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Cortical Lesions in a Sample of Egyptian Multiple Sclerosis Patients

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ABSTRACT

Background: multiple sclerosis is an inflammatory demyelinating disease with a neurodegenerative component mainly characterized by progressive accumulation of focal white matter (WM) lesions. The degree of cortical damage at baseline was associated with the progression of disability. Cognitive deficits could be better explained by cortical lesions (CLs) than by WM lesions. Fatigue in MS could be due to damage to the cortico striato thalamo cortical circuit. **Aim of the Work:** to detect (CLs) in MS patients and correlate these lesions with physical disability, cognitive dysfunction and fatigue. **Subjects and Methods:** a case-control study on 64 subjects including 44 known multiple sclerosis patients diagnosed according to revised McDonald's criteria 2017. **Results:** we observed a statistically significant difference between MS patients and healthy controls as regard number of (CLs), Symbol Digit Modality Test (SDMT), Fatigue Severity Scale (FSS) and P300 wave latencies and amplitudes. Secondary progressive (SPMS) subgroup was affected more than relapsing remitting (RRMS) subgroup. (CLs) were located mainly in temporal lobes. **Conclusion:** This study suggested that cortical affection is directly associated with physical and cognitive disability progression.

Keywords: Cortical Lesions, Multiple Sclerosis.

INTRODUCTION

Cognitive Impairment affects a large proportion of patients with MS and has a profound impact on their life activities. Although cognitive deficits have been observed from the early stages of the disease, they are more frequent in chronic progressive MS and tend to be worse over time[1]. It is recognized that fatigue, one of the most common and debilitating complaints associated with the disease. Fatigue may not impact upon any one particular domain of cognitive functioning, but rather acting to limit the overall capacity of individuals with MS to sustain mental activity[2]. MRI studies have shown that focal damage (i.e. cortical lesions) and diffuse damage (i.e. neuronal loss, widespread cortical thinning and damage to normal-appearing gray matter (NAGM)) occurs in all MS phenotypes and can be present early in the disease[3]. Despite its good sensitivity in detecting white matter lesions, conventional MRI (proton density, T2-weighted, FLAIR and pre- and post- gadolinium [Gd] T1-weighted sequences) is not adequate for the detection of(CLs), because such lesions are typically small, have poor contrast with the surrounding normal gray matter, and because of partial volume effects from the cerebrospinal fluid (CSF)[4]. Double inversion recovery (DIR) sequences markedly improved the sensitivity of MRI to detect (CLs)[5].

AIM OF THE WORK

To detect (CLs) in MS patients and correlate these lesions with physical disability, cognitive dysfunction and fatigue.

SUBJECTS AND METHODS

This study was carried out on 64 subjects during the period from February 2018 to August 2018. **The study was approved by the Ethics Board of Al-Azhar University. They were divided into two main groups: Group I:** included 20 healthy volunteers (15 females and 5 males). Their ages ranged between 23 and 43 years (with a mean age of 30.500 + 7.55 SD). All subjects were matched for age, sex, educational level with group II and free from any physical, neurologic, psychiatric or cognitive impairments. **Group II:** included 44 patients fulfilled the Revised McDonald's criteria for diagnosis of multiple sclerosis 2017[9] and this group included 32 females and 12 males. Their ages ranged between 21 and 45 years (with a mean of 28.568 ± 5.695 SD). A written informed consent was taken from patients and healthy controls before the start of the study. The study protocol was approved by the ethics committee of faculty of medicine El- Azhar University. ***Inclusion criteria:*** Age more than 18 years old, known cases of MS diagnosed according to revised McDonald's criteria 2017. ***Exclusion criteria:*** systemic diseases affecting cognition such as thyroid dysfunction, hepatic or renal impairment, history of diabetes or hypertension, history of drugs or alcohol abuse.

Methods:

All patients were subjected to: A-clinical assessment: Full history and neurological examination. **B-Assessment of disability:** using

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Expanded Disability Status Scale (EDSS) [6] It assesses five functional systems (pyramidal, cerebellar, brain stem, sensory, bowel and bladder). The severity of the EDSS is graded from 0 (normal neurological examination) to 10 (death due to MS). **C-Assessment of cognitive function:** using Symbol Digit Modality Test (SDMT) [7] as a rapid screening test. Examination of speed of visual information processing, complex visual scanning, and sustained attention. Participants have to verbally and / or by written form substitute meaningless symbols by the corresponding number. The score is the number of correct substitutions in 90 seconds. **D-Assessment of fatigue:** To assess the impact of fatigue on daily function, we used the Fatigue Severity Scale (FSS) [8] The scale consists of nine statements related to fatigue that subjects rate according to their level of agreement measured on a seven-point scale (1, indicating "strongly disagree" to 7 indicating "strongly agree"). The FSS has been shown to have a high degree of internal consistency, validity, and sensitivity to clinical changes. **E. Neurophysiological assessment (event related potential P300 wave**): The P300 component, or cognitive potential, is a positive potential elicited by the recognition of a rare stimulus (odd ball paradigm) within a series of frequent stimuli and corresponds to the largest positive wave after the N1-P2 complex. P300 depends upon some abilities, such as attention, discrimination and memory, and reflects cortical activity. **F. MRI brain with** Double Inversion Recovery (DIR) technique using a 1.5T MR scanner (Philips Medical Systems). **a. Image acquisition**: All images were acquired using a 1.5-T machine (PhilipsMedical Systems) with a 33-mT/mpower gradient and a 16-channel head coil. No major hardware upgrades of the scanner occurred during the study period, and bimonthly quality assurance sessions took place to guarantee measurement stability. The DIR images were acquired from each subject (both healthy volunteers and patients):: repetition time,15 631 milliseconds; echo time, 25milliseconds; inversion time,3400 milliseconds; delay, 325 milliseconds; echo train length,17; 50 contiguous axial slices with a thickness of 3.0 mm; matrixsize, 130_256; and field of view, 250_200 mm2. **b. Image analysis:** All images were assessed by experienced Neuroradiologists who was blinded to the patients' identity. On DIR images, particular attention was devoted to identifying artifacts; CLs were defined as those lesions confined to the cortical ribbon and not involving the underlying subcortical WM.

RESULTS

There was a direct positive correlation between (age, duration of illness, P300 latency, EDSS) and number of cortical lesions. There was inverse correlation between (MMS, SDMT, P300 amplitude) and number of cortical lesions.

Table (1): Comparison between numbers of cortical lesions and age, education years, psychometric tests (MMSE, SDMT), fatigue scale, neurophysiological tests (P300 latency and amplitude), duration of illness and EDSS

Correlations		
	Number of cortical lesions	
	r	P-value
Age	0.447	0.003*
Education (Years)	-0.194	0.213
MMSE	-0.449	0.003*
SDMT	-0.688	<0.001*
Fatigue scale	0.173	0.268
P300 Latency	0.636	<0.001*
P300 Amplitude	-0.658	<0.001*
Duration of illness	0.530	<0.001*
EDSS	0.655	<0.001*

Table (2): Comparison between numbers of cortical lesions in MS patients' subgroups

Type of MS	Number of cortical lesions						T-Test	
	Range			Mean	±	SD	t	P-value
RRMS	2	-	9	5.720	±	1.948	-4.702	<0.001*
SPMS	2	-	15	9.556	±	3.382		

There was highly significant difference in number of cortical lesions between MS patients' subgroups, where it was more in SPMS than RRMS.

Table (3): Comparison between sites of cortical lesions and MS patients' subgroups

	Type of MS						Chi-Square	
	RRMS		SPMS		Total			
	N	%	N	%	N	%	X^2	P-value
T	22	88.00	16	88.89	38	88.37	0.008	0.929
F	17	68.00	12	66.67	29	67.44	0.008	0.927
P	10	40.00	11	61.11	21	48.84	1.867	0.172
O	6	23.08	10	55.56	16	36.36	4.849	0.028*

T=Temporal; **F**=Frontal; **P**=Parietal; **O**=Occipital

Cortical lesions were mainly located in the temporal lobe, followed by the frontal and the parietal then occipital lobe in both RRMS and SPMS.

Table (4): Comparison of fatigue scale between MS patients' subgroups and control

Fatigue	Type of MS								Chi-Square	
	RRMS		SPMS		Controls		Total			
	N	%	N	%	N	%	N	%	X^2	P-value
<36 Scale	13	50.00	7	38.89	19	95.00	39	60.94		
>36 Scale	13	50.00	11	61.11	1	5.00	25	39.06	14.731	0.001*
Total	26	100.00	18	100.00	20	100.00	64	100.00		

There was highly significant difference between MS patients' subgroups and control as fatigue scale, being more affected in SPMS than RRMS.

Table (5): Comparison of EDSS between MS patients' subgroups

Type of MS	EDSS						T-Test	
	Range			Mean	±	SD	t	P-value
RRMS	1.5	-	3.5	2.481	±	0.608	-16.641	<0.001*
SPMS	4.5	-	6.5	5.528	±	0.581		

There was highly significant difference in EDSS between MS patients' subgroups, where it was more in SPMS than RRMS.

Table (6): Comparison of SDMT between MS patients' subgroups and control

Type of MS	SDMT						ANOVA	
	Range			Mean	±	SD	F	P-value
RRMS	38	-	58	49.346	±	5.506	62.335	<0.001*
SPMS	24	-	55	37.444	±	9.654		
Controls	55	-	68	61.450	±	4.186		
TUKEY'S Test								
R&S				R&C			S&C	
<0.001*				<0.001*			<0.001*	

There was highly significant difference between MS patients' subgroups and control as regard SDMT, being more affected in SPMS than RRMS.

Table (7): Comparison of P300 latency between MS patients' subgroups and control

	P300 Latency						ANOVA	
	Range			Mean	±	SD	F	P-value
RRMS	298	-	362	330.269	±	18.205	36.978	<0.001*
SPMS	310	-	420	366.389	±	32.156		
Controls	290	-	332	307.800	±	8.320		
TUKEY'S Test								
R&S				R&C			S&C	
<0.001*				0.002*			<0.001*	

There was a significant difference between MS patients' subgroups and control as regard P300 Latency, being more affected in SPMS than RRMS.

Table (8): Comparison of P300 Amplitude between MS patients' subgroups and control

Type of MS	P300 Amplitude						ANOVA	
	Range			Mean	±	SD	F	P-value
RRMS	5.5	-	13.5	9.192	±	2.371	56.057	<0.001*
SPMS	2.5	-	9	5.278	±	1.801		
Controls	9	-	18	13.275	±	2.663		
TUKEY'S Test								
R&S				R&C			S&C	
<0.001*				<0.001*			<0.001*	

There was highly significant difference between MS patients' subgroups and control as regard P300 Amplitude, being more affected in SPMS than RRMS.

DISCUSSION

In our study, there was no significant difference between MS patients and healthy volunteers as regard demographic data (age, sex and education years). Fatigue in MS can be described as a feeling of extreme mental or physical exhaustion. It is one of the most common symptoms of MS; some studies say up to 60-80% of patients with MS have fatigue and can affect MS patients for hours, days or even months.[9] In our study about 56.9% of MS patients were complaining of fatigue in comparison to 5% of control. SPMS patients were the most affected (61.1%) then RRMS (40.7%). This was in line with ***Jougleux-Vie et al.***[10] who reached to the same finding. Increased physical disability (high EDSS scores) was associated with increased fatigue symptoms, thus fatigue symptoms were more common in SPMS, this result is in in agreement with the finding of ***Jougleux-Vie et al***[10] We proved that cognitive impairment comes with more fatigue symptoms and this going with that of ***Nocentini et al.***[11]***; Diamond et al.***[12] and ***Mattioli et al.***[13]. The Mini-Mental State Examination (MMSE) is one of the most popular screens of cognitive functioning; however, it is not an ideal test for screening cognitive impairment in MS patients, this may be due to that the item composition of the MMSE does not appear to be well suited to the pattern of cognitive impairment associated with MS. Only 2/44 (4.54%) of patients had bad performance in the test and they were of SPMS subtype; this was

near to results of ***Swirsky-Sacchetti et al.*** [14]who reported a low sensitivity of the test to MS-related cognitive impairment. In our study, P300 latency was prolonged in MS patients than healthy volunteers. When comparing different subtypes of MS, the P300 latency was prolonged in SPMS more than RRMS. This delay appears to be due to a disorder in the processing of change in temporal sound patterns, this may be conceived as an extra time taken to compare the incoming sound with the contents of a temporally ordered sensory memory store (the long auditory store or echoic memory), which generates a response when the next expected frequency change fails to occur. This conclusion is in agreement with that of ***Ellger et al.*** [15]**,*Gerschlager et al.*** [16] and ***Ivica et al.*** [17]which compared event related potentials in different subtypes of MS in across-sectional study and obtained the same results. P300 amplitude was reduced in MS patients than healthy volunteer. When comparing different subtypes of MS, the P300 amplitude was reduced more in SPMS than RRMS. This finding confirm that found by ***Comi et al.***[18]; ***Ellger et al.*** [15] ***and Magnano et al.***[19] and ***Ivica et al.***[17]**.** In our study the ERPs (P300 wave latency and amplitude) was of benefit in detecting cognitive disability in MS patients even in subtle cases this is approved by its high accuracy, thus the P300 is a fruitful tool in clinical research to identify abnormalities of cognitive processing especially in early stages of the disease when cognitive deficits may be subtle and less frank than in later stages. This concur the recommendations of ***Ivica et al.*** [17]**.** Our study revealed a significant correlation between total CLs number and the presence of cognitive impairment. This goes with that of **Curti**[20]**Calabrese** [21]**, Damasceno**[22]**, Mike**[23]**, Nelson**[24]and **Roosendaal**[25]**.** We found that CLs were mainly located in the temporal lobe (88.3%), followed by the frontal (67.44%) and the parietal (48.84%) then occipital lobe lesions (36.36%) as shown in **table 3**. This accord that observed by **Calabrese *et al***. [26] who reported that CLs were more frequently in the temporal and frontal lobes, while the occipital lobe is less affected, but in contrast with that found by **Curti *et al***. [20] in that frontal lobe was the commonest lobe affected.

CONCLUSION

From our study we concluded that correlation between CLs and cognitive impairment in MS obviously has relevant clinical implications, however; large MRI longitudinal studies are needed to explore in details these implications. We also suggest the need for developing more sensitive MRI technologies to increase our capacity to investigate cortical pathology in MS and its complex interaction with GM and WM damage in the determination of MS-related CI. Fatigue is a common disabling symptom in MS patients and should be screened and managed appropriately. Following up cognitive deterioration in the MS patients using both psychometric tests and event related potentials (ERPs) is of benefit. Further studies of the effect of DMTs on cognitive functions and offering cognitive rehabilitation for MS patients are recommended. Following up MS patients by imaging should not be restricted to new plaque formation but also include other techniques to detect NAWM and NAGM pathology.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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