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" Volumetric Brain Parameters in Association with Cognitive functions in a Sample of Egyptian Multiple Sclerosis Patients"

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Abstract:

Background: Cognitive impairment is highly prevalent in multiple sclerosis (MS). Early detection of cognitive dysfunctions using radiological techniques may help in controlling and may prevent such complications.

Objectives: To assess the relationship between cognitive impairment and brain volumes in Egyptian MS patients.

Methods: A cross-sectional study was conducted including 50 Egyptian MS patients with diverse subtypes. Adult patients diagnosed with MS based on revised McDonald's 2017 criteria, free from other neurological or systemic disorder affecting brain structure and had EDSS $\leq$ 8. The recruited patients were subjected to cognition assessment using Montreal Cognitive Assessment (MoCA)test and brain volume estimation using magnetic resonance imaging (MRI). Demographic, clinical, and radiological data were compared using appropriate tests and SPSS software version 26.

Results: Out of 50 MS patients, MOCA was normal in 36% patients and abnormal in 64% patients. As regard regional brain volumes (Cortical, Cortical Normalized, left thalamus, right thalamus and lesion load) were statistically significant smaller in abnormal MOCA patients compared to normal with P-value were (0.004,0.001,0.002,0.001 and 0.004) respectively.

Conclusion: Early estimating brain volume in Egyptian MS patients may help in prediction of cognitive impairment among them. large sample size is required to assess the predictive value of volumetry.

Keywords: *Brain Volumetry - Cognition - Multiple Sclerosis*

Introduction:

Multiple sclerosis (MS) is an immune-mediated disease affecting the central nervous system (1). MS is gaining special attention among health care providers because it is considered one of the most common causes of disability among youth (2). The main cause of MS is still unknown, but pathological studies suggested abnormal immune reaction that results in sensitization of B-lymphocytes by the help of T-lymphocytes which secrete antibodies to attack glial cells called oligodendrocytes in the CNS which in the end causes the pattern of demyelination and remyelination of the neurons (3). The clinical picture varies widely according to the affected tract, but the diagnosis should follow the revised Macdonald's criteria by the aid of contrast enhanced magnetic resonance imaging and presence of oligoclonal bands in the cerebrospinal fluid (4). The relapsing remitting course of the disease is the most common. However, other phenotypes such as primary progressive and secondary progressive courses are getting special attention in clinical trials targeting preservation of brain volume and preventing further disability by preventing the clinical and subclinical attacks (5).

The loss of brain volume was reported in MS patients compared with normal controls in variable rates regardless of the disease course (6).The earliest affected areas of the brain are the frontal and superior temporal lobes, then it progresses to affect other eloquent brain areas such as motor cortex and pyramidal tract (7). Although MS had been believed to be a white matter disease in earlier studies, recent studies showed grey matter affection at various stages of the disease and among all phenotypes (8). The caudate nucleus and the thalamus along with cortical neurons were reported to be affected (9). During MS activity the White Matter (WM) volume can increase due to an inflammatory process which leads to an artificial increase in volume that masks the brain atrophy process (10). Detection of attacks was traditionally based on MRI with gadolinium enhancement to detect the activity of lesions (11). Newer techniques were developed to detect subclinical and grey matter attacks such as MRI volumetry (12). MRI volumetric studies use manual, semi-automated and fully automated methods to calculate the targeted brain volume (13).The fully automated technique is the most widely used because it speeds up the analysis and allows the use of complex data and integrates multiple modalities and algorisms of calculations (14). Global brain atrophy detected by MRI volumetry is a better prognostic tool compared with conventional MRI white matter load regarding motor disability (15). Also, cognitive decline was associated with loss brain volume in the Gray Matter(GM) of neocortex and basal ganglia along with widening of the third ventricle and atrophy of the corpus callosum (16). So, MRI volumetry is a clinically relevant tool to predict the motor disability and cognitive decline of MS patients which can help in modifying the line of

treatment (17). The lines of treatment in MS target the inflammatory mediators, T-lymphocytes, B-lymphocytes, and bone marrow according to disease severity (18). They can be categorized into platform therapy and high efficacy therapy (19). Escalation, induction, and lateral shifting are the strategies used to control disease activity according to factors such as the expanded disability status score (EDSS), MRI lesion burden, and the course of progression (20). The high efficacy disease modifying therapy was proven to decrease brain volume loss in patients with multiple sclerosis compared with platform therapies (21). To the best of our knowledge, cognitive impairment in relation to brain volume changes among Egyptian MS patients has not been studied. Therefore, we aimed to assess cognitive function in MS patients using Montreal Cognitive Assessment (MoCA) test. MRI volumetry to estimate whole, white matter, grey matter, and regional brain, and to study the relationship between the brain volume and cognitive impairment.

Methods:

Design

A cross-sectional study was conducted at neurology department of Al-Azhar University Hospital, Cairo, Egypt, during the period from august 2021 to February 2022. The study was approved by the Ethics Committee of the faculty of medicine, Al-Azhar university. Informed consent was taken.

Patients

A consecutive sample of MS patients including 50 patients was recruited. The inclusion criteria included adult patients aged 18 – 60 years, diagnosed with MS according to revised McDonald's 2017 criteria, EDSS $\leq$ 8, and no relapse within previous 3 months. However, patients with other causes of neurological or cognitive disorders were excluded including brain or spinal cord ischemia, brain or spinal tumor, infectious disease affecting neurological system, genetic disorders, systemic autoimmune disorders, brain or spinal trauma, or drug abuse affecting neurological system were excluded.

Assessments

The recruited MS patients were subjected to magnetic resonance imaging (MRI) upon outpatient hospital admission as a routine follow-up assessment. MRI-based longitudinal technique was utilized for the following assessments; lesion load assessment as volume in mm^3 using MIPAV (Medical Image Processing, Analysis and Visualization) software, whole brain volume in mm^3 , and regional brain volume mm^3. FMRIB Software Library (FSL) software (22) and Structural Image Evaluation using Normalization of Atrophy (SIENAX) method (23)

were used for brain volume estimation. Cognitive dysfunction was assessed using MOCA test; MoCA scores range between 0 and 30.patients with score < 26 were classified as abnormal score indicating cognitive dysfunction, while patients with score ≥ 26 were normal add 1 for every educated patient less than 12 years) (24).

Statistical analysis

Quantitative data were expressed as mean ± standard deviation (SD) and compared using independent samples t-test after ensuring data normality, while qualitative data were expressed as frequencies and percentages, and compared using Chi-square test after ensuring the test assumptions, otherwise extract Fisher test was used. All tests were conducted at 0.05 level of significance using Statistical package for the social sciences (SPSS) version. 26 software 2019.

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Results:

Table (1): Comparison between Normal and Abnormal MOCA multiple sclerosis patients regarding demographic and baseline factors

Variables	**Normal MOCA**	**Abnormal MOCA**	**P-value**
	No.= 18	**No.= 32**	
Age	31 ± 11.62	34.33 ± 9.68	0.283
Sex:			
Female	12 (66.7%)	21 (65.6%)	0.941
Male	6 (33.3%)	11 (34.4%)	
Phenotype:			
RRMS	13 (72.2%)	23 (71.9%)	
CIS	2 (11.1%)	4 (12.5%)	0.420
SPMS	2 (11.1%)	4 (12.5%)	
PPMS	1 (5.6%)	1 (3.1%)	
Disease duration to Image	2.44 ± 1.89	6.31 ± 4.86	0.002*`
Disease duration now	6.56 ± 3.28	8.94 ± 5.24	0.088
DMT Years	1.5 ± 0.71	2.17 ± 1.19	0.467
DMT Current:			
Interferon beta-1a	1 (50.0%)	6 (50.0%)	0.792
Fingolimod	1 (50.0%)	4 (33.3%)	
Interferon beta-1b	0 (0.0%)	2 (16.7%)	
EDSS	2.25 ± 1.82	3.66 ± 1.6	0.006*
PASAT	32.28 ± 7.72	48.59 ± 17.5	<0.001*

CIS; Clinically isolated syndrome, DMT; Disease modifying therapy, EDSS; The Expanded Disability Status Scale, PASAT; Paced Auditory Serial Addition Test, PPMS; Primary progressive multiple sclerosis, SPMS; Secondary progressive multiple sclerosis.

as regard age, sex, phenotype, disease duration now, DMT years and DMT current there are no statistically significant difference between normal and abnormal MoCA group while there are statistically significant difference as regarded disease duration to image, EDSS and

PASAT 3 (p 0.002 , p 0.006 and p<0.001 respectively) in comparing normal with abnormal MoCA group.

Table (2): Comparison between Normal and Abnormal MOCA multiple sclerosis patients regarding whole brain volume data

MRI data	**Normal MOCA**	**Abnormal MOCA**	**P-value**
	No.= 18	**No.= 32**	
WBV	974262.96 ± 131412.03	966442.84 ± 115934.25	0.828
WBV N	1441022.98 ± 103958.99	1418035.05 ± 115183.97	0.487
Maximal Brain Volume	1249268.06 ± 136916.45	1261344.9 ± 136234.16	0.765
Percentage Atrophy	0.78 ± 0.06	0.77 ± 0.06	0.489

MOCA; Montreal Cognitive Assessment, WBV; Whole brain volume, WBV N; Whole brain volume normalized.

as regard whole brain volume data between normal and abnormal MoCA group there were no statistically significant difference as regard; Whole brain volume, Whole brain volume normalized, Maximal Brain Volume and Percentage Atrophy with P-value of (0.828, 0.487 , 0.765 and 0.489) respectively in comparing normal with abnormal MoCA group.

Table (3): Comparison between Normal and Abnormal MOCA multiple sclerosis patients regarding regional brain volume and lesion load data

MRI data	Normal MOCA	Abnormal MOCA	P-value
	No.= 18	No.= 32	
GMV	507635.18 ± 66382.26	501861.75 ± 72081.42	0.781
GMV N	751729.57 ± 60740.28	731455.03 ± 103506.86	0.452
WMV	466627.78 ± 70465.6	465727.58 ± 62274.94	0.963
WMV N	689293.41 ± 58883.68	681578.11 ± 56670.44	0.651
Cortical	398688.24 ± 53321.77	451455.67 ± 61934.71	0.004*
Cortical N	590398.66 ± 47285.48	488745.57 ± 70784.91	<0.001*
Thalamus L	6811.38 ± 1049.27	6020.2 ± 1184.2	0.002*
Thalamus R	6629.91 ± 958.35	5456.38 ± 1186.86	0.001*
Caudate L	3191.92 ± 673.48	2943.12 ± 627.28	0.196
Caudate R	3226.84 ± 555.77	3151.51 ± 556.74	0.648
Putamen L	4112.17 ± 963.18	3884.67 ± 895.77	0.406
Putamen R	3985.63 ± 823.31	3804.38 ± 946.68	0.500
Pallidum L	1797.34 ± 903.09	1598.67 ± 700.92	0.391
Pallidum R	1707.48 ± 643.85	1610.78 ± 574.6	0.593
Hippo L	3179.91 ± 620.57	3264.46 ± 662.15	0.660
Hippo R	3246.41 ± 493.78	3296.18 ± 635.14	0.776
Amygdala L	1154.34 ± 214.35	1178.41 ± 251.18	0.734
Amygdala R	1162.13 ± 220.11	1141.16 ± 275.15	0.783
Brainstem	19415.92 ± 1805.7	19448.41 ± 2658.94	0.963
Lesion Load	12595.41 ± 18830.41	24996.62 ± 20593.31	0.004*

GMV; Grey matter volume, L; Left, N; Normalized, R; Right, WMV; White matter volume.

As regard regional brain volumes (Cortical, Cortical Normalized, left thalamus, right thalamus and lesion load) were statistically significant smaller in abnormal MOCA patients compared to normal with P-value were (0.004,0.001,0.002,0.001 and 0.004) respectively.

Discussion:

Brain volume is reduced in MS patients in different degrees in relation to MS disease progression (25), and it is supposed to be used for early diagnosis of MS (26). Moreover, brain volume changes in relation to cognitive score has been studied among MS patients in different countries (27).

In this study, significant associations were found between some regional brain volumes and

cognitive dysfunction. However, whole brain volume, white matter volume, and grey matter volumes were not significantly associated with the cognitive dysfunction in MS patients, although a numerical difference has been reported favoring patients with normal MOCA.

This results is consistent with Golan et al, as their study conducted on 91 MS patients reported significant correlations between global cognitive score and whole brain volume (r = 0.4), white matter volume (r = 0.4), and grey matter volumes (r = 0.25) (28).

Another study reported among 195 relapsing MS patients by Fenu et al showed significant correlations between three different cognition scores and each of normalized brain volume and normalized grey matter volume. However, nonsignificant correlation was found with normalized white matter volume (27).

Regionally, in our study we found significant associations between cognitive impairment and cortical, normalized cortical, left thalamus, and right thalamus volumes. This result is consistent with Golan et al, it reported significant correlation global cognitive score and thalamic volume in MS patients (r = 0.42). However, cortical grey matter volume was not significantly correlated with the global cognitive score (28). It was also reported significant correlations between different cognition scores and cortical grey matter volume which was consistent with our findings (27).

In disagreement with our findings, a study Houtchens et al aimed to assess thalamic atrophy and cognition among 79 MS patients using MRI and Minimal Assessment of Cognitive Function in Multiple Sclerosis test. The study reported significant association between MS and thalamic volume ($p < 0.0001$) and brain parenchymal fraction ($p < 0.001$), but no significant group difference between the patients with and without cognitive impairment subgroups (29).

In this study, lesion load was also larger in patients with cognitive dysfunction indicated by abnormal MOCA. In agreement with our results, fluid-attenuated inversion recovery (FLAIR) lesions and T1 black holes were significantly correlated with global cognitive score among 91 MS patients (28). But Houtchens et al study reported numerical, but not significant difference between MS patients with and without cognitive dysfunction in FLAIR lesion volume and T1 lesion volume (29).

We reported non-significant association between cognitive impairment and the following regional brain volumes; caudate, putamen, hippocampi, amygdala,, and brain stem volumes. Consistently, with Houtchens et al whom reported that hippocampi volume was not significantly correlated with the global cognitive score in MS patients (28). To the best of our knowledge, the other brain regions in relation to cognitive impairment in MS have not been studied.

Conclusion: Cortical and thalamic regional brain volumes may be more indicative for early detection of cognitive impairment in Egyptian MS patients. However, larger sample size is required to assess the detecting value of whole brain volume and grey matter volume. Early estimating brain volume and following MS patient up for developing cognitive impairment is required to be included in future studies.

Abbreviations:

CIS; Clinically isolated syndrome, DMT; Disease modifying therapy, EDSS; The Expanded Disability Status Scale, FSL; FMRIB Software Library, GMV; Grey matter volume, L; Left, MIPAV; Medical Image Processing, Analysis, and Visualization, MOCA; Montreal Cognitive Assessment, N; Normalized; , PASAT; Paced Auditory Serial Addition Test, PPMS; Primary progressive multiple sclerosis, R; Right ,SIENAX; Structural Image Evaluation using Normalization of Atrophy ,SPMS; Secondary progressive multiple sclerosis,,WBV;Whole brain volume, WBV N; Whole brain volume normalized, and WMV; White matter volume.

REFRENCES:

1. Barkhane Z, Elmadi J, Satish Kumar L, Pugalenthi LS, Ahmad M, Reddy S. Multiple Sclerosis and Autoimmunity: A Veiled Relationship. Cureus. 2022;14(4):e24294.
2. Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. Multiple sclerosis (Houndmills, Basingstoke, England). 2020;26(14):1816-21.
3. Huang WJ, Chen WW, Zhang X. Multiple sclerosis: Pathology, diagnosis and treatments. Experimental and therapeutic medicine. 2017;13(6):3163-6.
4. Hartung HP, Graf J, Aktas O, Mares J, Barnett MH. Diagnosis of multiple sclerosis: revisions of the McDonald criteria 2017 - continuity and change. Current opinion in neurology. 2019;32(3):327-37.
5. Klineova S, Lublin FD. Clinical Course of Multiple Sclerosis. Cold Spring Harbor perspectives in medicine. 2018;8(9).
6. Andravizou A, Dardiotis E, Artemiadis A, Sokratous M, Siokas V, Tsouris Z, et al. Brain atrophy in multiple sclerosis: mechanisms, clinical relevance and treatment options. Auto- immunity highlights. 2019;10(1):7.
7. Pagani E, Rocca MA, Gallo A, Rovaris M, Martinelli V, Comi G, et al. Regional brain atrophy evolves differently in patients with multiple sclerosis according to clinical phenotype. AJNR American journal of neuroradiology. 2005;26(2):341-6.
8. Klaver R, De Vries HE, Schenk GJ, Geurts JJ. Grey matter damage in multiple sclerosis: a pathology perspective. Prion. 2013;7(1):66-75.
9. Harrison DM, Oh J, Roy S, Wood ET, Whetstone A, Seigo MA, et al. Thalamic lesions in multiple sclerosis by 7T MRI: Clinical implications and relationship to cortical pathology. Multiple sclerosis (Houndmills, Basingstoke, England). 2015;21(9):1139-50.
10. Roosendaal SD, Bendfeldt K, Vrenken H, Polman CH, Borgwardt S, Radue EW, et al. Grey matter volume in a large cohort of MS patients: relation to MRI parameters and disability. Multiple sclerosis (Houndmills, Basingstoke, England). 2011;17(9):1098-106.
11. Saade C, Bou-Fakhredin R, Yousem DM, Asmar K, Naffaa L, El-Merhi F. Gadolinium and Multiple Sclerosis: Vessels, Barriers of the Brain, and Glymphatics. AJNR American journal of neuroradiology. 2018;39(12):2168-76.
12. Kalincik T, Vaneckova M, Tyblova M, Krasensky J, Seidl Z, Havrdova E, et al. Volumetric MRI markers and predictors of disease activity in early multiple sclerosis: a longitudinal cohort study. PloS one. 2012;7(11):e50101.
13. El Garhy NM, El Toukhy MM, Fatouh MM. MR volumetry in detection of brain atrophic changes in MS patients and its implication on disease prognosis: retrospective study. Egyptian Journal of Radiology and Nuclear Medicine. 2022;53(1):1-20.
14. Raji A, Ostwaldt A-C, Opfer R, Suppa P, Spies L, Winkler G. MRI-based brain volumetry at a single time point complements clinical evaluation of patients with multiple sclerosis in an outpatient setting. Frontiers in neurology. 2018;9:545.
15. Krauss W, Gunnarsson M, Nilsson M, Thunberg P. Conventional and synthetic MRI in multiple sclerosis: a comparative study. European radiology. 2018;28(4):1692-700.
16. Tóth E, Faragó P, Király A, Szabó N, Veréb D, Kocsis K, et al. The contribution of various MRI parameters to clinical and cognitive disability in multiple sclerosis. Frontiers in Neurology. 2019;9:1172.
17. Eshaghi A, Prados F, Brownlee WJ, Altmann DR, Tur C, Cardoso MJ, et al. Deep gray matter volume loss drives disability worsening in multiple sclerosis. Annals of neurology. 2018;83(2):210-22.
18. Rafiee Zadeh A, Ghadimi K, Ataei A, Askari M, Sheikhinia N, Tavoosi N, et al. Mechanism and adverse effects of multiple sclerosis drugs: a review article. Part 2. International journal of physiology, pathophysiology and pharmacology. 2019;11(4):105-14.
19. Stankiewicz JM, Weiner HL. An argument for broad use of high efficacy treatments in early multiple sclerosis. Neurology(R) neuroimmunology & neuroinflammation. 2020;7(1).

20. Casanova B, Quintanilla-Bordás C, Gascón F. Escalation vs. Early Intense Therapy in Multiple Sclerosis. Journal of personalized medicine. 2022;12(1).
21. Honce JM, Nair KV, Hoyt BD, Seale RA, Sillau S, Engebretson E, et al. Brain Atrophy Rates for Stable Multiple Sclerosis Patients on Long-Term Fingolimod versus Glatiramer Acetate. Front Neurol. 2020;11:1045.
22. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage. 2004;23:S208-S19.
23. Guo C, Ferreira D, Fink K, Westman E, Granberg T. Repeatability and reproducibility of FreeSurfer, FSL-SIENAX and SPM brain volumetric measurements and the effect of lesion filling +in multiple sclerosis. European radiology. 2019;29(3):1355-64.
24. Chou KL, Lenhart A, Koeppe RA, Bohnen NI. Abnormal MoCA and normal range MMSE scores in Parkinson disease without dementia: cognitive and neurochemical correlates. Parkinsonism & related disorders. 2014;20(10):1076-80.
25. Filippi M, Rovaris M, Iannucci G, Mennea S, Sormani M, Comi G. Whole brain volume changes in patients with progressive MS treated with cladribine. Neurology. 2000;55(11):1714-8.
26. Traboulsee A, Li D. The role of MRI in the diagnosis of multiple. Adv Neurol. 2006;98:125-46.
27. Fenu G, Lorefice L, Arru M, Sechi V, Loi L, Contu F, et al. Cognition in multiple sclerosis: Between cognitive reserve and brain volume. Journal of the Neurological Sciences. 2018;386:19-22.
28. Golan D, Doniger GM, Srinivasan J, Sima DM, Zarif M, Bumstead B, et al. The association between MRI brain volumes and computerized cognitive scores of people with multiple sclerosis. Brain and Cognition. 2020;145:105614.
29. Houtchens M, Benedict R, Killiany R, Sharma J, Jaisani Z, Singh B, et al. Thalamic atrophy and cognition in multiple sclerosis. Neurology. 2007;69(12):1213-23.