, r =-0.511, p =0.001), ii) EDSS was statistically different in the groups of patients with normal and abnormal Verbal Fluency test (patients with normal test had EDSS mean: 3.39, SD: 2.25, median: 3, and IQR: 4.25, while patients with abnormal test had EDSS mean: 5.84, SD: 1.82, median: 6, and IQR: 2.38; Mann-Whitney U test, p =0.001), iii) EDSS was statistically different in the groups of patients with normal and abnormal Osterreith Compex Figures test (patients with normal test had EDSS mean: 3.77, SD: 2.37, median: 3.5, and IQR: 4, while patients with abnormal test had EDSS mean: 5.89, SD: 1.77, median: 6, and IQR: 2.38; Mann-Whitney U test, p =0.001), iv) EDSS was statistically different in the groups of patients with normal and abnormal Greek Verbal Learning test (patients with normal test had EDSS mean: 3.36, SD: 2.33, median: 3.5, and IQR: 4, while patients with abnormal test had EDSS mean: 5.86, SD: 1.83, median: 6, and IQR: 2.75; Mann-Whitney U test, p =0.001), v) EDSS was statistically different in the groups of patients with normal and abnormal Trail Making test (patients with normal test had EDSS mean: 3.86, SD: 2.34, median: 3.5, and IQR: 4, while patients with abnormal test had EDSS mean: 5.67, SD: 2.06, median: 6, and IQR:3; Mann-Whitney U test, p =0.001).

Also, an effort was made to correlate ATHUS (as a continuous variable) and cognitive scores in MS patients. More specifically: i) a significant correlation was demonstrated between ATHUS and MMSE (Pearson correlation, r =-0,437, p =0.001), ii) ATHUS was statistically different in the groups of patients with normal and abnormal Verbal Fluency test (patients with normal test had ATHUS mean: 0.098, SD: 0.3, median: 0, and IQR: 0, while patients with abnormal test had ATHUS mean: 0.36, SD: 0.48, median: 0, and IQR: 1; Mann-Whitney U test, p =0.001), iii) ATHUS was statistically different in the groups of patients with normal and abnormal Osterreith Compex Figures test (patients with normal test had ATHUS mean: 0.12, SD: 0.33, median: 0, and IQR: 0, while patients with abnormal test had ATHUS mean: 0.4, SD: 0.49, median: 0, and IQR: 1; Mann-Whitney U test, p =0.001), iv) ATHUS was statistically different in the groups of patients with normal and abnormal Greek Verbal Learning test (patients with test had ATHUS mean: 0.11, SD: 0.32, median: 0, and IQR: 0, while patients with abnormal test had ATHUS mean: 0.38, SD: 0.49, median: 0, and IQR: 1; Mann-Whitney U test, p =0.001), v) ATHUS was statistically different in the groups of patients with normal and abnormal Trail Making test (patients with normal test had ATHUS mean: 0.1, SD: 0.31, median: 0, and IQR: 0, while patients with abnormal test had ATHUS mean: 0.43, SD: 0.5, median: 0, and IQR: 1; Mann-Whitney U test, p =0.001).

Discussion

The relationship between atherosclerosis and cognitive decline is an issue that has attracted research interest. Previous studies have shown an inverse relationship between subclinical atherosclerosis and cognitive function and lower cognitive test[31] results, mainly in elderly patients[9]. Although alterations of neck vessels have been reported in MS and few studies demonstrated the possible connection of vascular risk factors and MS prognosis[32], this is the first study to our knowledge which correlates directly the atherosclerosis of the carotid and femoral arteries not only with patient's motor disability but with lower cognitive function.

Our results suggest that the degree of atherosclerosis as it was assessed by the ATHUS score is directly related to low cognitive scores in the neuropsychometric tests and higher scores in the EDSS. However, the extent to which subclinical atherosclerosis is related to cognition and sensorimotor disability is not fully understood. This position might be clarified in larger studies of patients, aiming to establish the role of atherosclerosis detected on ultrasound in the prognosis of cognitive function and disability in patients with MS.

Cognitive decline is more pronounced with the progression of the disease. The relation between atherosclerosis, brain volume loss, motor disability, and cognitive deficit in MS has been largely unexamined, albeit other studies tried to demonstrate in the recent past the possible connection of vein insufficiency and MS progression with a debatable result[33]. The present study confirmed the group differences between MS patients and controls regarding motor disability and intellectual decline. We did also observe a significantly lower score in the neuropsychometric tests with arterial stenosis and IMT in MS patients. The increased atherosclerotic load influenced all cognitive functions.

Our study was a single-center cross-sectional single-blinded study, examining each patient at a single time point and has obvious limitations. The disease duration, exposure, and response to disease-modifying treatments in the past, time of diagnosis, and clinical presentation in the first attack, age, or gender have not been addressed. We recognize that the above details could potentially influence the results regarding cognitive decline and disability. We elected not to study the patients according to phenotype. The study was based on real-world data in a specific period with simple randomization. We accept the limitations that this selection of the sample imposes. The recruitment is ongoing. We try to increase the number of controls and the number of patients, particularly in the group of PP MS, so that the previously mentioned numbers at the end to be relatively equal to those of the groups of RR and SP MS and then to perform the analysis on a solid basis. We understand that the variability in testing methods and heterogeneous sample composition could result in differences in the evaluation of the impairment. We accept that we may miss how cognitive decline progresses over time. However, we are enthusiastic that the database of this study could be the basis of a large prospective and longitudinal study which could evaluate the progression of cognitive disability in relation to the progression of atherosclerosis[34].

We aspire that this study could increase the awareness of clinicians regarding the importance of monitoring the cognition in MS. Cognitive monitoring should be part of the evaluation of MS patients. Another point that became apparent during the data collection and analysis is that we lack a validated cognitive scale equivalent to EDSS, which could be a tool in the interpretation of the cognitive changes. The current work aims to incorporate the assessment of atherosclerosis of the carotid and femoral arteries and the cognitive assessment into MS clinics. We believe that preventive action for vascular risk factors should play an integral role in the management of patients with MS. The Neurologist should not only focus on the sensorimotor symptoms but recognize the importance of cognitive decline in MS patients, promote lifestyle changes, and implement pharmacological treatments, which may slow the effect of atherosclerosis and may also halt its impact to the higher cognitive function and motor disability of MS patients.

Conflict of interest

The authors have no financial issues related to the present article to disclose nor received any payment for travel, accommodations or meeting expenses.

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References

1. Sumowski JF, Benedict R, Enzinger C, Filippi M, Geurts JJ, Hamalainen P, et al. Cognition in multiple sclerosis. State of the field and prioroties for the future. Neurology. 2018; 90: 278-288.
2. McNicholas N, O'Connell K, Yap SM, Killeen RP, Hutchinson M, McGuigan C. Cognitive dysfunction in early multiple sclerosis: a review. QJM. 2018; 111: 359-364.
3. Ruano L, Portaccio E, Goretti B, Niccolai C, Severo M, Patti F, et al. Age and disability drive cognitive impairment in multiple sclerosis across disease subtypes. Mult Scler. 2017; 23: 1258-1267.
4. Guimarães J, Sá MJ. Cognitive dysfunction in multiple sclerosis. Front. Neurol. 2012; 3: 74.
5. Mollison D, Sellar R, Bastin M, Mollison D, Shandran S, Wardlaw J, et al, The clinico-radiological paradox of cognitive function and MRI burden of white matter lesions in people with multiple sclerosis: A systemic review and meta-analysis. PLoS One. 2017; 12: e0177727.
6. Krogias C, Christou I, Tsivgoulis G, Koutroulou I, Schroeder C, Lantinioti C, et al. Functional Neurosonology Reveals Impaired Cerebrovascular Reactivity in Multiple Sclerosis. J Neuroimaging. 2019; 29: 589-591.
7. Reis JP, Launer LJ, Terry JG, Loria CM, Zeki Al Hazzouri A, Sidney S, et al. Subclinical atherosclerotic calcification and cognitive functioning in middle-aged adults: the CARDIA study. Atherosclerosis. 2013; 231:72-77.
8. Rossetti HC, Weiner M, Hynan LS, Cullum CM, Khera A, Lacritz LH. Subclinical atherosclerosis and subsequent cognitive function. Atherosclerosis. 2015; 241: 36-41.
9. Sander K, Bickel H, Förstl H, Etgen T, Briesenick C, Poppert H, et al. Carotid-intima media thickness is independently associated with cognitive decline. The INVADE study. Int J Geriatr Psychiatry. 2010; 25: 389-394.
10. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 2014; 83: 278-286.
11. Palta P, Sharrett AR, Wei J, Meyer ML, Kucharska-Newton A, Power MC, et al. Central Arterial Stiffness Is Associated With Structural Brain Damage and Poorer Cognitive Performance: The ARIC Study. J Am Heart Assoc. 2019; 8: e011045.
12. Rafnsson SB, Deary IJ, Fowkes FG. Peripheral arterial disease and cognitive function. Vasc Med. 2009; 14: 51-61.
13. Connick P, Kolappan M, Bak TH, Chandran S. Verbal fluency as a rapid screening test for cognitive impairment in progressive multiple sclerosis. J Neurol Neurosurg Psychiatry. 2012; 83: 346-347.
14. Woods SP, Delis DC, Scott JC, Kramer JH, Holdnack JA. The California Verbal Learning Test--second edition: test-retest reliability, practice effects, and reliable change indices for the standard and alternate forms. Arch Clin Neuropsychol. 2006; 21: 413-420.
15. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011; 69: 292-302.
16. Olden M, Rosenfeld B, Pessin H, Breitbart W. Measuring depression at the end of life: is the Hamilton Depression Rating Scale a valid instrument? Assessment. 2009; 16: 43-54.
17. Fountoulakis KN, Tsolaki M, Chantzi H, Kazis A. Mini Mental

State Examination (MMSE): A validation study in Greece. Am J Alzheimers Dis Other Demen. 2000; 15: 342-345.
18. Vlahou CH, Kosmidis MH, Dardagani A, Tsotsi S, Giannakou M, Giazkoulidou A, et al. Development of the Greek Verbal Learning Test: reliability, construct validity, and normative standards. Arch Clin Neuropsychol. 2013; 28: 52-64.
19. Stegen S, Stepanov I, Cookfair D, Schwartz E, Hojnacki D, Weinstock-Guttman B, et al. Validity of the California Verbal Learning Test-II in multiple sclerosis. Clin Neuropsychol. 2010; 24: 189-202.
20. Zalonis I, Kararizou E, Triantafyllou NI, Kapaki E, Papageorgiou S, Sgouropoulos P, et al. A normative study of the trail making test A and B in Greek adults. Clin Neuropsychol. 2008; 22: 842-850.
21. Shin MS, Park SY, Park SR, Seol SH, Kwon, JS. Clinical and empirical applications of the Rey-Osterrieth Complex Figure Test. Nat Protoc. 2006; 1: 892-899.
22. Sachdev P, Kalaria R, O'Brien J, Skoog I, Alladi S, Black SE, et al. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. Alzheimer Dis Assoc Disord. 2014; 28: 206-218.
23. Paul J, Dasgupta S, Ghosh MK. Carotid artery intima media thickness as a surrogate marker of atherosclerosis in patient with chronic renal failure on hemodialysis. N Am J Med Sci. 2012; 4: 77-80.
24. Wikstrand J. Methodological considerations of ultrasound measurement of carotid artery intima-media thickness and lumen diameter. Clin Physiol Funct Imaging. 2007; 27: 341-345.
25. Baldassarre D, Hamsten A, Veglia F, de Faire U, Humphries SE, Smit AJ, et al. Measurements of carotid intima-media thickness and of interadventitia common carotid diameter improve prediction of cardiovascular events: results of the IMPROVE (Carotid Intima Media Thickness [IMT] and IMT-Progression as Predictors of Vascular Events in a High Risk European Population) study. J Am Coll Cardiol. 2012; 60: 1489-1499.
26. Paul J, Shaw K, Dasgupta S, Ghosh MK. Measurement of intima media thickness of carotid artery by B-mode ultrasound in healthy people of India and Bangladesh, and relation of age and sex with carotid artery intima media thickness: An observational study. J Cardiovasc Dis Res. 2012; 3: 128-131.
27. Lim TK, Lim E, Dwivedi G, Kooner J, Senior R. Normal value of carotid intima-media thickness--a surrogate marker of atherosclerosis: quantitative assessment by B-mode carotid ultrasound. J Am Soc Echocardiogr. 2008; 21: 112-116.
28. Simon A, Gariepy J, Chironi G, Megnien JL, Levenson J. Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk. J Hypertens. 2002; 20: 159-169.
29. Homma S, Hirose N, Ishida H, Ishii T, Araki G. Carotid plaque and intima-media thickness assessed by b-mode ultrasonography in subjects ranging from young adults to centenarians. Stroke. 2001; 32: 830-835.
30. Mozzini C, Roscia G, Casadei A, Cominacini L. Searching the perfect ultrasonic classification in assessing carotid artery stenosis: comparison and remarks upon the existing ultrasound criteria. J Ultrasound. 2016; 19: 83-90.
31. Mathiesen EB, Waterloo K, Joakimsen O, Bakke SJ, Jacobsen EA, Bønaa KH. Reduced neuropsychological test performance in asymptomatic carotid stenosis: The Tromsø Study. Neurology. 2004; 62: 695-701.
32. Cerqueira JJ, Compston DAS, Geraldes R, Rosa MM, Schmierer K, Thompson A, et al. Time matters in multiple sclerosis: can early treatment and long-term follow-up ensure everyone benefits from the latest advances in multiple sclerosis? J Neurol Neurosurg Psychiatry. 2018; 89.8: 844-850.
33. Romani A, Viselner G, Bergamaschi R, Bastianello S, Calliada F. 'Venous insufficiency' is not the cause of multiple sclerosis (MS) (but it could be a risk factor for MS and for different brain disorders). Funct Neurol. 2011; 26: 179-180.
34. Eijlers AJC, van Geest Q, Dekker I, Steenwijk MD, Meijer KA, Hulst HE, et al. Prediciting cognitive decline in multiple sclerosis: a 5-year follow-up study. Brain. 2018; 141: 2605-2618.