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Case-controlled Study

Carotid intima-media thickness measurements in patients with multiple sclerosis

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ABSTRACT

Objectives: The goal of this study was to evaluate the mean carotid intima-media thickness (CIMT) in patients with Multiple Sclerosis (MS).
Methods: In this cross-sectional study, 100 patients with MS were enrolled. Carotid intima-media thickness was measured by Doppler Ultrasonography. The mean CIMT was then compared between different groups of sex, age, body mass index (BMI), medications, and site of the MS plaques in the brain and cervical MRI. In addition, disease duration, annual relapse rate, and Expanded Disability Status Scale (EDSS) were compared between high and normal CIMT groups.
Results: Among 100 patients, Sixty-two percent of the patients were female. The mean age was 35.95 ± 9.32 years. Mean CIMT was 0.38 ± 0.2 mm, and 22% of the patients had abnormal CIMT measures. CIMT was significantly associated with higher age ($P = 0.01$) and prolonged disease duration ($P < 0.001$). CIMT was not associated with other disease factors or types of the disease-modifying drug ($P > 0.05$).
Conclusion: Multiple Sclerosis might be associated with carotid atherosclerotic vascular disease.

1. Introduction

Multiple Sclerosis (MS) is a chronic inflammatory and immune-mediated disease, causing disability in the young population [1]. It is estimated that near 2.8 million people around the world live with MS [2]. Early treatment is associated with longer survival in MS patients [3,4].

Atherosclerosis is a complex and chronic inflammatory disease, and chronic inflammation is a predictor of cardiovascular disease [5–7]. Subclinical atherosclerosis has been reported in multiple sclerosis patients [8]. Atherosclerosis is considered to be an important comorbidity in MS patients as it may lead to vascular diseases of the central nervous system, and deteriorate the neurologic disability and cognitive function in MS patients [9].

Inflammation of the arteries reduces the endothelial function and results in increased arterial stiffness [10,11]. Carotid artery intima-media thickness (CIMT), the thickness of the intimal and medial layer of the carotid artery wall, is a surrogate marker for assessing the risk of cardiovascular risk [12,13].

Knowing that MS is an inflammatory disease and is linked to atherosclerosis, assessing subclinical atherosclerosis in MS patients has been achievable via measuring the inflammatory cytokines and markers in the blood or cerebrospinal fluid (CSF) in the past [14]. Computed tomography angiography and bed-side transthoracic ultrasonography is efficient for the diagnosis of cardiovascular diseases such as pulmonary embolism [15]. However, by introducing CIMT as a non-invasive method for evaluating subclinical atherosclerosis, new tendencies have emerged to use it as a surrogate marker to assess the risk of

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atherosclerosis [12].

Few studies are available regarding the CIMT in MS patients and the difference in CIMT within different MS subtypes, and it is not still clear if there is any association between CIMT and different disease-modifying drugs used in MS. Herein, we have evaluated the CIMT in a group of multiple sclerosis patients to study subclinical atherosclerosis in patients with MS and some associations.

2. Materials and method

2.1. Study design and sampling

In this cross-sectional, observational study, one-hundred Multiple Sclerosis patients (diagnosed with revised Mc. Donald criteria 2017 [16] referring to a teaching tertiary neurology center hospital in (XXX) were evaluated. The study period was from June 2020 to June 2021. Inclusion criteria were age between 18 and 65 years old and disease duration ≤5 years. Exclusion criteria were significant underlying conditions affecting atherosclerosis (such as smoking, high cholesterol, and triglyceride levels, diabetes mellitus, dyslipidemia, hypertension, ischemic heart disease), any attack during the past month, use of glucocorticoids during the past 3 months, and the reluctance of the patients for continuing the participation.

2.2. Assessment of carotid intima-media thickness (CIMT)

To measure CIMT, duplex ultrasound (B-Mode) was utilized. The device was a Sonosite M-Turbo with an 8-Hz linear probe. IMT was calculated in a B-mode by a single expert attending professor with a license in the field of neuro-radiology. A portion of the common carotid artery without any evidence of atherosclerotic plaque was detected. According to the protocol, the mean IMT (intima-media thickness) was measured by calculating the thickness of the innermost two layers of intima-media in 10 mm before the bifurcation of the common carotid artery (CCA), where there were no atherosclerotic plaques. According to the American Echocardiographic Association, mean CIMT above 75th percentile for age, race, and gender was considered as a risk factor for cardiovascular events [17].

Then, we evaluated the association of CIMT in patients' sex, EDSS score, clinical course (Clinically Isolated Syndrome, Primary Progressive Multiple Sclerosis, Secondary Progressive Multiple Sclerosis, and Relapsing-Remitting Multiple Sclerosis), Body Mass Index (BMI), annual relapse rate, location of MRI plaques, and disease duration.

2.3. Statistical analysis

Categorical variables were described using frequency and percent, and continuous variables were described using mean and standard deviation (median and interquartile range in case of nonparametric distribution). To compare CIMT level within levels of a categorical variable with two levels or more than two levels, we used the independent samples T-test (Mann-Whitney *U* test in case of nonparametric distribution) and ANOVA tests, respectively. The Pearson correlation test was used to evaluate the correlation between the variables. To correct the effect of age and sex on CIMT, we used the ANCOVA test. P-value less than 0.05 was assumed significant.

2.4. Ethical considerations

No personal data of the patients was revealed. All patients signed informed consent and were notified that they could leave the study as they wished. Patients were not charged with any additional cost. We adhered to the 1964 Helsinki declaration and its further modifications. This study was approved by the institutional ethics committee.

Unique identifying number is: researchregistry7495.

The methods are stated in accordance with STROCSS 2021 guidelines [18].

3. Results

Of the 100 patients participating in the study, 62 (62%) were females. The mean age of the participants was 35.95 ± 9.32 years old. Near half of the patients had normal weight (51.5%). The relapsing-reemitting type was the most common type of Multiple Sclerosis (59%). Fifty-six percent of the patients received treatment, by which Rituximab was the most commonly used medication (39.3%). The median EDSS score was 2 ± 2, and the majority of the patients had an EDSS score of 4.5 or lower. The annual relapse rate was 2.17%. Ninety-two percent of the patients had periventricular brain lesions and 66% of the patients had lesions in their cervical spine. Twenty-two percent of the patients had increased carotid intima-media thickness compared to the normal population, adjusted for age. The mean carotid intima-media thickness was 0.38 ± 0.2 mm (95% CI: 0.34–0.42) (Table 1). Table 1 shows the basic characteristics of the study.

Although CIMT was higher in men, there was no significant difference in CIMT between the two sexes. There was a significant correlation between sex and CIMT ($r = 0.2$, $p = 0.042$). The mean CIMT was significantly higher in patients older than 40 years old ($p = 0.01$). Also, there was a significant correlation between age and CIMT ($r = 0.2$, $p = 0.033$). There was no significant difference in CIMT within BMI groups ($p = 0.7$), and there was no significant correlation between CIMT and BMI ($p = 0.8$) (Table 2).

After adjusting for age and sex, mean intima-media thickness did not show a significant difference in medication types, MS subtypes, EDSS score, and location of the lesions ($p > 0.05$) (Table 2). Table 2 shows the

Table 1
Baseline characteristics.

Variable		
Age (Years old)	Overall	35.95 (9.32)[a]
	≤40	69 (69) [b]
	>40	31 (31) [b]
Female Sex		62 (62)[b]
Body Mass Index (Kg/m^2)	Overall	24.8 (4.1)[a]
	Underweight	4 [4] [b]
	Normal weight	51 (51.5) [b]
	Overweight	34 (34.3) [b]
	Obese	10 (10.1) [b]
EDSS (Functional)	Overall	2 [2] [c]
	≤4.5	96 (96)[b]
	≥5	4 [4] [b]
Clinical Course	Relapsing-Remitting	59 (59) [b]
	Clinically Isolated Syndrome	19 [19] [b]
	Secondary Progressive	15 [15] [b]
	Primary Progressive	7 [7] [b]
Disease Duration (month)		30 (102)[c]
Disease-Modifying Drugs	No treatment	44 (44)[b]
	Rituximab	22 (39.3) [b]
	Glatiramer Acetate	6 (10.7) [b]
	Teriflunomide	3 (5.3) [b]
	Dimethyl Fumarate	6 (10.7) [b]
	Fingulimode	3 (5.3) [b]
	Interferon (IM)	11 (19.6) [b]
	Interferon (SC)	5 (8.9) [b]
Annual Relapse Rate (%)		2.17 (1.54)[a]
Brain Lesions' Location	Periventricular	92 (92) [b]
	Juxtacortical	62 (62) [b]
	Infratentorial	46 (46) [b]
Spinal Lesions' Location	Cervical	66 (66) [b]
	Thoracic	14 [14] [b]
Carotid Intima-Media Thickness	Overall (mm)	0.38 (0.20) [a]
	Normal	78 (78) [b]
	Increased	22 (22) [b]

EDSS: Expanded Disability Status Scale.
[a] Mean (Standard Deviation).
[b] Number (Percent).
[c] Median (Interquartile Range).

Table 2
Carotid intima-media thickness based on study characteristics.

Variable		Mean ± SD	95% Confidence Interval	P-Value
Sex	Male	0.43 ± 0.29	0.34–0.53	0.09
	Female	0.35 ± 0.10	0.32–0.37	
Age	≤40	0.35 ± 0.21	0.30–0.40	0.01
	>40	0.44 ± 0.12	0.40–0.49	
Body Mass Index (Kg/m^2)	Underweight	0.40 ± 0.08	0.27–0.52	0.7
	Normal Weight	0.4 0 ± 0.25	0.33–0.47	
	Overweight	0.35 ± 0.09	0.32–0.39	
	Obese	0.39 ± 0.15	0.27–0.50	
EDSS	≤4.5	0.38 ± 0.20	0.34–0.42	0.9
	≥5	0.37 ± 0.09	0.22–0.52	
Clinical Course	Clinically Isolated Syndrome	0.30 ± 0.09	0.25–0.34	0.7
	Relapsing-Remitting	0.40 ± 0.23	0.33–0.46	
	Secondary Progressive	0.40 ± 0.13	0.32–0.47	
	Primary Progressive	0.45 ± 0.07	0.38–0.52	
Disease Modifying Drugs (DMDs)	No treatment	0.37 ± 0.27	0.29–0.46	0.4
	Rituximab	0.42 ± 0.11	0.37–0.47	
	Glatiramer Acetate	0.35 ± 0.10	0.23–0.46	
	Teriflunomide	0.40 ± 0.17	0.03–0.83	
	Dimethyl Fumarate	0.36 ± 0.08	0.28–0.45	
	Fingulimode	0.50 ± 0.10	0.25–0.74	
	Interferon (intramuscular)	0.37 ± 0.11	0.29–0.44	
	Interferon (subcutaneous)	0.30 ± 0.07	0.21–0.38	
Periventricular Brain Lesion	Yes	0.27 ± 0.07	0.35–0.43	0.4
	No	0.39 ± 0.20	0.21–0.33	
Juxtacortical Brain Lesion	Yes	0.36 ± 0.11	0.33–0.45	0.1
	No	0.39 ± 0.23	0.32–0.40	
Infratentorial Brain Lesion	Yes	0.36 ± 0.11	0.32–0.39	0.6
	No	0.39 ± 0.23	0.33–0.47	
Cervical Spine Lesion	Yes	0.37 ± 0.11	0.34–0.40	0.2
	No	0.41 ± 0.30	0.30–0.51	
Thoracic Spine Lesion	Yes	0.36 ± 0.10	0.34–0.40	0.7
	No	0.38 ± 0.21	0.30–0.51	

difference in intima-media thickness among categorical variables of the study.

After adjusting for age and sex, patients with high intima-media thickness had longer durations of the disease. The median disease duration was 78 ± 90 months in patients with increased CIMT, and 21 ± 37 months in patients with normal CIMT ($p < 0.001$). There was no significant difference in annual attack rate between patients with normal or increased CIMT ($p = 0.2$). Also, there was no significant difference in functional EDSS between patients with normal and increased CIMT ($p = 0.6$).

4. Discussion

Our study was conducted on a group of 100 patients with Multiple Sclerosis. The main outcome of this study is estimating the mean CIMT measure in patients with multiple sclerosis. This study cannot thoroughly evaluate the factors affecting the CIMT, since there is no control group and the reference is the mean of the normal population.

Most of the patients (59%) were RRMS patients, but the study also contained a considerable number of CIS (19%), SPMS (15%), and PPMS (7%) patients. Slightly more than half of the patients (56%), were actively receiving MS medication, among which Rituximab was the most frequently prescribed drug (39.3%). Mean CIMT was 0.38 ± 0.2 mm. Other studies have found lower CIMT compared to our study. However, they have studied RRMS rather than other subtypes of the disease. This might be the reason for the different findings. As well, different nations might demonstrate different CIMT measures due to the anatomical and racial variations. Several studies are needed to confirm the measure. Age more than 40, and prolonged disease duration were related to high CIMT as predicted.

Despite having low EDSS scores, 22% of the patients had higher CIMT. We did not find any significant relationship between CIMT and the progression of neurologic disability (as measured by EDSS), although the very low sample size of the patients with EDSS scores higher than 4.5, limits the power of this study to evaluate this relationship. This finding assumes, albeit cautiously, a low but considerable population of patients with multiple sclerosis show increased CIMT which might impose MS patients to increased risk of developing coronary artery disease in the future. However, the latter presumption should be assessed in an appropriate longitudinal study with larger sample sizes.

The current evidence is rare and inconsistent in this regard. In a study by Yuksel et al., CIMT was found to be higher in patients with multiple sclerosis [19], compared to healthy subjects, whereas in another study by Omerzu et al., no difference was found [20]. This variation might be due to the dissimilar study designs, along with sample sizes, and possible races.

In our study, we found a significant correlation between age and sex with CIMT, but BMI was not associated with CIMT. Also, prolonged disease duration was associated with higher CIMT. There was no association between CIMT and MS clinical course, DMD types, and location of the lesions. We may conclude that perhaps different MS subtypes and different treatment panels might not affect the rate of subclinical atherosclerosis in patients with multiple sclerosis in the first 5 years from the MS diagnosis and it seems that longer disease duration is significantly associated with abnormal CIMT. It can be presumed that Multiple Sclerosis might affect subclinical atherosclerosis during the time. Because CIMT was not associated with the annual relapse rate along with the clinical course, and because the patients were not in acute disease phases, it can be suggested that perhaps the acute inflammations might not be the only reason for abnormal CIMT. These findings must be studied and validated by further well-designed studies.

To our knowledge, this is one of the first studies of its kind to evaluate CIMT among patients with Multiple Sclerosis. However, as mentioned above, this study is a cross-sectional study and findings just demonstrate some accompanying factors and not the cause-and-effect relationship.

5. Conclusion

CIMT among patients with Multiple Sclerosis Multiple Sclerosis might show a particular pattern.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Sources of funding

No funding was secured for this study.

Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent

Not applicable.

Registration of research studies

1. Name of the registry: Research Registry.
2. Unique Identifying number or registration researchregistry7495.

Hyperlink to the registration (must be publicly accessible): https://www.researchregistry.com/browse-the-registry#home/registrationdetails/61cc7fc5f02a6d001eff229f/

Guarantor

Dr Mohammad Reza Motamed and Dr. Zahra Mirzaasgari.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

Dr. Sara Esmaeili and Dr. Mohammad Taghi Joghataei: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr. Marjan rahimi farzanand, and Dr. Seyedeh Niloufar Rafiee Alavi and Dr. Negin Mahmoudi Hamidabad: Designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

Dr Mohammad Reza Motamed and Dr. Zahra Mirzaasgari: Coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

Declaration of competing interest

The authors deny any conflict of interest in any terms or by any means during the study.

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References

[1] D.M. Wingerchuk, B.G. Weinshenker, Disease modifying therapies for relapsing multiple sclerosis, BMJ (Clinical research ed) 354 (2016) i3518.
[2] C. Walton, R. King, L. Rechtman, W. Kaye, E. Leray, R.A. Marrie, et al., Rising prevalence of multiple sclerosis worldwide: insights from the Atlas of MS, Mult. Scler. 26 (14) (2020) 1816–1821, third ed.
[3] C. Solaro, M. Ponzio, E. Moran, P. Tanganelli, R. Pizio, G. Ribizzi, et al., The changing face of multiple sclerosis: prevalence and incidence in an aging population, Mult. Scler. 21 (10) (2015) 1244–1250.
[4] H.M.B. Lunde, J. Assmus, K.M. Myhr, L. Bø, N. Grytten, Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study, J. Neurol. Neurosurg. Psychiatr. 88 (8) (2017) 621–625.
[5] H. Brønnum-Hansen, N. Koch-Henriksen, E. Stenager, Trends in survival and cause of death in Danish patients with multiple sclerosis, Brain : J. Neurol. 127 (Pt 4) (2004) 844–850.
[6] J.P. Casas, T. Shah, A.D. Hingorani, J. Danesh, M.B. Pepys, C-reactive protein and coronary heart disease: a critical review, J. Intern. Med. 264 (4) (2008) 295–314.
[7] I. Kushner, M. Elyan, Why does C-reactive protein predict coronary events? Am. J. Med. 121 (7) (2008) e11.
[8] S.M. Ranadive, H. Yan, M. Weikert, A.D. Lane, M.A. Linden, T. Baynard, et al., Vascular dysfunction and physical activity in multiple sclerosis, Med. Sci. Sports Exerc. 44 (2) (2012) 238–243.
[9] R.A. Marrie, R. Rudick, R. Horwitz, G. Cutter, T. Tyry, D. Campagnolo, et al., Vascular comorbidity is associated with more rapid disability progression in multiple sclerosis, Neurology 74 (13) (2010) 1041–1047.
[10] A. Abou-Raya, S. Abou-Raya, Inflammation: a pivotal link between autoimmune diseases and atherosclerosis, Autoimmun. Rev. 5 (5) (2006) 331–337.
[11] P. Libby, Inflammation in atherosclerosis, Nature 420 (6917) (2002) 868–874.
[12] P. Willeit, L. Tschiderer, E. Allara, K. Reuber, L. Seekircher, L. Gao, et al., Carotid intima-media thickness progression as surrogate marker for cardiovascular risk: meta-analysis of 119 clinical trials involving 100 667 patients, Circulation 142 (7) (2020) 621–642.
[13] M.A. Espeland, D.H. O'Leary, J.G. Terry, T. Morgan, G. Evans, H. Mudra, Carotid intimal-media thickness as a surrogate for cardiovascular disease events in trials of HMG-CoA reductase inhibitors, Curr. Contr. Trials Cardiovasc. Med. 6 (1) (2005) 3.
[14] W.T. Hu, J.C. Howell, T. Ozturk, U. Gangishetti, A.L. Kollhoff, J.M. Hatcher-Martin, et al., CSF cytokines in aging, multiple sclerosis, and dementia, Front. Immunol. 10 (480) (2019).
[15] N. Farzan, P. Ghezelbash, F. Hamidi, A. Zeraatchi, Pulmonary thromboembolism with transthoracic ultrasound and computed tomography angiography, Clin. Res. J 15 (12) (2021) 1337–1342.
[16] A.J. Thompson, B.L. Banwell, F. Barkhof, W.M. Carroll, T. Coetzee, G. Comi, et al., Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria, Lancet Neurol. 17 (2) (2018) 162–173.
[17] A.M. Johri, V. Nambi, T.Z. Naqvi, S.B. Feinstein, E.S.H. Kim, M.M. Park, et al., Recommendations for the assessment of carotid arterial plaque by ultrasound for the characterization of atherosclerosis and evaluation of cardiovascular risk: from the American society of echocardiography, J. Am. Soc. Echocardiogr. : official publication of the American Society of Echocardiography 33 (8) (2020) 917–933.
[18] G. Mathew, R. Agha, S. Group, Strocss 2021: strengthening the reporting of cohort, cross-sectional and case-control studies in surgery, Int. J. Surg. 96 (2021) 106165.
[19] B. Yuksel, P. Koc, E. Ozaydin Goksu, E. Karacay, F. Kurtulus, Y. Cekin, et al., Is multiple sclerosis a risk factor for atherosclerosis? Journal of neuroradiology = Journal de neuroradiologie 48 (2) (2021) 99–103.
[20] T. Omerzu, J. Magdič, R. Hojs, U. Potočnik, M. Gorenjak, T.H. Fabjan, Subclinical atherosclerosis in patients with relapsing-remitting multiple sclerosis, Wien Klin. Wochenschr. (2021), https://doi.org/10.1007/s00508-021-01862-7.