The Egyptian Rheumatologist

ISSN 1110-1164

ORIGINAL ARTICLE

Cognitive Dysfunction in Systemic Lupus Erythematosus

Yasser Ezzat[1], Ahmed Hamdy[1], Fadia Zyada[2], Hebatallah Kamel[3] and Ayman Ismail[4]

[1]Rheumatology and Rehabilitation Department, Fayoum University, [2]Psychiatric Department, [3]Neurophysiology Department, [4]Radiology Department, Cairo University

Abstract

Introduction: Is to investigate and detect the incidence of cognitive dysfunction in SLE patients by the different psychiatric methods of assessment and to correlate them to disease activity by SLEDAI, functional disability index by HAQ, the presence of antiphospholipid antibodies (APL) and the findings of neuroimaging by MRI, and EEG P300 latency and amplitude.

Subjects and Methods: Thirty female patients with SLE had been studied in this work. They were selected according to the ACR criteria for diagnosing SLE (Hochbers, 1997), their age ranged between 17 and 37 years with a mean of 25.37 +SD of 4.468, mean age of onset of 20.6+77 y, mean disease duration of 5.92+3.72 years. This represents Group_I, as well as 20 healthy controls of matched age and sex, their mean age was 29.47+5.5, this represents Group II (Table 1). Both groups were subjected to different psychometric testing to detect behaviorual changes and cognitive dysfunction such as subtests of 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 as well as, health assessment questionnaire by HAQ, presence of APL antibodies and also to the MRI findings and EEG changes, P300 (latency and amplitude).

Results: The results of WAIS, logical memory subtest of Wechsler scale and Trail Making tests, showed statistically significant difference ($P<0.05$) between patients and controls on the arithmetic subtests, of WAIS while there was highly statistically significant difference ($P<0.001$) in information, vocabulary, picture arrangement, picture completion and block design subsets of WAIS, logical memory (A), logical memory (B) subsets of Wechsler memory scale. Other subsets did not show statistically significant difference. The results of verbal IQ and full scale IQ subsets of WAIS were 43.3% while performance IQ was 33.3%, there was 86.7% of cognitive dysfunction according to the results of logical memory among SLE patients 43.33% showed organic impairement, 33.33% showed functional impairment, according to trail making (A) while 16.7% showed functional impairment, while there was no organic impairment (Table 3). As regards APL antibodies there were positive significant correlation between APL titre and SLEDAI score ($P<0.001$, $r=0.768$). 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 ($P<0.05$) between cognitive dysfunction and HAQ. Again, there was statistically significant difference between cognitive dysfunction and P300 amplitude and latency ($P<0.05$).

Conclusion: There was a high evidence of the presence of cognitive dysfunction in SLE patients in our study. A positive significant correlation between APL titre and SLEDAI score, but there was no statistically significant difference between cognitive dysfunction and APL subtypes. P300 had statistically significant correlation with cognitive dysfunction. There were many MRI findings in our SLE patients (70%) but they were not correlating with cognitive dysfunction.

Key words: ASLE, cognitive dysfunction, SLEDAI, HAQ, APL, MRI, EEG.

Egypt. Rheumatologist Vol. 32, No. 1, Jan.-Jun. 2010: 1-19

INTRODUCTION

Central nervous system neuropschiatric lupus (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[1]. Disturbances of mental function are the most common symptom.

Because of the varied diagnostic criteria associated with these manifestations, the ACR has formulated case definitions reporting standards and diagnostic testing recommendations for the 19 neuropschiatric SLE syndromes[2].

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[3].

One clue to the diagnosis is that most acute psychiatric episodes occur during the first two years after the onset of SLE[4,5].

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 neuropschiatric symptoms can occasionally be made by a saying for specific auto-antibodies such as antineuronal antibodies[6-8].

Anti-ribosomal P antibodies are commonly present in association with lupus psychosis and depression[9,10]. Cognitive defects may be associated with the presence of elevated levels of antineuronal antibodies, APL or antibodies to N-methyl D-aspartate (NMDA) receptors[11,12].

Concerning APL, it induces a procoagulant state[13] and are associated with focal manifestations of NPSLE such as stroke[14] and seizures[15].

Persistently elevated levels of anticardiolipin antibodies are associated with decline in cognitive function[6,16] possibly due to thrombosis within vessels of minute caliber.

Intrathecal production of APL in patients with NPSLE[17], their association with diffuse cognitive impairment and evidence of in-vitro modulation of neuronal function[18], raise the alternative possibility of a direct pathogenic effect on neurons.

Cytokines may function as neuromodulators as well as inflammation mediators[19]. Initial studies showed association between increased intracranial levels of IL-6 and seizures[20] and between increased CSF levels of interferon-α and lupus psychosis[21].

Subsequent studies provided evidence of intrathecal production of IL-6[22-24] and identified other candidate cytokines such as IL-10[25], IL-2[26] and IL-8[27] which may be produced by neuronal cells and glial cells[21,22].

One study identified a relationship between pro-inflammatory serum IL-6 production and learning deficits in SLE patients[28]. Another demonstrated a correlation between elevated levels of CRP, which is a non specific marker of inflammation and deficits in information processing[29].

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[30].

The aim of our study is to detect cognitive dysfunction in SLE patients and to correlate them to the presence of auto-antibodies and MRI findings.

MATERIALS AND METHODS

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

They were divided into two groups:

Group I: Thirty female SLE patients with a mean age of onset of 20.6+77 y and a mean disease duration of 5.92+3.72 y.

Group II: Twenty healthy subjects with matching age and sex.

Criteria of inclusion was based on the revised ACR criteria[31]. 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.

Laboratory investigations:
The patients were subjected to the following laboratory investigations:

- ESR, CRP, CBC.
- Urine analysis.
- 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, MRI of the brain Assessment of disease activity:

Using (SLEDAI), Bombarier et al.(32) 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 graded according to SLEDAI score into:
- Mild activity 0-10.
- Moderate activity 10-20.
- Severe activity 20-45.
- Very severe activity > 45.

Assessment of HAQ disability index was done according to the method of Fries et al.[33]

All subjects in the study were subjected to the following psychometric tools:
1. Wechsler Adult Intelligence Scale (WAIS) (Weschsler, 1944, 1955, 1987)[34,35].
2. Logical memory subsets of Wechsler.
3. Trail making test (part A and part B) (Reitany, 1958)[36].

Neuroimaging:
MRI with Doppler was done to all patients, to detect any changes in the brain.

were searched for

Periventricular hyperintensities, infarcts, hemorrhages, cerebral atrophy and small focal lesions Kowal et al.[8] ~~but inconsistent relationship to aspects of cognitive dysfunction had been correlated to disease activity, medications given and MRI findings~~. The results were statistically tabulated.

RESULTS

Thirty patients with SLE were included in this study, their age ranged between 17 and 37 with a mean of 25.37 +SD of 4.468, mean age of onset of 20.6+77 y mean disease duration of 5.92+3.72 years. These represents Groups I.

Group II: Twenty healthy controls of matched age and sex their mean age was 29.47+5.50 (Table 1).

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

	Mean ±SD	Range
Patients age in ys (n=30)	25.37±4.468	17-37
Control (n=20)	29.47±5.50	20-40
Disease duration	4.55±3.92	1-15

On comparing the SLE patients and control group on WAIS, logical memory subsets of Wechsler memory scale and Trail Making test, there were statistically significant difference ($P<0.05$) on the Arithmetic subsets of WAIS while there was highly statistically significant difference ($P<0.001$) in information, vocabulary, picture arrangement, picture completion and block design subsets of WAIS, logical memory (A), logical memory (B) subsets of Wechsler memory scale. Other subsets 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 subsets of WAIS was 43.3% while performance IQ subsets of WAIS was 33.3%, the percentage of cognitive dysfunction according to the results of logical memory scale was 86.7%. Among SLE patients, 43.33% showed functional impairment, 33.33% showed organic impairment according to Trail Making (A) while 16.67% showed functional impairment, while there was no organic impairment according to Trail Making (B) (Table 3).

Table (4) shows that out of 30 patients studied, 12 patients had APL antibodies (40%) 9 patients with positive ACL IgG (30%), 3 patients with positive IgM (10%) and 6 patients with positive LA (20%).

Table (5) there was positive significant correlation between ACL antibodies and systemic SLEDAI score ($P<0.001$).

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

Figure (1) showing the comparison between APL positive and APL negative patients as regards the different psychologic testing and it shows more impairment in APL positive group.

Table (7) this table shows that the ~~SLPADI~~ ranges between 0-40 with a mean of 22+12.70 while the HAQ ranges between 0-3 with a mean of 1.32+57.6.

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.

	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 (S)
	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 (H.S)
	Case	7.17	2.276	
Picture arrangement	Control	11.95	3.045	0.000 (H.S)
	Case	8.29	1.802	
Picture completion	Control	11.53	1.954	0.001 (H.S)
	Case	9.03	2.593	
Block design	Control	12.74	3.124	0.000 (H.S)
	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	1.0370E2	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.

	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: Shows 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 dys	APL	ACL		LA
		IgG	IgM	
Verbal IQ	P-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
IOGICAL 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 cocases			

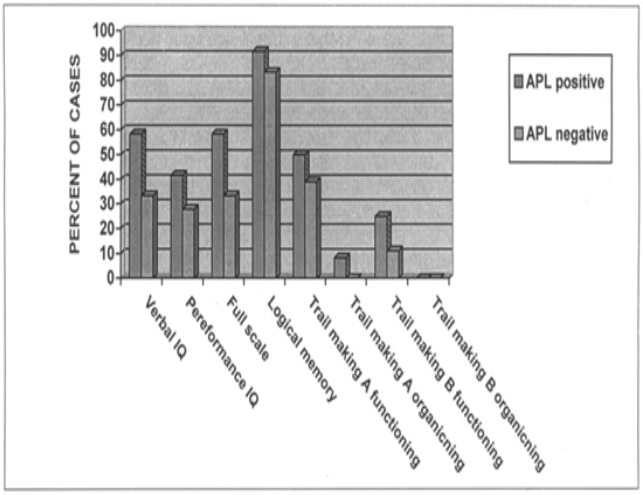

Figure 1: Showing the comparison between APL positive and APL negative patients as regards the different psychologic testing and it shows more impairment in APL positive group.

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 symbole	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

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=<0.05) between arithmetic subsets of WAIS and disease activity index while there was statistically significant difference between Trail Making Test (par B) and functional disability detected by HAQ (Table 8).

Table (10) 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.

Figure (2) it shows that 82% receiving steroids 65% with NSAIDS, 60% with Azathioprine, 56% with HCQ, 50% with cyclo, phosphamide 33% with MTX 12% with MMF.

Remove table 9

~~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	22-37
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 ~~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 ~~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 and amplitude between SLE and control groups.

	SLE group (mean ±SD) N=20	Control group (mean ±SD) N=20
P300 latency (msec)	3.36±5.95	304.39±20.91

Table 13: Correlation between cognitive function in SLE patients and P300 (latency and amplitude) and correlation between SLEDAI and HAQ disability index 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 frequency	EEG paroxysms
N (20)	13	8
%	65%	40%

Table 15: Correlation between cognitive dysfunction in SLE patients and EEG frequency.

	EEG abnormality	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	11	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 symbole	Normal	7	11.00	±2.708	0.382
	Abnormal	13	9.77	±3.032	
Verball 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	12	73.17	±34.745	
Trail making (B)	Normal	7	1.06432	±13.45185	0.837
	Abnormal	13	1.01462	±61.31424	

Table ~~16~~ 9: Correlation between cognitive function in SLE patients and EEG paroxysm.

	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	7	8.55	1.695	3.557
	Abnormal	11	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 symbole	Normal	12	10.42	2.678	0.695
	Abnormal	8	9.88	3.399	
Verball 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	7	84.43	39.736	
Trail making (B)	Normal	12	1.0283E2	18.01430	0.975
	Abnormal	8	1.0375E2	78.13678	

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

Table (12) this table shows that the mean of P300 latency among SLE patients was more than 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 (P<0.05) between P300 amplitude and digit span subset of WAIS while there was no statistically significant difference between other subsets and P300 latency and amplitude (Table 13).

Table (14) this table shows that 40% among SLE patients had generalized EEG paroxysms while 65% had abnormal EEG frequency.

On correlating cognitive dysfunction and EEG findings, it showed no statistically significant difference between either EEG frequency (Table 15) or EEG paroxysms (Table 16) in SLE patients.

On correlating cognitive dysfunction and EEGfindings, it showed no statistically significant difference between 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 than occurrence of EEG paroxysms.

As regards MRI findings in our SLE patients they were 10 patients having periventricular hyperintensities, 5 patients with infarcts, 3 patients with hemorrages, one patient with cerebral atrophy, 2 patients with small focal lesions and 9 patients with normal MRI findings 10 (33.3%), 5 (16.7%), 3 (10%), 1 (3.3%), 2 (6.7%), normal (30%).

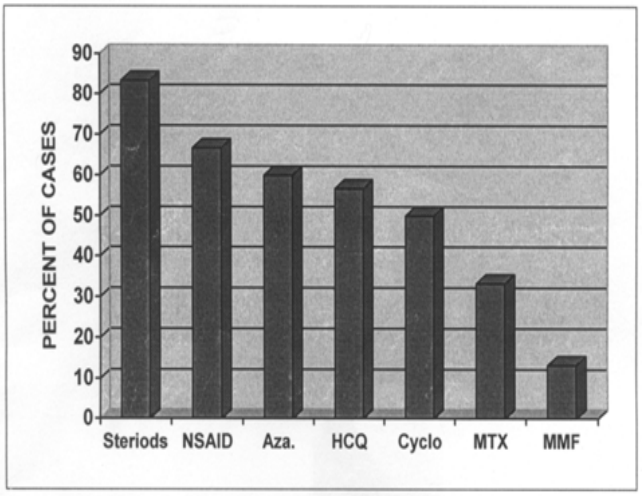

Figure 2: Showing the percentage of medications given to the patients.

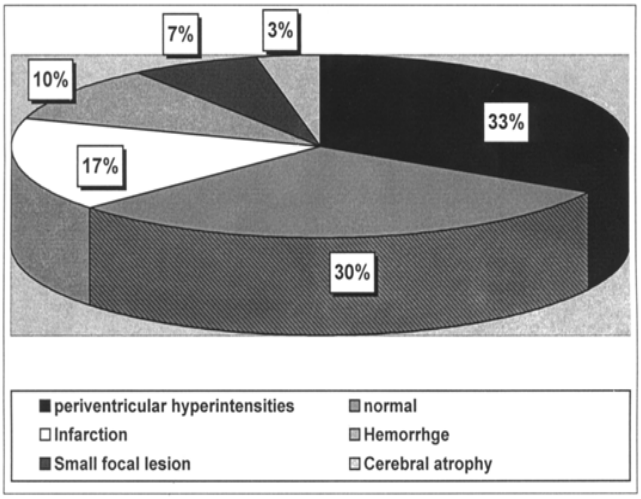

Figure 3: There was no statistically significant difference between these findings and cognitive dysfunction (P = 0.367).

DISCUSSION

Problems with cognitive function and skills are common in patients with SLE with or without stroke, seizure disorder and major psychiatric disorder[37].

Cognitive dysfunction has a variable impact on employment, functional outcome and health related quality of life[38,39].

Cognition is usually studied by administration and interpretation of standardized behavioural tests to examine cognitive domains such as attention, memory, reasoning, executive skills, language, visuoperception and sensory motor.

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[6,14,40,41].

Dominant patterns of cognitive defects have not emerged and it is clear that cognitive dysfunction in SLE is not a single syndrome.

During this work, we had tried to study 30 patients with SLE as regards their cognitive dysfunction by special tests including Wechsler adult intelligence scale (WAIS), logical meory, subtest of Wechsler memory scale and Trail Making scale and to compare them with 20 normal 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, there were statistically significant difference (P<0.05) on the arithmetic subsets of WAIS while there was highly statistically significant difference (P < 0.001),

in information, vocabulary, picture arrangement, picture completion and block design subsets of WAIS, logical memory (A), logical memory (B) subsets of Wechsler memory scale. Other subsets did not show statistically significant differences (Table 2).

The percentage of cognitive dysfunction among SLE patients according to the results of verbal IQ and full scale IQ subsets of WAIS was 43.3% while performance IQ subsets of WAIS was 33.3%, the percentage of cognitive dysfunction according to the results of logical memory was 86.7%. Among SLE patients, 43.33% showed functional impairment, 33.33% showed organic impairment according to Trail Making while 16.67% showed functional impairment, but there was no organic impairment (Table 3).

This coincides with the study of Saoudian et al.[42] who stated in their study that cognitive dysfunction (CD) has been reported to occur frequently in SLE patients and this CD was transient, persistent or progressive. Persistence or progression in any where varies from 17 to 93% of patients, and this variation may be due to patients with low intelligence who score low and false negative determinations i.e., with high native intelligence.

Chronic rheumatic disease cause pain, fatigue and depression which may affect cognitive dysfunction. When Saoudian and his colleagues[42] studied their 96 SLE patients using the wilcoxon sign rank test, they had found 17.2% of the patients had CD and most of them had persistent deficits when followed after 6 months. However, most of SLE patients had normal CD when remained stable or improved over 6 months. This study suggests in a community based population, that significant CD is uncommon.

In another study done by Melanie et al.[43] they stated that cognitive dysfunction is prevalent among neuropsychiatric syndromes associated with SLE, but exhibit a significant degree of heterogeneity both within and between patient variability. Common association of CD were concomitant or past neuro-pschiatric disease, use of corticosteroids, emotial disturbance and antiphospholipid syndrome. They stated that cognition is the sum of intellectual functions that result in thought. These functions include reception of external stimuli, information processing, learning and expression. CD can be categorized as complex attention, verbal memory, perceptual skills, reasoning and judgment, insight and awareness. Disruption of any individual function leading to the production of normal thoughts within any domain can be considered CD.

In their study of 50 Rt. handed SLE patients, 30 Rt. handed healthy subjects matched for age, sex as controls, Glanz et al.[44] had found CD in 50% of patients with SLE and 20% of the healthy controls. Patients with SLE were impaired on measures of psychomotor speed/fluency, verbal speed fluency and verbal memory.

This pattern of performance on neuropsychological testing was consistent with Lt. hemisphere brain dysfunction. They suggested immune mediated effects on specific brain regions in a subgroup of patients with SLE.

On correlating CD in our patients and disease activity index (SLEDAI), WAIS scaling had shown statistically significant difference ($P < 0.05$) in digit span, arithmetic full scale IQ, also this applies to functional disability index (HAQ) (Table 8).

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 ($P<0.05$) between P300 amplitude and digit span subset of WAIS while there was no statistically significant difference between other subsets and P300 latency and amplitude (Table ~~13~~ 12).

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

Denburg[7], had related the presence of CD in SLE in part to the presence of antiphospholipid antibodies which carry with them important therapeutic implications.

Whitelaw et al.[45] had a significant negative correlation with duration of disease in his APL positive group (16 patients) in six out of eight psychological testing and one out of eight in the APL negative group. This suggests that APL syndrome may be involved in the psychological involvement in SLE patients. A larger group of patients need to be studied to conform, this observation. This applies also to our study, as we had found 12 out of 30 SLE patients with APL antibodies.

Tade et al.[46] had found in his study of 137 children with SLE that there was positive correlation between ACL titer with disease activity score (SLEDAI). This also applies to our patients (Table 5).

But they had found no correlation between LAC, anti B2 GPI and other neuropsychiatric manifestations.

In (2008), Petri et al.[47] had reported measurable cognitive impairment in 30-75% in recently diagnosed SLE patients. She had found that the Automated Neurophysiological Assessment Metrics (ANAM) scored significantly lower than controls on 4 of 9 ANAM subsets.

These cognitive deficits were particularly striking, because SLE patients in her study were not selected for the presence of neuropsychiatric manifestations, had mild SLE-related disease/damage and were recently diagnosed with SLE. She suggested that deficits in cognitive efficiency and sustained attention are present early in the course of SLE, in the absence of other significant neuropsychiatric manifestations.

Kozora et al.[37] had confirmed the findings of Petri et al.[47] as she had found no significant differences between non-NPSLE patients and controls on a cognitive impairment index

(CII) of 67 non-NPSLE, 20.9% and 13.8% of controls were impaired. Patients with SLE scored higher on depressive symptoms ($P < 0.001$) and perceived cognitive difficulties ($P = 0.001$) compared with controls and she had concluded that there were no differences between non-NPSLE patients and controls on CII, only there were slightly lower CII scores in non-NPSLE patients and they demonstrated specific decline in the areas of attention, memory and reasoning.

Again, Olazaran et al.[48] had found within the non-NPSLE, all cognitive domains appeared similary affected and correlations were found between cognitive dysfunction and less skilled occupation ($r = 0.41$, $P = 0.02$) and between cognitive complaints and depressive symptoms ($r = 0.35$, $P = 0.05$). He concluded that cognitive dysfunction was rather frequent in non-NPSLE patients and seems to negatively impinge on social functioning.

Bruyn,[49] had suggested the concept of hypercoagulability in SLE patients that may cause cognitive dysfunction and psychosis in patients with SLE and this concept had diverted the direction of therapy from immunosuppression towards anticoagulation.

It was discovered that medications used to treat SLE can develop symptoms like those of C.N.S lupus. Psychosis can appear due to antimalarials in very high doses, headache, dizziness can be provoked by NSAIDS, corticosteroids cause moods swings, psychosis, depression, agitation, confusion, if they are taken in high doses, anti-hypertensive medication may be associated with depressions.

A study discovered that people that have both lupus and sjogren syndrome may be predisposed to develop vasculitis or cognitive dysfunction.

Factors significantly associated with declining cognitive function were consistently positive APL, prednisone use, diabetes, higher depression scores and less education.

Regular aspirin use is associated with improved cognitive function in older patients with SLE in conjunction with the presence of other vascular risk factors.

Regular prednisone use is associated with decreased cognitive functioning in middle age patients with SLE.

Although this prednisone effect was independent of measures of SLE associated disease activity, the authors cannot exclude the possibility that consistent prednisone use is an indicative for more severe disease.

In our study we did not find in relation between cognitive dysfunction and EEG frequency and paraoxysms (Table ~~15, 16~~).

On the contrary Koutrovmanidis et al.[50] suggested that EEG abnormalities are common and should be considered in a PL-positive patients with neuropsychiatric symptoms even in the absence of MRI abnormalities.

Wiad Lek et al.[51] examined 83 SLE patients with a mean disease duration of the seven years and had found that 41 cases had pathological EEG, only six patients had epileptic attaks so its was an evident disproportion between the number of patients with epilepsy and the number of paroxysmal changes in EEG, this agrees with our results as there was 40% with generalized EEG paroxysms and 65% with abnormal EEG frequency while non of the patients experienced an epileptic attack.

Ito et al.[52] had studied 17 patients with SLE and had found significant prolongation of P300 latency with and without cognitive dysfunction and had concluded that P300 can be applied to evaluate the cognitive aspects of CNS lupus.

Khedr et al.[53] studied 30 consecutive patients with SLE and 25 age- and sex-matched volunteers as a control group. They were subjected to neurological and rheumatological tests and an extensive battery of neurophysiological tests, besides Wechsler adult intelligence scale. And they concluded that Neurophysiological abnormalities are fairly common in SLE patients whether symptomatic or asymptomatic. The use of such tests favors a true incidence of nervous system involvement, more accurate diagnosis and may lead to better clinical care before the development of debilitating CNS and peripheral nervous system.

In another study by ~~Eman et al.,~~[54] showed that 12.5% of the patients were asymptomatic.

Ramirez et al.[55] tried to investigate the possible effects of the daily stress experienced during a six months period on the cognitive functions of patients with SLE and he concluded that daily stress was related to impairments in visual memory, fluency and attention in patients with SLE. This effect was not found with other emotional variables, such as depression and anxiety.

MRI findings in our SLE patients were 10 patients having periventricular hyperintensities, 5 patients with infarcts, three patients with hemorrhages, one patient with cerebral atrophy, two patients with small focal lesions and 9 patients with normal MRI findings 10 (33.3%), 5 (16.7%), 3 (10%), 1 (3.3%), 2 (6.7%), normal (30%).

This is shown in Figure (3) and there was no statistically significant difference between these findings and cognitive dysfunction.

Buća et al.[56] tested 10 patients (9 females, 1 male) with clinical manifestations of neuropsychiatric SLE (NP-SLE). MRI abnormalities were seen in all of patients, while in 9 patients abnormalities in neuropsychological and neurophysiologic tests (p300) have been proved. The most common structural brain change, detected by MRI, was cortical atrophy (in 8 out of 10 patients). Cortical atrophic brain changes have been established in 7 out of 9 patients with cognitive dysfunction. Because of already known correlation of cortical atrophy with cognitive dysfunction in SLE patients, without neuropsychiatric manifestation, so

neuropsychological examination is required in every patient with SLE.

RECOMMENDATION

We recommend that every SLE patient should be examined by the different psychologic testing and MRI to detect early neuropshiatric manifestation as it could be reversible by treatment.

REFERENCES

1. West SG, Emlen W, Wener MH, and Kotzin BL. Neuropsychiatric lupus erythematosus: A 10-year prospective study on the value of diagnostic tests. Am.J.Med. 1995 Aug;99(2):153-63.

2. ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum. 1999 Apr;42(4):599-608.

3. Singer J and Denburg JA. Diagnostic criteria for neuropsychiatric systemic lupus erythematosus: The results of a consensus meeting. The Ad Hoc Neuropsychiatric Lupus Workshop Group. J.Rheumatol. 1990 Oct.;17(10):1397-402.

4. Fisk JD, Eastwood B, Sherwood G, and Hanly JG. Patterns of cognitive impairment in patients with systemic lupus erythematosus. Br.J.Rheumatol. 1993;32(Suppl 3):458-62.

5. Waterloo K, Omdal R, Sjöholm H, Koldingsnes W, Jacobsen EA, Sundsfjord JA, et al. Neuropsychological dysfunction in systemic lupus erythematosus is not associated with changes in cerebral blood flow. J.Neurol. 2001;248(7):595-602.

6. Hanly JG, Hong C, Smith S, and Fisk JD. A prospective analysis of cognitive function and anticardiolipin antibodies in systemic lupus erythematosus. Arthritis Rheum. 1999 Apr;42(4):728-34.

7. Denburg SD, Carbotte RM, and Denburg JA. Cognitive impairment in systemic lupus erythematosus: A neuropsychological study of individual and group deficits. J.Clin.Exp.Neuropsychol. 1987 Aug;9(4):323-39.

8. Kowal C, DeGiorgio LA, Nakaoka T, Hetherington H, Huerta PT, Diamond B, et al. Cognition and immunity: Antibody impairs memory. Immunity 2004 Aug.;21(2):179-88.

9. Bonfa E, Golombek SJ, Kaufman LD, Skelly S, Weissbach H, Brot N, et al. Association between lupus psychosis and anti-ribosomal P protein antibodies. N.Engl.J.Med. 1987 Jul 30;317(5):265-71.

10. Isshi K and Hirohata S. Differential roles of the anti-ribosomal P antibody and antineuronal antibody in the pathogenesis of central nervous system involvement in systemic lupus erythematosus. Arthritis Rheum. 1998 Oct;41(10):1819-27.

11. Carbotte RM, Denburg SD, and Denburg JA. Prevalence of cognitive impairment in systemic lupus erythematosus. J.Nerv.Ment.Dis. 1986 Jun;174(6):357-64.

12. Omdal R, Brokstad K, Waterloo K, Koldingsnes W, Jonsson R, and Mellgren SI. Neuropsychiatric disturbances in SLE are associated with antibodies against NMDA receptors. Eur.J.Neurol. 2005 May;12(5):392-8.

13. Hanly JG. Antiphospholipid syndrome: An overview. CMAJ 2003 Jun 24;168(13):1675-82.

14. Love PE and Santoro SA. Antiphospholipid antibodies: Anticardiolipin and the lupus anticoagulant in Systemic Lupus Erythematosus (SLE) and in non-SLE disorders. Prevalence and clinical significance. Ann. Intern.Med. 1990;112(9):682-98.

15. Sanna G, Bertolaccini ML, Cuadrado MJ, Laing H, Khamashta MA, Mathieu A, et al. Neuropsychiatric manifestations in systemic lupus erythematosus: Prevalence and association with antiphospholipid antibodies. J.Rheumatol. 2003 May;30(5):985-92.

16. Menon S, Jameson Shortall E, Newman SP, Hall Craggs MR, Chinn R, and Isenberg DA. A longitudinal study of anticardiolipin antibody levels and cognitive functioning in systemic lupus erythematosus. Arthritis Rheum. 1999;42(4):735-41.

17. Martinez Cordero E, Rivera Garcia BE, and Aguilar Leon DE. Anticardiolipin antibodies in serum and cerebrospinal fluid from patients with systemic lupus erythematosus. J.Invest.Allerg.Clin. Immun. 1997;7(6):596-601.

18. Chapman J, Cohen Armon M, Shoenfeld Y, and Korczyn AD. Antiphospholipid antibodies permeabilize and depolarize brain synaptoneurosomes. Lupus 1999;8(2):127-33.

19. Vitkovic L, Bockaert J, and Jacque C. "Inflammatory" cytokines: Neuromodulators in normal brain? J.Neurochem. 2000;74(2):457-71.

20. Hirohata S and Miyamoto T. Elevated levels of interleukin-6 in cerebrospinal fluid from patients with systemic lupus erythematosus and central nervous system involvement. Arthritis Rheum. 1990;33(5):644-9.

21. Shiozawa S, Kuroki Y, Kim M, Hirohata S, and Ogino T. Interferon-alpha in lupus psychosis. Arthritis Rheum. 1992;35(4):417-22.

22. Hirohata S and Hayakawa K. Enhanced interleukin-6 messenger RNA expression by neuronal cells in a patient with neuropsychiatric systemic lupus erythematosus. Arthritis Rheum. 1999; 42 (12): 2729-30.

23. Jara LJ, Irigoyen L, De Ortiz MJ, Zazueta B, Bravo G, and Espinoza LR. Prolactin and interleukin-6 in neuropsychiatric lupus erythematosus. Clin.Rheumatol. 1998;17(2):110-4.

24. Trysberg E, Carlsten H, and Tarkowski A. Intrathecal cytokines in systemic lupus erythematosus with central nervous system involvement. Lupus 2000;9(7):498-503.

25. Rood MJ, Keijsers V, van der Linden MW, Tong TQ, Borggreve SE, Verweij CL, et al. Neuropsychiatric systemic lupus erythematosus is associated with imbalance in interleukin 10 promoter haplotypes.

Ann.Rheum.Dis. 1999 Feb;58(2):85-9.

26. Gilad R, Lampl Y, Eshel Y, Barak V, and Sarova Pinhas I. Cerebrospinal fluid soluble interleukin-2 receptor in cerebral lupus. Br.J.Rheumatol. 1997 Feb;36(2):190-3.

27. Shiozawa S, Kuroki Y, Kim M, Hirohata s, and Ogino T. Inflammatory cytokines in SLE. Arthritis Rheum. 1994;40:512-27.

28. Kozora E, Laudenslager M, Lemieux A, and West SG. Inflammatory and hormonal measures predict neuropsychological functioning in systemic lupus erythematosus and rheumatoid arthritis patients. J.Int. Neuropsychol.Soc. 2001 Sep;7(6):745-54.

29. Shucard JL, Gaines JJ, Ambrus Jr. J, and Shucard DW. C-reactive protein and cognitive deficits in systemic lupus erythematosus. Cogn. Behav.Neurol. 2007;20(1):31-7.

30. Belmont HM, Abramson SB, and Lie JT. Pathology and pathogenesis of vascular injury in systemic lupus erythematosus. Interactions of inflammatory cells and activated endothelium. Arthritis Rheum. 1996 Jan;39(1):9-22.

31. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997 Sep;40(9):1725.

32. Bombardier C, Gladman DD, Urowitz MB, Caron D, and Chang CH. Derivation of the SLEADI. A disease activity index for lupus patients. Arthritis Rheum. 1992;35(6):630-40.

33. Bruce B and Fries JF. The stanford health assessment questionnaire: A review of its history, issues, progress and documentation. J.Rheumatol. 2003;30(1):167-78.

34. Wechsler D. Manual for the weschsler adult intelligence scale. New York: The Physiological Corporation; 1955.

35. Weschsler D. Manual for the wechsler memory scale-revised. San Antonio, TX.: The Psychological Corporation; 1987.

36. Reitan RM, Wolfson D. The halstead-reitan neuropsychological test battery: Theory and clinical interpretation. 2nd ed. Tucson, AZ: Neuropsychology Press; 1993.

37. Kozora E. Neuropsychological functioning in systemic lupus erythematosus. In: Morgan JE, Ricker JH, editors. Textbook of clinical neuropsychology New York: Tailor & Francis; 2008. pp. 636-59.

38. Ginsburg KS, Wright EA, Larson MG, Fossel AH, Albert M, Schur PH, et al. A controlled study of the prevalence of cognitive dysfunction in randomly selected patients with systemic lupus erythematosus. Arthritis Rheum. 1992;35(7):776-82.

39. Panopalis P, Julian L, Yazdany J, Gillis JZ, Trupin L, Hersh A, et al. Impact of memory impairment on employment status in persons with systemic lupus erythematosus. Arthritis Rheum. 2007;57(8):1453-60.

40. Bluestein HG and Zvaifler NJ. Brain-reactive lymphocytotoxic antibodies in the serum of Patients with systemic lupus erythematosus. J.Clin.Invest. 1976;57(2):509-16.

41. Hay EM, Huddy A, Black D, Mbaya P, Tomenson B, Bernstein RM, et al. A prospective study of psychiatric disorder and cognitive function in systemic lupus erythematosus. Ann.Rheum.Dis. 1994;53(5):298-303.

42. Saoudian M, Khan M, Adhikari A, Brunner T, Luggen H, and Michae E. Cognitive dysfunctionin patients with systemic lupus erythematosus. Arthritis Rheum. 2009;60(Suppl).

43. Harrison MJ and Ravdin LD. Cognitive dysfunction in neuropsychiatric systemic lupus erythematosus. Curr.Opin.Rheumatol. 2002;14(5):510-4.

44. Glanz BI, Schur PH, Lew RA, and Khoshbin S. Lateralized cognitive dysfunction in patients with systemic lupus erythematosus. Lupus 2005;14(11):896-902.

45. Whitelaw DA, Spangenberg JJ, Rickman R, Hugo FH, and Roberts M. The association between the antiphospholipid antibody syndrome and neuropsychological impairment in SLE. Lupus 1999;8(6):444-8.

46. Avcin T, Benseler SM, Tyrrell PN, Cucnik S, and Silverman ED. A followup study of antiphospholipid antibodies and associated neuropsychiatric manifestations in 137 children with systemic lupus erythematosus. Arthritis Rheum. 2008;59(2):206-13.

47. Petri M, Naqibuddin M, Carson KA, Sampedro M, Wallace DJ, Weisman MH, et al. Cognitive function in a systemic lupus erythematosus inception cohort. J.Rheumatol. 2008;35(9):1776-81.

48. Olazarán J, López Longo J, Cruz I, Bittini A, and Carreño L. Cognitive dysfunction in systemic lupus erythematosus: Prevalence and correlates. Eur.Neurol. 2009;62(1):49-55.

49. Bruyn GA. Controversies in lupus: Nervous system involvement. Ann.Rheum.Dis. 1995;54(3):159-67.

50. Lampropoulos CE, Koutroumanidis M, Reynolds PP, Manidakis I, Hughes GR, and D'Cruz DP. Electroencephalography in the assessment of neuropsychiatric manifestations in antiphospholipid syndrome and systemic lupus erythematosus. Arthritis Rheum. 2005 Mar;52(3):841-6.

51. Góra MK, Dobrzyńska L, Mierzejewska E, and Koseda Dragan M. EEG examination in patients with systemic lupus erythematosus. Wiad.Lek. 2003;56(5-6):220-6.

52. Ito J, Suwazono S, Kimura J, and Shibasaki H. Auditory event-related potentials in patients with systemic lupus erythematosus. Eur.Neurol. 1993;33(5):373-7.

53. Khedr EM, Khedr T, Farweez HM, Abdella G, and El Beih EAS. Multimodal electroneurophysiological studies of systemic lupus erythematosus. Neuropsychobiol. 2001;43:204-12.

The Egyptian Rheumatologist; Vol. 32, No. 1, Jan. - Jun. 2010: 1-19

54. ~~Eman~~. EEG abnormalities in SLE. J.Neuphysiol. 2001;60:50-5.

55. Peralta Ramírez MI, Coín Mejías MA, Jiménez Alonso J, Ortego Centeno N, Callejas Rubio JL, Caracuel Romero A, et al. Stress as a predictor of cognitive functioning in lupus. Lupus 2006;15(12): 858-64.

56. Buca A, Perkovic D, Martinovic Kaliterna D, Vlastelica M, and Titlić M. Neuropsychiatrie systemic lupus erythematosus: Diagnostic and clinical features according to revised ACR criteria. Coll.Antropol. 2009;33(1):281-8.