Cognitive Dysfunction in Systemic Lupus Erythematosus

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Background: Is to investigate and detect the incidence of cognitive dysfunction in SLE patients by the different psychometric methods of assessment and to correlate them to disease activity by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), functional disability index by Health Assessment Questionnaire (HAQ), the presence of Antiphospholipid antibodies (APL) and EEG, P300 (latency and amplitude).

Subjects & Methods: 30 female patients with SLE had been studied in this work. They were selected according to the American College of Rheumatology (ACR) criteria for diagnosing SLE (The American College of Rheumatology, 1999), their age ranged between 17 and 37 years with a mean age of onset 25.37+SD of 4.468, mean disease duration of 5.92+3.72 years. This represents group I, as well as 20 healthy controls of matched age and sex. This represents group II. Both groups were subjected to different psychometric testing to detect cognitive dysfunction including Wechsler Adult Intelligence Scale (WAIS), Logical Memory Subtests of Wechsler Memory Scale and Trail Making test (part A and part B). The results of testing were correlated with disease activity measurement by SLEDAI and Health Assessment Questionnaire (HAQ), presence of Antiphospholipid antibodies (APL) and also EEG changes, P300 (latency and amplitude).

Results: The results showed statistically significant difference between SLE patients and controls on the arithmetic subtests of WAIS while there was highly statistically significant difference in information, vocabulary, picture arrangement, picture completion and block design subsets of WAIS, logical memory (A) and (B) subsets of Wechsler memory scale. The percentage of cognitive dysfunction among SLE patients according to verbal IQ and Full scale IQ subtests of WAIS was 43.3% while performance IQ was 33.3%, the percentage of cognitive dysfunction according to logical memory scale was 86.7%. Also, 43.3% showed functional impairment, 33.3% showed organic impairment according to Trail Making (A) While 16.7% showed functional impairment. As regards APL antibodies there were positive significant correlation between APL titre and SLEDAI score. As regards the correlation between cognitive dysfunction and APL subtypes, there was no statistically significant difference in the percentage of patients with any APL subtypes and patients with cognitive dysfunction. Also there was statistically significant difference between cognitive dysfunction and HAQ. In addition there was statistically significant difference between cognitive dysfunction and P300 (amplitude and latency). There were 13 patients with abnormal EEG frequency and 8 patients with generalized EEG paroxysms, while there were 12 patients having abnormal P300 latency and 7 patients with abnormal P300 amplitude.

Conclusion: There was a high evidence of the presence of cognitive dysfunction in SLE patients in the study. A positive significant correlation between APL titre and SLEDAI score, but there was no statistically significant difference between cognitive dysfunction and APL subtypes. Some of SLE patients have abnormal EEG and abnormal P300 latency and amplitude.

Keywords: SLE, Cognitive dysfunction, SLEDAI, HAQ, APL, EEG.

Abbreviations:
SLEDAI: Systemic Lupus Erythematosus Disease Activity Index
HAQ: Health Assessment Questionnaire
EEG: Electroencephalogram
ACR: American College of Rheumatology
WAIS: Wechsler Adult Intelligence Scale
APL: Antiphospholipid antibodies
SLE: Systemic Lupus Erythematosus
IQ: Intelligent Quotient

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INTRODUCTION

Neuropsychiatric Lupus Erythromatosis (NPSLE) refers to the manifestations that develop secondary to involvement of the CNS in patients with SLE. These clinical features are characterized by some investigators as either diffuse e.g., organic brain syndrome, coma, depression and psychosis or complex e.g. organic brain syndrome with stroke or seizure and psychiatric presentation with stroke or seizure disturbances of mental function are the most common symptoms (West, et al. 1995).

A psychiatric disturbance due to CNS lupus is a diagnosis of exclusion, all other possible causes of the observed symptoms must therefore be considered,

including infection, electrolyte abnormalities, renal failure, drug effects, mass lesions, arterial emboli and primary psychiatric disorders (Such as bipolar disorder or severe stress disorder) resulting from a chronic life threatening disease (Miguel, et al. 1994).

The term lupus cerebritis refers to the neuropschiatric manifestations of lupus that appear to have an organic rather than a specific pathophysiologic mechanisms. The distinction between organic and functional causes of some neuropsychiatric symptoms can occasionally be made by a saying for specific auto-antibodies such as antineuronal antibodies (Hanly, et al. 1999 and Denburg, et al. 1987).

Cognitive defects may be associated with the presence of elevated levels of antineuronal antibodies, APL or antibodies to N-methyl D-aspartate (NMDA) receptors (Carbotte, et al. 1986 and Omdal, et al. 2005).

Many investigators have tried to characterize the antigenic targets of antineuronal antibodies in SLE. The NMDA is present at high density in the hippocampus, a neuroanatomic structure that is closely linked to learning and memory (Hanly, et al. 2006).

In a recent study, found an elevated levels of anti-NR2 antibodies which is a subtype of NMDA, in the CSF more frequently in patients with diffuse NPSLE of whom 12.5% had cognitive dysfunction (Arinuma, et al. 2008).

Concerning APL, it induces a procoagulant state (Bonfa, et al. 1987) and are associated with focal manifestations of NPSLE such as stroke (Bonfa, et al. 1987).

Persistently elevated levels of anticardiolipin antibodies are associated with decline in cognitive function, possibly due to thrombosis within vessels of minute caliber (Hanly, et al. 1999 and Menon, et al. 1999).

Intrathecal production of APL in patients with NPSLE (Martinez-Cordero, et al. 1997), their association with diffuse cognitive impairment and evidence of in-vitro modulation of neuronal function, raise the alternative possibility of a direct pathogenic effect on neurons (Chapman, et al. 1999).

Cytokines may function as neuromodulators as well as inflammation mediators (Vitkovic, et al. 2000). Initial studies showed association between increased intracranial levels of IL-6 and seizures (Hirohata and Miyamoto, 1990) and between increased CSF levels of interferon-α and lupus psychosis (Shiozawa, et al. 1992).

Subsequent studies provided evidence of intrathecal production of IL-6 (Isshi and Hirohata, 1998 and Trysberg, et al. 2004), and identified other candidate cytokines such as IL-10, IL-2 and IL-8 (Trysberg, et al. 2004) which may be produced by neuronal cells and glial cells (Shiozawa, et al. 1992 and Isshi and Hirohata, 1998).

One study identified a relationship between pro-inflammatory serum IL-6 production and learning deficits in SLE patients (Kozora, et al. 2001). Another demonstrated a correlation between elevated levels of CRP, which is a non specific marker of inflammation and deficits in information processing (Trysberg, et al. 2004).

In patients with NPSLE, especially those with cognitive impairment, levels of metalloproteinases (MMP-a) are elevated in the serum (Trysberg, et al. 2004) and the CSF (Trysberg, et al. 2004).

The correlation between CSF MMP-a levels, proinflammatory cytokines and biomarkers of neural and glial degradation in SLE patients suggests that enhanced production of MMP-a is linked to CNS damage in SLE (Trysberg, et al. 2004).

Some authors implicated the role of vascular abnormalities in patients with NPSLE, such as no inflammatory microvasculopathy caused by leucocyte plugging, mediated by complement and endothelial cell activation (Trysberg, et al. 2004).

The neuropeptides oxytocin, vasopressin, calcitonin gene related peptide and substance P have been linked to behavioral and cognitive changes in animal and human studies (Trysberg, et al. 2004).

A functional (Psychological) process is assumed in a patient with cognitive defects who has none of these antibodies, a negative MRI and EEG and psychometric testing that rules out organic disease.

Clinical studies showed a variable impact of cognitive dysfunction in SLE (Trysberg, et al. 2004; Kozora, et al. 2001 and Hirohata and Hayakawa, 1999).

Studies in SLE focusing on measurement of the integrity of blood brain barrier, distinguishing between cognitive dysfunction and normal cognition and differentiating anatomic and functional abnormalities are all possible (Kozora, 2008).

The aim of our study is to detect cognitive dysfunction in SLE patients and to correlate them to the presence of auto-antibodies and to correlate them to EEG, P30 latency and amplitude findings.

SUBJECTS AND METHODS

30 patients with SLE has been collected from the Rheumatology and Rehabilitation Department, Cairo University Hospital. As well as 20 healthy subjects, as a control comprised the material of this work.

They Were Divided Iinto Two Groups:

Group I: 30 female SLE patients with a mean age of onset of 25.37+4.46 y and a mean disease duration of 4.55+3.92y.

Group II: 20 female healthy subjects with matching age and sex.

Criteria of inclusion were based on the revised ACR criteria (Hochberg, 1997). The patients were subjected to a questionnaire adopted for SLE which includes history taking, present history, general and locomotor system examination.

We had excluded mental retardation, history of depressive disorders, other major psychiatric disorders and organic mental disorders.

Participants in this study provided written consent to undergo neurophysiological testing and other measures.

Laboratory Investigations:

The patients were subjected to the following laboratory investigations:
- ESR, CRP, CBC.
- Renal function: Bun and serum creatinine.
- Urine analysis for the presence of proteinuria, hyaline or granular casts, RBC's.

Serologic Tests:

ANA, Anti DNA, ACL: IgG
IgM
Lupus anticoagulants
C3, C4

Medications Given:

Whether the patient is taking corticosteroids, hydroxychloroquine, Azathioprine, NSAIDS, Mycophenolate Mofotil, cyclophosphamide or Methotrexate.

Imaging Techniques:

Chest x-ray, Echocardiography, abdominal U.S, Assessment of disease activity:
- Using (SLEDAI) (Bombardier, et al. 1992). The SLEDAI consists of 24 variables covering 9 organ systems and some immunological tests scored according to weights.

The final weight calculated with maximum score possible is 105.

Grading of Disease Activity:

Disease activity was detected according to SLEDAI score into:
- Mild activity 0-10.
- Moderate activity 10-20.
- Severe activity 20-45.
- Very severe activity >45.

Assessment of Health Assessment Questionnaire (HAQ) disability index was done (Bruce and Fries, 2003).

All Subjects in the Study Were Subjected to the Following Psychometric Tools to Detect Cognitive Dysfunction:

1. Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1944; Wechsler, 1955 and Wechsler, 1981).
2. Logical memory subsets of Wechsler Memory Scale (Wechsler, 1987).
3. Trail Making test (part A and part B) (Reitan, 1958).

Neurophysiological Testing:

20 out of the 30 SLE patients where subjected to:
- Conventional EEG.
- P300 (latency and amplitude).

RESULTS

On comparing the SLE patients and control group on WAIS, logical memory subsets of Wechsler memory scale and Trail Making test (part A and part B), there were statistically significant difference ($P < 0.05$) on the Arithmetic subtest of WAIS while there was highly statistically significant difference ($P < 0.001$) in information, vocabulary, picture arrangement, picture completion and block design subtest of WAIS, logical memory (A), logical memory (B) subtests of Wechsler memory scale. Other subtests did not show statistically significant differences (Table 2).

The percentage of cognitive dysfunction among SLE patients according to the results of the verbal IQ and Full scale IQ subtests of WAIS was 43.3% while performance IQ subtests of WAIS was 33.3%, the percentage of cognitive dysfunction according to the results of logical memory scale was 86.7%. Among SLE patients, 43.3% showed functional impairment, 33.3%

showed organic impairment according to Trail Making (A). While 16.7% showed functional impairment, there was no organic impairment according to Trail Making (B) (Table 3).

There was no statistically significant difference in the percentage of patients with any APL subtypes and patients with cognitive dysfunction in (Table 6).

On correlating cognitive dysfunction in SLE patients and disease activity index (SLEDAI), WAIS scale had shown statistically significant difference (P <0.05) between disease activity and digit span, arithmetic, full scale IQ, also there was highly statistically significant difference (P= <0.001) between arithmetic subtest of WAIS and disease activity index while there was statistically significant difference between Trail Making Test (part B) and functional disability detected by HAQ (Table 8).

As shown in this table there was highly statistically significant differences (P <0.05) between disease duration, HAQ and SLEDAI. There was highly statistically significant differences (P <0.001) between HAQ and SLEDAI.

Table (11) shows that 12 (60%) among SLE pt. had abnormal P300 latency while there was 7(35%) had abnormal P300 amplitude.

Table (12) shows that the mean of P300 latency among SLE patients was more than the control group.

The above table shows that there was a statistically significant correlation between Digit span subtest of WAIS and P300 amplitude showing that the lower the P300 amplitude, the worse the Digit span. while there was no statistically significant difference between other subsets and P300 latency and amplitude (Table 13).

Table (14) shows that 40% among SLE patients had abnormal EEG paroxysms while 65% had slowing of EEG.

On correlating cognitive dysfunction and EEG findings, it showed no statistically significant difference between either EEG frequency (Table 15).

Table (16) shows that there was a statistically significant correlation between information subtest of WAIS and the occurrence of EEG paroxysm, showing that the worse the information, the more the occurrence of EEG paroxysms.

Table 1: Descriptive statistics in SLE patients and control groups:

	Mean+SD	Range
Patients age in ys (n= 30)	25.37+4.46	17-37
Control (n= 20)	29.47+5.50	20-40
Disease duration	4.55+3.92	1-15

Table 2: Comparison between SLE patients and control groups according to the results of the subtests of WAIS, logical memory subtests of Wechsler memory scale and Trail Making test (A&B):

	Type	Mean	Std. deviation	P-value
Information	Control	11.42	1.465	0.000 (H.S)
	Case	7.17	2.640	
Comprehension	Control	12.95	1.779	0.293
	Case	12.23	2.921	
Digit span	Control	9.89	2.558	0.000
	Case	6.70	1.822	
Arithmetic	Control	10.21	1.475	0.010*
	Case	8.30	2.867	
Similarities	Control	10.89	1.560	0.918
	Case	10.83	2.260	
Vocabulary	Control	12.32	2.473	0.000**
	Case	7.17	2.276	
Picture arrangement	Control	11.95	3.045	0.000**
	Case	8.29	1.802	
Picture completion	Control	11.53	1.954	0.001**
	Case	9.03	2.593	
Block design	Control	12.74	3.124	0.000**
	Case	8.97	2.906	
Object assembly	Control	12.05	2.198	0.229
	Case	11.10	2.917	
Digit symbol	Control	12.42	1.835	0.006
	Case	10.40	3.092	
Verbal IQ	Control	109.89	9.938	0.000**
	Case	89.77	16.328	
Performance IQ	Control	114.11	12.337	0.000**
	Case	94.87	19.292	
Full scale IQ	Control	112.00	11.776	0.000**
	Case	93.07	13.570	
Deterioration index	Control	5.93	4.284	0.094
	Case	10.77	14.446	
Logical memory (A)	Control	11.79	1.813	0.000**
	Case	8.23	2.176	
Logical memory (B)	Control	12.7895	2.27496	0.000**
	Case	9.5667	2.28463	
Trail making (A)	Control	47.16	26.897	0.112
	Case	60.24	27.663	
Trail making (B)	Control	97.5263	60.18986	0.684
	Case	103.7052	44.97060	

Significant <0.05 Highly significant <0.001

Table 3: Percentage of cognitive dysfunction among SLE patients according to the results of the subtests of WAIS, logical memory subtests of Wechsler memory scale and Trail Making (A&B):

	WAIS			Logical memory	Trail making (A)		Trail making (B)	
	Verbal IQ	Performance IQ	Full scale IQ		Functional	Organic	Functional	Organic
Number	13	10	13	26	13	1	5	0
Percent	43.3%	33.3%	43.3%	86.7%	43.33%	3.33%	16.67%	0%

Table 4: Percentage of APL antibodies between SLE patients:

N	APL	ACL		LA
		IgG	IgM	
30	12	9	3	6
Percentage	40%	30%	10%	20%

Table 5: Showing the correlation between ACL titre and SLEDAI score:

N	ACL	SLEDAI	P	R
30	208+1.52	22.00+1.7	<0.001	0.768

Table 6: Showing the correlation between cognitive dysfunction and APL subtypes:

Cognitive dysfunction	APL	ACL		LA
		IgG	IgM	
Verbal IQ	P= 0.176	P= 0.1000	P= 0.1000	P= 0.360
Performance IQ	P= 0.461	P= 1.000	P= 1.000	P= 1.000
Full scale	P= 0.176	P= 1.000	P= 1.000	P= 0.672
Logical memory	P= 0.632	P= 1.000	P= 0.360	P= 1.000
Trail making	P= 0.547	P= 0.691	P= 1.000	P= 0.672
Trail Making A (organic)	P= 0.400	P= 0.300	P= 0.100	P= 0.200
Trail Making B (functional)	P= 0.364	P= 0.143	P= 1.000	P= 0.254
Trail Making B (organic)	No statistics because it is a constant being absent in all 30 studied cases			

Table 7: SLEDAI and HAQ data:

Data		Number of patients (30)
SLEDAI	Range	0-40
	Mean+SD	22.00+12.70
HAQ	Range	0-3
	Mean+SD	1.32+576

Table 8: Correlation between cognitive dysfunction in SLE patients and disease activity by SLEDAI and functional disability by HAQ:

		SLEDI	HAQ
Information	Pearson correlation	0.209	0.395
	Sig. (2-tailed)	0.494	0.182
Comprehension	Pearson correlation	0.418	0.400
	Sig. (2-tailed)	0.155	0.176
Digit span	Pearson correlation	0.645*	0.325
	Sig. (2-tailed)	0.017	0.279
Arithmetic	Pearson correlation	0.748**	0.464
	Sig. (2-tailed)	0.003	0.110
Similarities	Pearson correlation	-0.092	0.199
	Sig. (2-tailed)	0.765	0.515
Vocabulary	Pearson correlation	0.000	0.056
	Sig. (2-tailed)	1.000	0.856
Picture arrangement	Pearson correlation	0.388	-0.016
	Sig. (2-tailed)	0.213	0.959
Picture completion	Pearson correlation	0.359	0.166
	Sig. (2-tailed)	0.228	0.588
Block design	Pearson correlation	-0.090	0.073
	Sig. (2-tailed)	0.770	0.813
Object assembly	Pearson correlation	-0.215	-0.289
	Sig. (2-tailed)	0.481	0.338
Digit symbol	Pearson correlation	0.538	0.496
	Sig. (2-tailed)	0.058	0.085
Verbal IQ	Pearson correlation	0.364	0.133
	Sig. (2-tailed)	0.222	0.664
Performance IQ	Pearson correlation	-0.177	-0.093
	Sig. (2-tailed)	0.562	0.762
Full scale IQ	Pearson correlation	0.667*	0.497
	Sig. (2-tailed)	0.013	0.084
Deterioration index	Pearson correlation	0.242	0.224
	Sig. (2-tailed)	0.427	0.461
Logical memory (A)	Pearson correlation	0.066	0.118
	Sig. (2-tailed)	0.831	0.702
Logical memory (B)	Pearson correlation	0.407	0.337
	Sig. (2-tailed)	0.168	0.261
Trail making (A)	Pearson correlation	-0.573	-0.250
	Sig. (2-tailed)	0.051	0.433
Trail making (B)	Pearson correlation	-0.503	-0.579*
	Sig. (2-tailed)	0.80	0.38

Table 9: Laboratory findings of SLE patients:

Patients (n= 30)	Mean+SD	Range
ESR	31.6+14.2	10-80
HB (g/dl)	10.4+1.10	8-12.7
WBC's	6.4601+3.337	1-16
Lymphocytes	11.032+986.1	223.7
Platelets	264.6+85.052	110-451
C3 (n= 90-110 mg/dL)	70.2+45.8	13.4-180
C4 (n= 10-40 mg/L)	19.2+11.7	4.3-42
Creatinine	1.02+0.59	0.3-3.2
AST	23.4+6.69	18-50
24 h proteins gm/day	0.82+0.91	0-4.3

Table 11: P300 findings in SLE patients:

SLE	P300 latency (msec)	P300 amplitude (µv)
N= 20	12 (60%) pt. had abnormal P300 latency	7 (35%) pt. had abnormal P300 amplitude

Table 12: Comparison regarding P300 latency between SLE and control groups:

	SLE group (mean+SD) N= 20	Control group (mean+SD) N= 20
P300 latency (msec)	336.0+5.95	304.39+20.91

Table 10: Correlation between age and disease duration, HAQ, parameter of disease activity (SLEDAI):

		Age	Disease duration	SLEDI	HAQ
Age	Pearson correlation	1	-0.060	0.066	0.075
	Sig. (2-tailed)		0.768	0.730	0.694
	N	30	30	30	30
Disease duration	Pearson correlation	-0.060	1	-0.605**	-0.519**
	Sig. (2-tailed)	0.768		0.001	0.006
	N	30	30	30	30
SLEDI	Pearson correlation	0.066	-0.605**	1	0.706**
	Sig. (2-tailed)	0.730	0.001		0.000
	N	30	30	30	30
HAQ	Pearson correlation	0.075	-0.519**	0.706**	1
	Sig. (2-tailed)	0.694	0.006	0.000	
	N	30	30	30	30

Table 13: Correlation between SLEDAI , HAQ and cognitive function in SLE patients and P300 (latency and amplitude):

		P300 latency	P300 amplitude
SLEDI	Pearson correlation	-0.274	0.419
	Sig. (2-tailed)	0.242	0.66
HAQ	Pearson correlation	-0.124	0.151
	Sig. (2-tailed)	0.602	0.526
Information	Pearson correlation	-0.171	0.301
	Sig. (2-tailed)	0.472	0.197
Comprehension	Pearson correlation	0.119	0.038
	Sig. (2-tailed)	0.618	0.874
Digit span	Pearson correlation	-0.325	0.500*
	Sig. (2-tailed)	0.163	0.025
Arithmetic	Pearson correlation	-0.271	0.238
	Sig. (2-tailed)	0.249	0.312
Similarities	Pearson correlation	0.038	0.095
	Sig. (2-tailed)	0.872	0.690
Vocabulary	Pearson correlation	0.023	-0.008
	Sig. (2-tailed)	0.924	0.973
Picture arrangement	Pearson correlation	-0.313	0.359
	Sig. (2-tailed)	0.206	0.144
Picture completion	Pearson correlation	-0.243	0.336
	Sig. (2-tailed)	0.302	0.148
Block design	Pearson correlation	-0.132	0.177
	Sig. (2-tailed)	0.578	0.455
Object assembly	Pearson correlation	-0.236	0.367
	Sig. (2-tailed)	0.316	0.112
Digit symbole	Pearson correlation	-0.271	-0.040
	Sig. (2-tailed)	0.249	0.869
Verball IQ	Pearson correlation	-0.311	0.326
	Sig. (2-tailed)	0.181	0.161
Performance IQ	Pearson correlation	-0.321	0.346
	Sig. (2-tailed)	0.168	0.135
Full scale IQ	Pearson correlation	-0.232	0.320
	Sig. (2-tailed)	0.325	0.170
Deterioration index	Pearson correlation	0.103	-0.163
	Sig. (2-tailed)	0.664	0.491
Trail making (A)	Pearson correlation	0.266	-0.200
	Sig. (2-tailed)	0.271	0.412
Trail making (B)	Pearson correlation	0.090	-0.143
	Sig. (2-tailed)	0.707	0.549
Logical memory	Pearson correlation	0.256	0.358
	Sig. (2-tailed)	0.277	0.121

Table 14: EEG findings abnormality among SLE patients:

	EEG slowing	EEG paroxysms
N (20)	13	8
%	65%	40%

Table 15: Correlation between cognitive function in SLE patients and EEG Frequency:

	EEG Frequency	N	Mean	+SD	P
Information	Normal	7	8.86	+2.545	0.191
	Abnormal	13	6.92	+3.252	
Comprehension	Normal	7	12.29	+2.984	0.803
	Abnormal	13	12.62	+2.663	
Digit span	Normal	7	7.29	+1.380	0.214
	Abnormal	13	6.15	+2.075	
Arithmetic	Normal	7	8.43	+1.397	0.903
	Abnormal	13	8.23	+4.045	
Similarities	Normal	7	10.86	+2.340	0.733
	Abnormal	13	11.23	+2.279	
Vocabulary	Normal	7	7.71	+1.254	0.817
	Abnormal	13	7.46	+2.665	
Picture arrangement	Normal	7	9.00	+1.732	0.233
	Abnormal	13	7.91	+1.868	
Picture completion	Normal	7	9.57	+1.988	0.555
	Abnormal	13	8.77	+3.193	
Block design	Normal	7	8.57	+4.117	0.795
	Abnormal	13	9.00	+3.082	
Object assembly	Normal	7	12.00	+3.606	0.372
	Abnormal	13	10.62	+3.015	
Digit symbol	Normal	7	11.00	+2.708	0.382
	Abnormal	13	9.77	+3.032	
Verbal IQ	Normal	7	95.14	+7.105	0.411
	Abnormal	13	87.69	+22.548	
Performance IQ	Normal	7	102.43	+9.572	0.221
	Abnormal	13	94.38	+18.795	
Full scale IQ	Normal	7	97.86	+7.335	0.315
	Abnormal	13	92.15	+17.160	
Deterioration index	Normal	7	9.64	+7.793	0.933
	Abnormal	13	9.27	+10.051	
Logical memory	Normal	7	19.5714	+3.64492	0.184
	Abnormal	13	16.9231	+4.29072	
Trail making (A)	Normal	7	53.57	+12.150	0.172
	Abnormal	13	73.17	+34.745	
Trail making (B)	Normal	7	1.06432	±13.45185	0.837
	Abnormal	13	1.01462	±61.31424	

Table 16: Correlation between cognitive function in SLE patients and EEG paroxysms:

	EEG paroxysms	N	Mean	+SD	P
Information	Normal	12	8.67	3.257	0.057
	Abnormal	8	6.00	2.138	
Comprehension	Normal	12	12.67	2.605	0.746
	Abnormal	8	12.25	3.012	
Digit span	Normal	12	7.17	1.467	0.075
	Abnormal	8	5.62	2.200	
Arithmetic	Normal	12	8.67	2.229	0.558
	Abnormal	8	7.75	4.621	
Similarities	Normal	12	11.08	2.466	0.969
	Abnormal	8	11.12	2.031	
Vocabulary	Normal	12	7.42	1.621	0.753
	Abnormal	8	7.75	3.059	
Picture arrangement	Normal	12	8.55	1.695	3.557
	Abnormal	8	8.00	2.160	
Picture completion	Normal	12	9.17	2.657	0.826
	Abnormal	8	8.88	3.182	
Block design	Normal	12	8.33	3.576	0.417
	Abnormal	8	9.62	3.114	
Object assembly	Normal	12	11.08	3.605	0.978
	Abnormal	8	11.12	2.748	
Digit symbol	Normal	12	10.42	2.678	0.695
	Abnormal	8	9.88	3.399	
Verbal IQ	Normal	12	90.92	21.305	0.862
	Abnormal	8	89.38	15.362	
Performance IQ	Normal	12	98.00	15.626	0.797
	Abnormal	8	96.00	18.431	
Full scale IQ	Normal	12	96.00	13.136	0.500
	Abnormal	8	91.38	16.919	
Deterioration index	Normal	12	9.88	8.697	0.784
	Abnormal	8	8.96	10.271	
Logical memory	Normal	12	19.3333	3.28449	0.049
	Abnormal	8	15.6250	4.59619	
Trail making (A)	Normal	12	55.17	15.385	0.104
	Abnormal	8	84.43	39.736	
Trail making (B)	Normal	12	1.0283E2	18.01430	0.975
	Abnormal	8	1.0375E2	78.13678	

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DISCUSSION

Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) is one of the most difficult manifestations of lupus to diagnose. Measurement of serum brain autoantibodies and assessment of cognitive function by electroneurophysiological studies (EEG) and P300 have contributed to an earlier and a more specific diagnosis of (NPSLE) (Mostafa, et al. 2009).

Primary central nervous system (CNS) involvement is common in SLE patients, thus any area of the brain, the spine or the nervous system may be affected. Some of the symptoms are cognitive alterations, seizures, psychosis and headaches (Paran, et al. 2009).

The spectrum of central nervous system manifestations of systemic lupus erythematosus (SLE) is very broad and has been found to include subtle subclinical cognitive dysfunction which may be detected only by the lengthy process of detailed neuropsychological evaluation (Mulherin, et al. 1993).

In SLE, deficits commonly appear in attention and information processing, learning, memory, and executive function. Most patients have a fluctuating and evanescent pattern of cognitive dysfunction with only a minority showing progressive decline (Waterloo, et al. 2001; Hay, et al. 1994; Hanly, et al. 1994 and Bluestein and Zvaifler, 1976).

During this work, we had tried to study 30 patients with SLE as regards their cognitive dysfunction by psychometric tests including Wechsler Adult Intelligence Scale (WAIS), logical memory subtests of Wechsler memory scale and Trail Making test and to compare them with 20 healthy controls of matched age and sex.

On comparing SLE patients and control groups on WAIS, logical memory subsets of Wechsler memory scale and Trail Making test, there were statistically significant difference on arithmetic subtest of WAIS and there were highly statistically significant difference according to information, vocabulary, picture arrangement, picture completion and block design subtests of WAIS. Also, there were highly statistically significant difference according to logical memory (A) and (B) subtests of Wechsler memory scale while other subtests did not show statistically significant differences (Table 2).

SLE patients performed worse than healthy controls on working memory, verbal comprehension, perceptual reasoning and Visual-spatial processing which are measured by Wechsler Adult Intelligence Scale (WAIS). Also, we found in this study that SLE patients are less than control groups on psychomotor speed which is detected by digit symbol but with no statistically significant differences.

In addition, SLE patients performed worse than healthy controls on verbal memory which is measured by logical memory subtests of Wechsler memory scale. SLE patients had less performance on Trail Making test A which measure attention, Trail Making test B which measure executive functions and complex attention.

The percentage of cognitive dysfunction among SLE patients according to the results of verbal IQ and full scale IQ subtests of WAIS was 43.3% while performance IQ was 33.3% (Table 3)

According to the results of logical memory, 86.7% of SLE has cognitive dysfunction. Also, 43.3% showed functional impairment, 33.3% showed organic impairment according to Trail Making (A). While 16.7% showed functional impairment, while there was no organic impairment according to Trail Making (B) (Table 3).

This result is consistent with a study that found the prevalence of cognitive impairment in Systemic Lupus Erythematosus (SLE) ranges between 14% and 90% (Brey, et al. 2002).

Also, in another study, cognitive impairment was identified in 50% of patients with SLE and 20% of healthy controls. Patients with SLE were impaired on measures of psychomotor speed/fluency, verbal speed/fluency and verbal memory (Sabbadini, et al. 1999).

The study is also agreed with a study performed on Twenty one female patients with clinically quiescent SLE, In all patients, examination included measurement of full-scale intelligence quotient (IQ), verbal and performance IQ as well as verbal and visual memories. In addition, premorbid intelligence was estimated. Nine patients (43%) gave a history of neuropsychiatric (NP) disease. No difference was identified between the results of the neuropsychological evaluation in these 9 patients and in either the other SLE patients or in control. Sixteen patients were re-evaluated 1 year later. A comparison of measured full-scale IQ with the estimated premorbid intelligence identified a subgroup of 3 patients who demonstrated a significant reduction in intelligence. Unlike the other 13 patients, these 3 patients had multiple (3 or more) other features of cognitive impairment (Mulherin, et al. 1993).

The alterations in the nervous system and neuropsychological functioning in patients with systemic lupus erythematosus (SLE) have been the subject of numerous studies, with impairments found in diverse areas, among which memory, attention, verbal fluency, cognitive flexibility and visuomotor coordination are the most noteworthy, and with a prevalence of impairment of about 25% (Brey, et al. 2002).

In addition, in some cases short and long term memory processing and verbal and visual-spatial information processing are affected. Attention may also be significantly compromised, especially in SLE that present with neuropsychiatric manifestations (Sabbadini, et al. 1999).

There was an alterations in episodic memory in patients with systemic lupus erythematosus. Patients with SLE demonstrated worse performance than the control subjects on visual memory tests (Buća, et al. 2009).

In another study to assess verbal memory impairment in SLE found that learning ability was impaired in SLE patients with a poor and inefficient learning strategy as reflected by an impaired learning curve, repeated omissions and impaired retrieval. This pattern of memory deficit resembles that seen in patients with frontal lobe damage (Paran, et al. 2009).

However, the results of the study inconsistent with another study by Carlomagno, et al. (2000) did not detect any clinically important change in cognitive function over a 1 year period using an instrument designed for use in detecting intellectual damage of a global nature. This held true even in subjects who were cognitively impaired at baseline. Among 17 SLE patients referred for neuropsychological evaluation (cognitive complaints), Skeel, et al. (2000) describes declines in expressive language, speed of processing and attention compared with estimates of premorbid function; no decline in memory was detected. These findings suggest that perhaps a consequence specifically inherent to SLE, but generic to SLE flare, may be damaging to the nervous system.

There was another study that state that daily stress is related to impairments in visual memory, fluency and attention in patients with SLE i.e. the greater the daily stress, the lower the score on visual memory, fluency and total attention speed (Peralta Ramirez, et al. 2006).

On studying the correlation between APL subtypes and cognitive dysfunction in our patients there was no statistically significant difference between them (Table 6).

This is consistent with a study that concluded that there was no association between the presence of autoantibodies and subsets of cognitive dysfunction. These results suggest that circulating autoantibodies to brain antigens are not responsible for the abnormalities in cognitive function in SLE patients (Hanly, et al. 1994).

But the results of the study inconsistent with some prospective studies that have confirmed the role of antiphospholipid antibodies (aPL) in the pathogenesis of cognitive impairment, especially if present at persistently high titers (Denburg and Denburg, 2003).

On correlating cognitive dysfunction in SLE patients and disease activity index (SLEDAI), WAIS scale had shown statistically significant difference between disease activity and digit span, arithmetic, full scale IQ, also there was highly statistically significant difference between arithmetic subtest of WAIS and disease activity index while there was statistically significant difference between Trail Making Test (part B) and functional disability detected by HAQ (Table 8).

Also, there was highly statistically significant differences between disease duration, HAQ and SLEDAI. There was highly statistically significant differences between HAQ and SLEDAI (Table 10).

The results of the study disagree with Fisk, et al. (1993) who concluded that increased disease activity was associated with impaired immediate memory and concentration which may represent transient and diffuse central nervous system effects. Although corticosteroid use was associated with poor word list recall.

Gladman, et al. (2000) therefore employed a different approach to determine the impact of organ system disease activity on current cognitive performance. They developed a multiple regression model to identify predictors of cognitive impairment in SLE patients with no disease activity at the time of testing. Among the various clinical manifestations, only previous vasculitis and higher activity scores at initial presentation (SLEDAI >10) were predictive of xcognitive impairment. Thus, cognitive dysfunction may be caused by previous disease or its treatment.

Along these lines, Kozora, (2008) hypothesized a role for IL-6 (an inflammatory mediator) and various hormones known to be abnormal in SLE in the development of cognitive dysfunction. These hormones include cortisol, dehydroepiandrosteron (DHEA), and DHEA-S (the inactive form). Although IL-6 and cortisol levels did not differentiate SLE patients without neuropsychiatric disease from rheumatoid arthritis patients or healthy controls, DHEA and DHEA-S levels were lower in SLE patients. Lower levels of DHEA and DHEA-S have been reported in different dementia syndromes. Using hierarchical regression modeling to determine the influence of these substances on cognition, IL-6 and DHEA-S were found to account for a unique portion of the variance in measures of learning and attention after controlling for depression and corticosteroid use.

In a study on Fifteen women with SLE and 15 healthy controls to examine functional ability in people with SLE by comparing a self-report and a performance-based test. Participants completed a self report of daily living skills, the Health Assessment Questionnaire (HAQ). Actual performance during activities of daily living was evaluated with the Assessment of Motor and Process Skills (AMPS). Measures of cognition and disease activity were also collected. Health

Assessment Questionnaire (HAQ) scores of patients with SLE indicated only very mild disability while scores on the Assessment of Motor and Process Skills (AMPS) to assess actual performance during activities of daily living that indicate ineffective skill performance and potential safety risks. In the participants with SLE, cognitive status correlated significantly with the processing component and disease severity correlated with the motor component of the Assessment of Motor and Process Skills (AMPS) The HAQ did not correlate with the Assessment of Motor and Process Skills (AMPS). This study suggests that cognitive deficits were more related to scores on the performance-based test of functional ability rather than the self-report. The performance-based test appeared to provide information that was not gained through self-report and measures of disease activity and gross cognition (Poole, et al. 2006).

But the results of the study inconsistent with a study by Toloza, et al. (2010) who found that health-related quality of life is not strongly associated with disease activity or organ damage. Contributors to poor quality of life in patients with SLE include fatigue, fibromyalgia, depression, and cognitive dysfunction.

In the study we investigated 20 out of the 30 patients with systemic lupus erythematosus with conventional EEG and P300 (latency and amplitude) (Table 11) shows that 12(60%) among SLE patients had abnormal P300 latency while there was 7(35%) had abnormal P300 amplitude.

Also, Table (12) shows that the mean of P300 latency among SLE patients was more than that in the control group.

The correlation between cognitive function and P 300 latency and amplitude and its relation to disease activity and functional disability, had shown statistically significant difference between P300 amplitude and digit span subtest of WAIS while there was no statistically significant difference between other subtests and P300 latency and amplitude (Table 13).

40% among SLE patients had abnormal EEG paroxysms while 65% had slowing of EEG (Table 14).

On correlating cognitive dysfunction and EEG findings, it showed no statistically significant difference between either EEG frequency (Table 15).

Table (16) shows that there was a statistically significant correlation between information subtest of WAIS and the occurrence of EEG paroxysm, showing that the worse the information, the more the occurrence of EEG paroxysms.

This is agree with Ito, et al. (1993) studied auditory event-related potentials (ERPs) in 17 patients with systemic lupus erythematosus. Latencies of N100 and P200 components were normal in all patients, whereas the latencies of target P300 and non target P300 components were significantly prolonged in SLE patients with and without cognitive dysfunction. The P300 component of ERPs can be applied to evaluate the cognitive aspects of central nervous system manifestations in SLE patients.

Ante Coín-Mejías, et al. (2008) tested 10 patients (9 females, 1 male) with clinical manifestations of neuropsychiatric systemic lupus erythematosus. A disorder of amplitude and latency extension P300 of audio-evoked potential was observed in eight patients according to EEG In five female patients we found non specific diffuse paroxysmal disrhytmic changes on EEG, while in two female patients diffuse and parietotemporal focal changes were shown. Normal EEG was registered in three patients.

Mostafa, et al. (2009) in their study on Neuropsychiatric Systemic lupus erythematosus (NPSLE) found that (62.5%) had abnormal EEG, six (75%) had P300 abnormalities. They concluded that serum antineuronal antibodies and electroneurophysiological studies may be reliable parameters for diagnosis and early prediction of (NPSLE), especially when combined together, before clinical manifestations ensue.

However, the results of the study inconsistent with another study by Gladman, et al. (2000) stated that neither psychiatric symptoms nor any neurophysiologic tests performed (technetium brain scan, EEG, and QEEG) were associated with cognitive impairment. Thus, cognitive dysfunction may be caused by previous disease or its treatment.

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الملخص العربى

اختلال الوظائف المعرفية في مرض الذئبة الحمراء

إن الهدف من هذه الدراسة هو معرفة وجود اختلال الوظائف المعرفية في المرضي المصابين بالذئبة الحمراء وذلك باستخدام المقاييس النفسية لمعرفة مدي ارتباط اختلال الوظائف المعرفية بنشاط المرض وذلك باستخدام مؤشر لقياس نشاط المرض (SLEDAI) ومقياس العجز الوظيفي (HAQ) وكذلك التنبؤ بمدي ارتباط الاختلال في الوظائف المعرفية بوجود مضادات الفوسفوليبد وأيضا لمعرفة مدي ارتباط اختلال الوظائف المعرفية بحدوث تغيرات في تخطيط كهربية الدماغ EEG والاستجابة العصبية للمنبهات P3000 فقد تم دراسة ٣٠ مريضة بمرض الذئبة الحمراء ولقد تم اختيارهم وفقا لمعايير الكلية الأميركية لأمـراض الروماتيزم لتشخيص مرض الذئبة الحمراء لسنه (١٩٩٩) حيث بلغ متوسط أعمارهم ٢٥,٣ ومتوسط مدة المرض ٣,٧ سنة وهذه تمثل المجموعة الأولى وبمقارنتهم بعدد ٢٠ من الأصحاء واللاتي تمثلن المجموعة الثانية. وتم تطبيق مقياس وكسلر للذكاء للكشف عن الخلل في الوظائف المعرفية واختبار فرعي الذاكرة المنطقية لمقياس وكسلر لقياس الذاكرة وكذلك مقياس المسار (Trail Making test) ومعرفة مدي ارتباط النتائج بنشاط المرض باستخدام مؤشر لقياس نشاط المرض (SLEDAI) ومقياس العجز الوظيفي (HAQ) ولقد خلص البحث إلى وجود أدلة تنبئ عن وجود اختلال في الوظائف المعرفية في مرضى الذئبة الحمراء. وثمة علاقة إيجابية ذات دلالة إحصائية بين وجود الأجسام المضادة ونشاط المرض (SLEDAI) ولكن لا توجد فروق ذات دلالة إحصائية بين اختلال الوظائف المعرفية ووجود الأجسام المضادة ونشاط المرض (٠) كما تبين أن بعضا من مرضى الذئبة الحمراء لديهم تغيرات في تخطيط كهربية الدماغ EEG وكذلك تغيرات في الاستجابة العصبية للمنبهات P300.