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Executive Functions Impairment in Patients with Multiple Sclerosis in Relation to Lesion Burden in MRI: A Case-Control Study

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ABSTRACT

Background: Multiple Sclerosis (MS) is a chronic demyelinating autoimmune disease impacting the central nervous system. It manifests through various neurological dysfunctions, including cognitive impairments, especially in executive functions.

Objective: This study aimed to explore the relationship between executive function impairment and lesion burden in MS as evidenced by MRI.

Results: The MS patients demonstrated lower scores in the five words test (learning median score 4 vs. 5, $p<0.001$; recall median score 4.5 vs. 5, $p<0.001$) and Stroop Color-Word Test (SCWT) (median score in color naming 73.5 vs. 82.5, $p=0.001$). MRI assessments revealed a median of 6 lesions, predominantly in the parietal (84.8%) and frontal (78.3%) lobes. A significant positive correlation was found between the number of lesions and color test score ($r=0.493$, $p=0.001$) and a negative correlation with recall score ($r=-0.334$, $p=0.023$).

Conclusions: The study demonstrated that there was a relationship between executive functions impairment in MS and lesion burden in MRI. This can be observed through significant difference between MS patients and healthy control group in tests of working memory and inhibition. Also, our findings suggest that site, number of lesions and brain atrophy in MRI correlated significantly with tests of working memory and inhibition.

Keywords: Executive functions impairment, Multiple sclerosis, Lesion burden, MRI.

INTRODUCTION

Multiple sclerosis (MS) is a long-term autoimmune condition that targets the central nervous system, marked by recurring demyelinating events within the white matter of the brain. Such events lead to axonal harm that intensifies progressively [1]. The origins of MS remain partially unclear, though it's thought to result from an interplay of genetic predispositions and environmental influences, including lack of vitamin D and exposure to certain viruses, initiating an immune attack against the myelin coatings [2].

Recent studies have observed an increasing trend in both the prevalence and incidence of MS globally, indicating a rising public health concern. MS is categorized into various types, including Primary Progressive MS (PPMS), Secondary Progressive MS (SPMS), and Relapsing-Remitting MS (RRMS) with diagnosis relying on the McDonald Criteria. These criteria necessitates evidence of disease spread in time and space, ascertained through clinical and imaging assessments [3, 4].

Neurological symptoms in MS are diverse, affecting motor, sensory, and visual functions. Cognitive and psychiatric issues are significant, with 40-65% of patients experiencing neuropsychological changes, which are severe in 6-10% of cases [5]. Impairments in attention, memory, processing speed, and executive functions are common, particularly in the later stages of the disease [6].

In diagnosing MS, MRI is essential revealing CNS lesions that vary in size, number, and location. While,

MRI-detected brain atrophy shows a moderate association with cognitive decline in MS patients, it does not serve as a conclusive predictor [7]. Studies show a strong correlation between cognitive impairment and overall lesion burden, as well as brain atrophy in MRI, reflecting the complex nature of MS pathology [8, 9].

Therefore, this study aimed to assess the correlation between executive function impairment and lesion burden in MRI in multiple sclerosis.

PATIENTS AND METHODS

Study design and population: This case-control study was carried out on 92 participants recruited from the Neuropsychiatry Outpatient Clinic of Benha University Hospital between March 2023 and November 2023. The study was carried out with two equal-sized groups. The first group, known as the study group, consisted of patients diagnosed with RRMS. The second group, serving as the control group, was comprised of healthy cases (age- and sex-matched).

Inclusion criteria: Patients of both sexes aged between 20 and 40 years old, patients diagnosed with relapsing-remitting multiple sclerosis (Revised McDonald criteria

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for the diagnosis of multiple sclerosis 2017) [10], with the last attack being more than three months, and average IQ.

Exclusion criteria: Patients with other types of multiple sclerosis, including SPMS, PPMS, PRMS, and clinical isolated syndrome. Multiple sclerosis patients who were in relapse or had experienced a relapse within the past three months, as well as those who had undergone corticosteroid therapy. Patients with comorbid medical, neurological, or psychiatric disorders, cognitive sequelae, or mental retardation.

METHODS

All participants were subjected to the following:

1. **A semi-structured interview including questions about:**

The assessment for MS involved detailed history taking, covering socio-demographic data like age, sex, residency, marital status, special habits of medical importance, occupation, education, number of life attacks, and treatment plan. This is complemented by a comprehensive general, medical, and neurological examination. Diagnosis of MS is then made using the Revised McDonald 2017 criteria.

2. **Psychometric assessment:**

Technical card about assessment of special cognitive functions test: Developed by **Ben Eisa (2014)** [11], this Arabic language test assesses working memory, learning, and recall. It comprises a working memory test measuring memory capacity, a numerical memory test with normal and reverse sequences, and a five-word test where test-takers recall words immediately and after a delay, with cues provided if necessary. The entire test takes about 20 to 30 minutes to complete.

The Stroop Colour-Word Interference Test (SCWT): The Stroop test, established by Stroop in 1992, assesses cognitive inhibition and inhibitory control by requiring participants to perform tasks under interference [12]. It involves three trials: reading color names, naming the colors of squares, and identifying the ink color of differently colored words while ignoring the word itself. The test, given orally, records errors and measures the time taken to complete each task, with the final trial's time serving as the raw score.

3. **Radiological assessment:**

All participants underwent a comprehensive radiological examination using brain MRI, which included standard T1-weighted images (T1WI), T2-weighted images (T2WI), and fluid-attenuated inversion recovery (FLAIR) images for each individual [7]. Furthermore, a cervical MRI was performed, capturing both T1WI and T2WI. The evaluation of these MRI scans focused on detecting hyperintense areas on T2WI and FLAIR images, indicative of lesions. These lesions were then mapped and classified according to their location within specific anatomical regions such as the frontal, parietal, temporal, occipital lobes, cerebellum, brain stem, and spinal cord. This process also included evaluations for signs of brain atrophy. The analysis adopted metrics like the total volume or area of lesions and the number or scores of lesions to assess the extent of overall brain lesion load [13].

Sample size calculation:

The sample size was calculated by Stata Corp. 2021. Stata Statistical Software: Release 17. College Station, TX: Stata Corp LLC., based on the correlation test model and **Sperling *et al.*** [14], who correlated executive function impairment in patients of multiple sclerosis to lesion burden in MRI, using the following formula [15], using α error 5% and a power of 80%:

$$N = \left[\frac{Z_\alpha + Z_\beta}{0.5 * \ln\left[\frac{1+r}{1-r}\right]}\right]^2 + 3$$

$Z\alpha$ = The standard normal deviation for α of 0.05 = 1.96, $Z\beta$ = The standard normal deviation for power of 80% = 0.84, r = Expected mean correlation coefficient (r=0.4) [14], thus required minimal sample size was 46 subjects per group.

Ethical considerations: The study was done after being accepted by The Research Ethics Committee, Benha University. All patients provided written informed consents prior to their enrolment. The consent form explicitly outlined their agreement to participate in the study and for the publication of data, ensuring protection of their confidentiality and privacy. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data from the study were processed using the IBM SPSS software, version 20.0. For parametric datasets, descriptive statistics such as mean ± standard deviation were used, while non-parametric data were described using median and range. Qualitative data were analyzed through the calculation of frequencies and percentages. The study employed Chi-square tests to examine categorical data, Student's t-tests for quantitative data with normal distribution, Pearson's correlation coefficients to identify relationships, and Mann-Whitney tests for data not following a normal distribution. Statistical significance was established at a p-value ≤ 0.05.

RESULTS

There was a statistically significant difference regarding socioeconomic status and residency. On the other hand, both groups were comparable regarding age, sex distribution, marital status, occupation, education, and habits (Table 1).

Table (1): Demographic data of the studied groups

Variable		Study group (n=46)	Control group (n=46)	P value
Age (years)	Median (IQR)	34 (27 - 40)	30.5 (26 - 37)	0.295
	Range	18 - 40	18 - 40	
Sex	Male	20 (43.5%)	17 (37%)	0.524
	Female	26 (56.5%)	29 (63%)	
Marital status	Single	11 (23.9%)	12 (26.1%)	0.568
	Married	33 (71.7%)	34 (73.9%)	
	Divorced	2 (4.3%)	0 (0%)	
Occupation	Not working	13 (28.3%)	10 (21.7%)	0.609
	Student	6 (13%)	9 (19.6%)	
	Working	27 (58.7%)	27 (58.7%)	
Education	Secondary school	6 (13%)	3 (6.5%)	0.359
	Diploma	11 (23.9%)	16 (34.8%)	
	Bachelor's degree	29 (63%)	27 (58.7%)	
Socioeconomic state	Low	11 (23.9%)	10 (21.7%)	**0.002***
	Moderate	29 (63%)	15 (32.6%)	
	High	6 (13%)	21 (45.7%)	
Habits	No	38 (82.6%)	40 (87%)	0.562
	Smoking	8 (17.4%)	6 (13%)	
Residency	Rural	14 (30.4%)	26 (56.5%)	**0.012***
	Urban	32 (69.6%)	20 (43.5%)	

Data are presented as frequency (%) unless otherwise mentioned, *: Statistically significant as P value<0.05

MS patients elicited significantly decreased five-word test scores (learning and recall) than the control (P<0.001). On the other hand, there was no statistically significant difference between both groups in numerical memory test scores. By comparing both groups, patients with MS evidenced significantly lower SCWT scores (word, color, and color of word) in 45 seconds compared to the controls (P<0.001, 0.001, 0.006 respectively). As for the rate of SCWT errors, MS patients made significantly more errors identifying colors and colors of words than the controls (P=0.001, <0.001, respectively). Meanwhile, word errors were insignificantly different between both studied groups (Table 2).

Table (2): Technical card about special cognitive function tests assessment and Stroop color-word test (SCWT) score in 45 seconds assessment of the studied groups

Variable		Study group (n=46)	Control group (n=46)	P value
Numerical memory test	Normal sequence	10.5 (10 - 12)	12 (9 - 13)	0.566
	Reverse sequence	5 (4 - 7.25)	6 (4 - 9)	0.061
Five words test	Learning	4 (4 – 5)	5 (5 - 5)	**<0.001***
	Recall	4.5 (4 – 5)	5 (5 - 5)	**<0.001***
Word				
Score	Median (IQR)	73 (68.75 - 86.25)	93 (89 - 110)	**<0.001***
Errors	0	44 (95.7%)	46 (100%)	0.495
	1	2 (4.3%)	0 (0%)	
Color				
Score	Median (IQR)	73.5 (60 - 79.25)	82.5 (73.75 - 98.25)	**0.001***
Errors	0	36 (78.3%)	46 (100%)	
	1	7 (15.2%)	0 (0%)	**0.001***
	2	2 (4.3%)	0 (0%)	
	3	1 (2.2%)	0 (0%)	
Color of word				
Score	Median (IQR)	43.5 (38 - 55.5)	51 (45.75 - 57)	**0.006***
Errors	0	18 (39.1%)	41 (89.1%)	
	1	9 (19.6%)	2 (4.3%)	
	2	5 (10.9%)	2 (4.3%)	**<0.001***
	3	5 (10.9%)	1 (2.2%)	
	4	5 (10.9%)	0 (0%)	
	5	4 (8.7%)	0 (0%)	

The median number of lesions detected by MRI in MS patients was 6. Most lesions and were found in the parietal (84.8%) and frontal lobes (78.3%). while the spinal cord, cerebellar and occipital lesions accounted for 58.7%, 34.8% and 28.3% of the total ones respectively. Moreover, 17.4% of patients elicited brain atrophy (Table 3).

Table (3): MRI results of MS patients

Variable		Study group (n=46)
Number of lesions	Median (IQR)	6 (5 – 7)
Location of lesions	Parietal	39 (84.8%)
	Frontal	36 (78.3%)
	Spinal cord	27 (58.7%)
	Cerebellum	16 (34.8%)
	Occipital	13 (28.3%)
	Temporal	9 (19.6%)
	Fronto parietal	5 (10.9%)
	Midbrain	2 (4.3%)
	Pontine	2 (4.3%)
	Medulla oblongata	2 (4.3%)
Brain atrophy	Yes	8 (17.4%)

There was a significant positive correlation between the number of lesions and each color test score (r=0.493, P=0.001) and color of word test errors (r=0.352, P=0.016). Meanwhile, an inverse correlation of a significant value was detected between the number of lesions and each recall score (r=-0.334, P=0.023) and color test errors (r=-0.519, P<0.001). Additionally, there was no significant correlation between the number of lesions and numerical memory test scores, learning scores in five-word tests, and SCWT, including word score and errors and color of word score (Table 4).

Table 4: Correlation between the number of lesions and executive function test scores in MS patients

Executive function tests	Number of lesions	
	rs	P value
Numerical memory test		
Normal sequence	0.199	0.185
Reverse sequence	0.23	0.125
Five words test		
Learning	-0.005	0.972
Recall	-0.334	**0.023***
SCWT Word		
Score	0.233	0.119
Errors	-0.213	0.154
Color		
Score	0.493	**0.001***
Errors	-0.519	**<0.001***
Color of word		
Score	0.236	0.115
Errors	0.352	**0.016***

rs: Spearman's rank correlation coefficient.

DISCUSSION

Multiple sclerosis (MS) is a chronic autoimmune disease marked by relapsing demyelinating lesions in the brain, leading to various neurological and cognitive impairments. The complexity of its pathology and the increasing global prevalence make MS a significant public health concern. Recent studies have shown a correlation between cognitive impairment in MS patients and MRI findings, particularly lesion burden and brain atrophy, although these associations are not always consistent [16].

Regarding socioeconomic status and residency, our results were in line with **Dong *et al.*** [17] who found that there was no statistical difference regarding age, sex, educational level, and smoking. In disagreement with our study, **ELshebawy *et al.*** [18] reported that low educational level was a predictor of cognitive impairment. Also, in contrast to our study, **Uher *et al.*** [19] reported that age, educational level, and unemployment have statistically significant differences in relation to cognitive impairment.

Concerning daily executive function (EF) abilities, our findings align with those proposed by **Till *et al.*** [20] indicating that individuals with pediatric-onset MS might encounter challenges in daily EFs spanning various functional areas. This is evidenced by clinically high scores observed in approximately 20% of the participants on at least one scale of the BRIEF (Behavior Rating Inventory of Executive Functions).

In relation to the frequency of errors on the SCWT, our outcomes concur with those identified by **Cortez *et al.*** [21] who reported that one-third (33.33%) of MS patients exhibited a higher number of errors and experienced increased reaction times. This was particularly noticeable on the aspects of the Stroop test that demand inhibitory control and working memory.

Regarding scores in words test and SCWT (Stroop color-word test), including word and color scores and errors and color of word score, our results are in agreement with **ELshebawy *et al.*** [18] who reported that longer disease duration and frequent relapses were predictors of cognitive impairment. Our study also agrees with **Dong *et al.*** [17] who reported that disease duration, average disease attacks, and EDSS score were predictors of cognitive impairment with p values of 0.044, 0.004 and 0,004 respectively.

Concerning the findings from MRI examinations, our research found some concordance with the observations of **Cortez *et al.*** [21] regarding the predominant impact of demyelinating lesions in the subcortical white matter areas of the frontal and occipital lobes, as well as the periventricular zone. Similarly, **Saad *et al.*** [7] findings align to an extent indicating that demyelinating lesions within the cortical regions are primarily situated in the frontal lobe, with decreasing prevalence towards the temporal, parietal and occipital lobes, and finally, the cerebellar area [7].

Contrastingly, our results diverge from those of **Abou-Elmaaty *et al.*** [22] who reported no significant variance in lesion distribution between cognitively impaired and unimpaired MS patients across all examined brain regions, except for the temporal lobe. This discrepancy is somewhat echoed in the study by **Paul *et al.*** [23] who found no significant differences in T1 and T2 lesion volumes between RRMS patients with and without

cognitive deficits. These outcomes hint at the possibility that focal white matter lesions alone do not fully account for cognitive dysfunction in MS, suggesting the involvement of other factors, such as damage to the normal-appearing white and gray matter. However, in alignment with our findings, **Abou-Elmaaty *et al.*** [22] observed that brain atrophy was significantly more prevalent among MS patients exhibiting cognitive abnormalities compared to those without. A statement reported by **Camp *et al.*** [24] who noted a correlation between cognitive decline and various MRI metrics, including the total T2 lesion volume, overall cerebral volume, dimensions of the corpus callosum, and the size of the third ventricle, highlighting the complex interplay between structural brain changes and cognitive outcomes in MS [24].

LIMITATIONS

The study's limitations include a small sample size potentially affecting statistical significance, lengthy questionnaires causing participant boredom and possibly inaccurate responses, and an incomplete assessment of executive functions, suggesting a need for further research on omitted components.

RECOMMENDATION

Further well-designed randomized studies on large geographical scale and on larger sample size and longer period of follow up. Further studies are recommended to be conducted on other types of MS patients e.g. secondary progressive MS and primary progressive MS. Further studies about factors that may affect executive functions in MS e.g. fatigue and depression could be assessed and the correlation between them and executive functions should be determined. Screening for executive functions impairment should be done in all MS patients and proper treatment should be offered and developing more sensitive MRI technologies.

CONCLUSION

The study demonstrated that there was relationship between executive functions impairment in MS and lesion burden in MRI. This could be observed through significant difference between MS patients and healthy control group in tests of working memory and inhibition. Also, our findings suggest that site, number of lesions and brain atrophy in MRI correlated significantly with tests of working memory and inhibition. These finding not only advance our understanding of cognitive decline in MS but also pave the way for more approaches to enhance cognitive wellbeing of individuals with this complex neurological disorder.

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REFERENCES

1. **Lassmann H (2018)**: Multiple Sclerosis Pathology. Cold Spring Harb Perspect Med., 8: 276-79.
2. **Tiwari S, Lapierre J, Ojha C *et al.* (2018)**: Signaling pathways and therapeutic perspectives related to environmental factors associated with multiple sclerosis. J Neurosci Res., 96: 1831-46.
3. **Siger M (2022)**: Magnetic Resonance Imaging in Primary Progressive Multiple Sclerosis Patients : Review. Clin Neuroradiol., 32: 625-41.
4. **Klineova S, Lublin F (2018)**: Clinical Course of Multiple Sclerosis. Cold Spring Harb Perspect Med., 8: 317-24.
5. **Migliore S, Ghazaryan A, Simonelli I *et al.* (2017)**: Cognitive Impairment in Relapsing-Remitting Multiple Sclerosis Patients with Very Mild Clinical Disability. Behav Neurol., 2017: 7404289.
6. **Borkowska A, Daniluk B, Adamczyk K (2021)**: Significance of the Diagnosis of Executive Functions in Patients with Relapsing-Remitting Multiple Sclerosis. Int J Environ Res Public Health, 18: 123-29.
7. **Saad M, Bilal M, Gabr W *et al.* (2019)**: The Diagnostic Role of Brain MRI in Detection of Multiple Sclerosis Related Cognitive Impairment. Behav Brain Sci., 9: 313.
8. **DeLuca G, Yates R, Beale H *et al.* (2015)**: Cognitive impairment in multiple sclerosis: clinical, radiologic and pathologic insights. Brain Pathol., 25: 79-98.
9. **Abou Elmaaty A, Flifel M, Zarad C (2019)**: Correlation between brain magnetic resonance imaging, cognitive dysfunction and physical dysability in multiple sclerosis. Egypt J Neurol Psychiatr Neurosurg., 55: 54.
10. **Thompson A, Banwell B, Barkhof F *et al.* (2018)**: Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol., 17: 162-73.
11. **Ben-Eisa Z (2014):** Technical card on cognitive function tests: Generation Center for Scientific Research: Lectures of the Educational Training and Teacher Preparation Course: Sidi Mohammed Ben Abdullah University, Cognitive Sciences Laboratory - Fez - Morocco 2014 .Available from: https://shorturl.at/bCEOR.
12. **Stroop J (1992)**: Studies of interference in serial verbal reactions. Journal of Experimental Psychology: General, 121: 15.
13. **Mollison D, Sellar R, Bastin M *et al.* (2017)**: The clinico-radiological paradox of cognitive function and MRI burden of white matter lesions in people with multiple sclerosis: A systematic review and meta-analysis. PLoS One, 12: 177727.
14. **Sperling R, Guttmann C, Hohol M *et al.* (2001)**: Regional magnetic resonance imaging lesion burden and cognitive function in multiple sclerosis: a longitudinal study. Archives of neurology, 58: 115-21.

15. B**rowner W, Newman T, Cummings S *et al.* (2022):** Designing clinical research. 4 ed: Lippincott Williams & Wilkins, 2022: 98.
16. **Lemus H, Warrington A, Rodriguez M (2018)**: Multiple Sclerosis: Mechanisms of Disease and Strategies for Myelin and Axonal Repair. Neurol Clin., 36: 1-11.
17. **Dong X, Xu G, Wang J *et al.* (2022)**: Clinical and MRI predictors of cognitive decline in patients with relapsing-remitting multiple sclerosis: A 2-year longitudinal study. Mult Scler Relat Disord., 65: 103838.
18. **Elshebawy H, Fahmy E, Elfayoumy N *et al.* (2021)**: Clinical predictors to cognitive impairment in multiple sclerosis patients. Egypt J Neurol Psychiatr Neurosurg., 57: 1-6.
19. **Uher T, Krasensky J, Sobisek L *et al.* (2018)**: Cognitive clinico-radiological paradox in early stages of multiple sclerosis. Ann Clin Transl Neurol., 5: 81-91.
20. **Till C, Ho C, Dudani A *et al.* (2012)**: Magnetic resonance imaging predictors of executive functioning in patients with pediatric-onset multiple sclerosis. Arch Clin Neuropsychol., 27: 495-509.
21. **Aldrete-Cortez V, Duriez-Sotelo E, Carrillo-Mora P *et al.* (2013)**: [Correlation between demyelinating lesions and executive function decline in a sample of Mexican patients with multiple sclerosis]. Neurologia, 28: 394-9.
22. **Abou Elmaaty A, Flifel M, Zarad C (2019)**: Correlation between brain magnetic resonance imaging, cognitive dysfunction and physical dysability in multiple sclerosis. Egypt J Neurol Psychiatr Neurosurg., 55: 1-8.
23. **Paul R, Beatty W, Schneider R *et al.* (1998)**: Cognitive and physical fatigue in multiple sclerosis: relations between self-report and objective performance. Appl Neuropsychol., 5: 143-8.
24. **Camp S, Stevenson V, Thompson A *et al.* (1999)**: Cognitive function in primary progressive and transitional progressive multiple sclerosis: a controlled study with MRI correlates. Brain, 122 (Pt 7): 1341-8.