

Diagnostic and Prognostic Values of Single Photon Emission Computed Tomography in Neuropsychiatric Manifestations of Systemic Lupus Erythematosus: An Egyptian Study

Kamel F, AL-Gogary A, Khodeir A, Haroun El Rasheed A, Youssef N, AL-Shishtawy H

Abstract

Although systemic lupus erythematosus (SLE) with involvement of central nervous system (CNS), which is often called neuropsychiatric SLE (NPSLE), is one of the most important manifestations of SLE, yet there is no single test to date that serves as the gold standard for its diagnosis. So, the aim of this work was to study the diagnostic value of SPECT in CNS affection in SLE patients as well as to study its prognostic value in these patients. Also, we set out to study the role of prolactin and anti-ribosomal antibodies (anti-P) in CNS affection in SLE patients. Moreover, we aimed to detect the possible relationship between findings using SPECT and the different disease parameters. We studied 30 Egyptian SLE female patients diagnosed according to the American College of Rheumatology (ACR) criteria for the classification of SLE (1999). Ten normal healthy subjects were also included as a control group. SLE patients were categorized into 3 groups: Group I with major NPSLE (n=7); Group II with only minor NPSLE (n=3); and Group III without NPSLE (n=20). They had undergone physical as well as neurological history and examination; followed by assessment of disease activity using SLE Disease Activity Index (SLEDAI). Assessment for psychiatric morbidity using General Health Questionnaire (GHQ), followed by ICD-10 Symptom Checklist for those exceeding the cutoff point on the GHQ. Then they were psychometrically assessed using Beck Depression Inventory (BDI), Hamilton Anxiety Scale (HAS), and Wechsler Memory Scale (WMS). Also, they had undergone laboratory investigations including prolactin and anti-ribosomal antibodies (anti-P); EEG; CT; as well as SPECT. On the other hand, controls were subjected to GHQ to ensure that they were free from psychiatric morbidity, laboratory investigations, and SPECT. Abnormal SPECT scan was found in 83% of group I as compared to 33% of group II. However, normal SPECT scan was found in 72% of group III and in 100% of the control group. Moreover, prolactin and anti-P antibody level were the only disease parameters that showed a significant association with cerebral hypoperfusion detected on SPECT. It was also found that SPECT findings were correlated with changes that occur within the six months follow-up period in neuropsychiatric symptoms as well as with follow-up SPECT findings. So, it might be promising as a prognostic tool in NPSLE. These results confirm that SPECT is a sensitive tool both for the diagnosis as well as the prognosis of CNS involvement in SLE.

Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune, multi-system disease with a broad spectrum of clinical manifestations. SLE with involvement of central nervous system (CNS), which is

often called neuropsychiatric SLE (NPSLE), is one of the most important manifestations of SLE. The condition may be both neurological and psychiatric (*ACR, 1999*). The clinical manifestations of NPSLE may be obvious-for example,

psychosis, stroke, and epilepsy, or there may be more subtle symptoms, such as headache and neurocognitive dysfunction (*Denburg et al., 1994*).

Neuropsychiatric events are seen in 14-75% of SLE patients with a wide range of clinical syndromes (*McCune & Golbus, 1988*), yet they are the least understood. NPSLE was shown by *Jonsson et al. (1989)* to be a predictor of a high frequency of flares and to be a major cause of longstanding functional impairment as well as being associated with high mortality rate. Although NPSLE is a serious manifestation of the disease, yet there is no single test to date that serves as the gold standard for the diagnosis of NPSLE.

Moreover, the diagnosis of NPSLE can be difficult as it has to be differentiated from neuropsychiatric complications that result from hypertension, drugs, infections, uremia, and metabolic changes. Thus, the occurrence of neurological and psychiatric symptoms may create a diagnostic challenge, and a determination of the origin of symptoms may be impossible when it is based solely on clinical information. The uncertainty of the origin of the symptoms is particularly troubling, because if intrinsic brain involvement is suspected, medications such as chemotherapeutic agents with severe side effects may be prescribed. Therefore, a misdiagnosis that results in over-or under-treatment is a serious risk for patients who have NPSLE.

Single photon emission computerized tomography has been used to evaluate regional cerebral blood flow and proves accurate in detecting many neurological and psychiatric diseases (*Lewis et al., 1992*). The advantages of SPECT are that it is non-invasive, enables anatomic imaging of lesions and most important it is a mean of

functional imaging. Radiopharmaceutical uptake in the brain can be quantified and therefore function of brain can be known. Altered perfusion reflects abnormal function; therefore we can get information regarding reversibility of a lesion by objectively documenting improvement in its perfusion (*Kovacs et al., 1995*).

So, the aim of this work was to evaluate the diagnostic value of SPECT in CNS affection in SLE patients as well as to study it as a prognostic tool in these patients. Also, we set out to study the role of prolactin and anti-ribosomal antibodies (anti-P) in CNS affection of SLE patients. Last but not least, we aimed to detect the possible relationship between findings using SPECT and the different disease parameters.

Methods

Hypotheses

1-There is a positive association between cerebral hypoperfusion detected by HMPAO-SPECT and the presence of neuropsychiatric manifestations in SLE patients.

2- There is a positive association between cerebral hypoperfusion detected by HMPAO-SPECT and the different disease parameters.

Thirty consecutive SLE female patients diagnosed according to the 1999 criteria of the American College of Rheumatology (ACR) for the diagnosis of SLE were included in this study. They were selected from SLE patients who used to attend the Outpatient Clinic of the Rheumatology and Rehabilitation Department as well as from the inpatient units of the Internal Medicine Department of Ain Shams University Hospitals.

Pregnant as well as nursing females were excluded from the study. Patients with past history of epilepsy or psychiatric disorders as well as patients with apparent steroid-induced psychiatric disorder were excluded from the study. Also, we had to exclude patients with liver disease or those on contraceptive pills or taking drugs that interfere with prolactin levels as typical antipsychotics, oestrogen, and bromocriptine.

Ten normal healthy subjects were included in the study as a control group. They were selected from employees in the Department of the Rheumatology and Rehabilitation as well as patients' relatives. They were matched for age, sex, and socioeconomic status with SLE patients.

An informed oral consent was taken from all participants in the study.

Every patient was subjected to the following:

- Full medical history taking.
- A thorough clinical examination.
- Neurological examination.
- General Health Questionnaire (GHQ) to identify psychiatric morbidity. It was initially developed as a first stage screening instrument for psychiatric illness in order to identify potential "cases" which could then be verified and the nature of which could be determined by using a second stage instrument. Used in this way, the GHQ was found to be an effective measure of case identification when validated in a number of studies based on general practice or clinical attenders. The short 28-item version was the one used in this study. The cutoff score used was 4/5 (a score within the range of 0-4 representing absence of psychopathology) (*Goldberg & Williams,*

1983). The Arabic version used in this study is by *Okasha et al. (1988)*.

- Patients exceeding the cutoff point on the GHQ were diagnosed using the ICD-10 Symptom Checklist (*Janca et al., 1994*). It consists of a symptom list that may help the user to check the presenting symptoms plus considering the possible psychiatric syndromes according to the ICD-10 Research Diagnostic Criteria.

Neuropsychiatric symptoms:

The diagnosis of NPSLE was made on the basis of clinical as well as ICD-10 Symptom Checklist after the exclusion of other causes of neuropsychiatric symptoms, as required by American College of Rheumatology (*ACR, 1999*).

Classification of NPSLE was adapted from *ACR (1999)* as well as *How et al. (1985)*, in which major or minor neurological and psychiatric symptoms were operationally defined as follows: 1) major neurological symptoms which include seizures, focal motor/sensory deficits, or altered consciousness; 2) minor neurological symptoms which include paraesthesia with no objective findings, clumsiness with no objective findings, headache, or pseudopapilloedema; 3) major psychiatric symptoms which include psychotic or mood disorders; or 4) minor psychiatric symptoms which include cognitive dysfunction, adjustment disorders, anxiety disorders, dissociative disorder, or emotionally labile disorder.

It is worth mentioning that *ACR (1999)* included the neuropsychological abnormalities with the neuropsychiatric abnormalities of SLE. Therefore, these symptoms have become one more sign of the involvement of the central nervous system.

Psychometric testing:

1-Wechsler Memory Scale (*Wechsler, 1945*). It provides a broad assessment of predominantly short-term memory and learning. It takes 45 minutes to administer and is formed of the following subtests: information, orientation, mental control, logical memory, visual reproduction, digit span, and paired associate learning. Normal value for individuals below 35 years is 68.1 ± 6.5 and for individuals above 35 years is 58.8 ± 7.1 . The criteria for the presence of cognitive impairment were based on impairment in the global memory or on impairment in at least three of the seven independent areas of cognitive function (*Hanly et al., 1993*). The Arabic version used in this study is by *Ghanem (1981)*.

2-Beck Depression Inventory (*Beck & Steer, 1993*). It is a self-applied questionnaire consisting of 21 items that include cognitive components of depression to a greater degree than the behavioral and somatic ones. It is not a diagnostic instrument, but instead it provides a measure of the depth of the depression in patients with any diagnosis. The scores on this instrument can be classified into: (0-9) no depression, (10-16) mild depression, (17-29) moderate depression and (≥ 30) severe depression. The Arabic version used in this study was by *Abdel Khalek (1996)*.

3-Hamilton Anxiety Scale (*Hamilton, 1976*). It is the most widely utilized assessment scale for anxiety symptoms, and was originally intended to be used to evaluate individuals who are already diagnosed with anxiety disorders. The scores on this instrument can be classified into: (<17) mild anxiety, (18-24) mild to moderate anxiety and (25-30) moderate to severe anxiety. The Arabic version used in this study is by *Fatim (1992)*.

SLE disease activity index

SLE disease activity index (SLEDAI) according to *Bombardier et al. (1992)* was performed. It consists of 24 descriptors with pre-assigned severity weights. The total SLEDAI score can range from 0 (no activity) to 105 (maximum activity). Patients with a score > 10 were considered active. The SLEDAI has been shown to be sensitive to changes in lupus activity measured by the treating physician.

Neurophysiology:

EEG.

Laboratory investigations:

- CBC.
- ESR.
- Serum creatinine.
- AST and ALT.
- Complete urine analysis.
- ANA.
- Detection of anti-ds-DNA autoantibody, which was performed using Autostat II autoantibody test kit supplied by Congent Diagnostic Ltd.
- Antiribosomal antibodies (anti-P) by ELISA using a kit that was supplied from ORGENTEC diagnostic GmbH Kupferbergterrasse 17-19 D-55116 Mainz Germany. Values ≥ 3.8 IU were considered to be seropositive.
- Serum prolactin hormone level by ELISA using a kit that was supplied from EUROGENETICS. N.V. Transportstraat 4-3980 tessenderlo Belgium. Prolactin levels were determined during the first part of the menstrual cycle (between the 5th and the 8th day) (hyperprolactinemia was considered ≥ 19.1 ng/ml).

Radiological investigations:

- Plain-x ray chest.
- Computerized axial tomography scan of the brain was done for the ten cases with clinical symptoms of CNS affection (NPSLE).
- Brain SPECT.

Brain SPECT Technique:

Twenty-seven patients and 10 controls were subjected to steady state measurement of cerebral blood flow. Imaging commenced 20 minutes after IV injection of 13 mCi (480 MBq) Tc-99m hexamethylene-propylene amine oxime (HMPAO). The imaging device was a single head rectangular sophy XRT gamma camera mounted to parallel hole high resolution collimator and connected to one-line computer system.

The camera head was allowed to rotate 360 around the patient's head with the cantho-metal line perpendicular to the camera surface at the anterior start point. Image acquisition was through "the step and shoot methods" acquiring 64 frames through the entire 360 circular rotation. Images were reconstructed using appropriate filter (Butter worth) in the transverse, sagittal and coronal planes.

Reading of SPECT: Method applied was visual analysis, all rCBF studies of patients and control were examined blind to the diagnosis.

Normal tracer uptake:

Typically there is symmetric distribution of tracer uptake in both hemispheres. The basal ganglia, occipital cortex and cerebellum will appear darker (white color) than the other regions (yellow color).

Absent tracer uptake:

It has the appearance of a bite or wedge taken out of the brain.

Reduced but not absent tracer uptake:

It appears thin or "less intense" in comparison to equivalent regions seen in normal studies. It varies from mild (orange color) to severe (green color).

Increased tracer uptake:

It appears to have "greater intensity" than the equivalent region seen in normal studies.

The definition of SPECT abnormalities was derived from criteria formulated by *Lin et al. (1997)* as follows: a single lesion or multiple small lesions confined to two lobes or less was considered to be a focal pattern, whereas the presence of lesions involving three or more lobes was regarded as a diffuse pattern.

SPECT was done for 27 patients at the beginning of the study as one patient with NPSLE died before she undergoes SPECT scanning and two patients without NPSLE refused to undergo SPECT scanning. SPECT was repeated 6 months later for 24 patients who were still alive and consenting. So, this study is considered as a longitudinal one.

So, patients had undergone physical as well as neurological history and examination; followed by assessment of disease activity using SLEDAI. Then patients were screened for psychiatric morbidity using GHQ followed by ICD-10 Symptom Checklist for those exceeding the cutoff of the GHQ. Also, they were psychometrically assessed using Wechsler Memory Scale, Beck Depression Inventory, and Hamilton Anxiety Scale. Also, they had undergone laboratory investigations; EEG; CT; as well

as SPECT. All patients who were still alive and consenting were clinically as well as psychiatrically re-assessed, including repeating the psychometric testes, six months later. They had undergone a second SPECT scan after these six months as well.

On the other hand, controls were subjected to GHQ to ensure that they were free from psychiatric morbidity, laboratory investigations, and SPECT.

Statistical Methods

The results were analyzed using the Statistical Package for the Social Science (SPSS) version 11.2.

The following statistical methods have been used in this work:

- Student test: "t-value" for comparison between means of the independent groups of patients.
- Probability of error: "P-value" used to indicate the level of significance.
- Chi-Square test: "X²" which is used for comparison between two or more observed frequency distributions.

Results

This study was carried out on 30 SLE female patients and 10 healthy matched controls. The age of patients ranged from 14-44 years (mean $\pm$ SD 25.5 $\pm$ 8.7 years). The age of the controls ranged from 17-40 years (mean $\pm$ SD 24.3 $\pm$ 5.7 years). Mean disease duration was 8 ($\pm$ 5.6 years).

CNS affection in the patients' group:

Major CNS affection was present in 7 (23.3%) patients; 3 (10%) of them presented with seizures and cerebrovascular accident. This was associated with organic mood (affective) disorder, organic depressive disorder (moderate depression)

in 2 of them (66.67%) and organic mood (affective) disorder, organic depressive disorder (severe depression) in the third. Two (6.7%) with cerebrovascular accident associated with organic mood (affective) disorder, organic depressive disorder (severe depression) and 2 (6.7%) with organic delusional (schizophrenia-like) disorder. It is worth mentioning that three patients developed coma and died, and all of them had major psychiatric manifestations as follows: 1) a patient presenting with cerebrovascular accident, seizures as well as organic mood (affective) disorder, organic depressive disorder (severe depression); 2) another patient with cerebrovascular accident as well as organic mood (affective) disorder, organic depressive disorder (severe depression); and 3) a patient with organic delusional (schizophrenia-like) disorder. On the other hand, one of the patients started by coma and recovered and she had cerebrovascular accident, seizures as well as organic mood (affective) disorder, organic depressive disorder (moderate depression).

Only minor CNS affection was present in 3 (10%) patients: two of them (6.7%) had migraine as well as cognitive impairment and one (3.33%) had only organic anxiety disorder (moderate to severe). However, it is worth mentioning that all patients with major NPSLE had minor symptoms as well.

It is also worth mentioning that all patients with NPSLE in this study, whether minor or major, had both neurological as well as psychiatric disorders, except for the two patients who had organic delusional (schizophrenia-like) disorder.

Cognitive functions assessment in patients' group:

Impairment of cognitive function was present in 9 (30%) patients, 7 of them had major CNS affection and two had only minor NPSLE.

Electro - encephalography (EEG):

EEG was done to all patients. It was found to be abnormal in 3 cases (10%); two of them with and one without clinical CNS affection.

Serum prolactin hormone level:

It was found that 9 (30%) patients had hyperprolactinemia (≥ 19.1 ng/ml). Moreover, there was a highly significant association ($P < 0.001$) between hyperprolactinemia and CNS manifestations of SLE.

Anti-ribosomal antibodies (anti-P):

It was found that 26 patients (86.7%) were seropositive (i.e., ≥ 3.8 IU). Although 100% of patients with CNS affection had anti-P antibodies, yet this proportion was not significantly different ($P > 0.05$) in those with and without CNS affection.

Computerized tomography (CT) scans:

CT scan was done to all patients with CNS affection ($n = 10$ patients). It was found to be abnormal in only 2 patients with major CNS affection.

SPECT scan findings:

SPECT scan was performed on 27 patients and 10 controls: Six patients with major NPSLE; 3 patients with only minor NPSLE; and 18 patients without NPSLE. One patient with major NPSLE died before SPECT scan and two patients without NPSLE refused to undergo SPECT scan.

All controls showed normal SPECT scan findings (100%) and 16 SLE patients (59.3%) showed normal findings of SPECT scan. Eleven patients (40.7%) showed abnormal SPECT scan; 3 of them (11.1%) showed focal uptake defect and the other 8 patients (29.6%) showed diffuse uptake defects.

*** Patients with major NPSLE ($n = 6$)**

Five of them had abnormal SPECT scan. Using the sensitivity test for SPECT in detecting rCBF abnormalities, it was found to be about 83% in patients with major NPSLE affection.

*** Patients with only minor NPSLE ($n = 3$)**

SPECT scan was abnormal in 1 out of 3 (33.3%) patients with only minor NPSLE.

*** Patients without NPSLE ($n = 18$)**

Thirteen of them had normal SPECT scan. Thus SPECT had a specificity of about 72%.

Anatomic location of perfusion defects:

Our results showed that hypoperfusion commonly affected the frontal lobes (10 out of 11, 91%), followed by the parietal lobes (7 out of 11, 64%) and the temporal lobes (6 out of 11, 55%), while the occipital lobes (3 out of 11, 27%) and cerebellum (2 out of 11, 18%) were the least common areas of hypoperfusion.

Association of SPECT scans with CT results:

*** Patients with major NPSLE ($n = 6$)**

CT scan showed abnormalities in only one patient in the form of infarction but it was normal in the other five. SPECT scan was found to be abnormal in the patient with abnormal CT scan findings and in 4 out of 5 patients with normal CT scan. SPECT had

100% sensitivity in detecting CT abnormalities in patients with major NPSLE and 83% sensitivity in detecting major NPSLE.

*** Patients with only minor NPSLE (n =3)**

CT scan was normal in all of them. SPECT scan was abnormal in 1 out of 3 (33.3%) patients with only minor NPSLE.

Association of SPECT scans with EEG results:

*** Patients with major NPSLE (n =6)**

EEG showed abnormalities in 2 patients suffering from cerebrovascular accident and seizures; however, it was normal in the other 4 patients. SPECT scan was abnormal in only one out of the two patients with abnormal EEG and abnormal in all patients with normal EEG. SPECT appears to be less sensitive than EEG in detecting seizures as a manifestation of NPSLE.

*** Patients with only minor NPSLE (n =3)**

EEG was normal in all of them. SPECT was abnormal in one out of 3 patients.

*** Patients without NPSLE (n =18)**

EEG was normal in 17 patients and abnormal in only one patient. SPECT scan was abnormal in that patient with abnormal EEG and in 4 out of 17 with normal EEG.

Association of SPECT findings with clinical manifestations:

There was no correlation between SPECT and clinical manifestations, including SLEDAI, other than CNS involvement.

Association of SPECT findings with laboratory parameters:

There was significant correlation of SPECT findings with anti-P-antibodies level

($P < 0.05$) and serum prolactin hormone level ($P < 0.05$), but there was no correlation with the results of other laboratory investigations ($P > 0.05$).

Follow-up SPECT after 6 months:

SPECT analysis was repeated to twenty-four patients, as two patients with major NPSLE and one patient without NPSLE died before the second SPECT scan.

*** Patients with major NPSLE (n =6)**

Same findings was found in three out of the four (75%) with major NPSLE and improvement in only one out of four (25%). It is worth mentioning that three of these patients died, one before the first SPECT and two before the second SPECT (i.e., 42.86% mortality in patients with major NPSLE).

*** Patients with only minor NPSLE (n =3)**

Worsening in 2 out of the 3 (66.56%) patients with minor NPSLE.

*** Patients without NPSLE (n =18)**

Same findings were found in all patients without NPSLE. Improvement occurred in 1 of the 2 patients (50%) with long disease duration who received cyclophosphamide during the 6 months period between the two SPECT scans.

Mortality rate in this sample:

Four patients were dead by the end of the study, i.e., 13.33% mortality rate. So, three patients with major NPSLE (i.e., 42.86%) as compared to one patient without NPSLE (i.e., 5%) and none of the patients with minor NPSLE were dead by the end of the study. The difference was statistically significant ($P < 0.05$) among the three groups.

Table (1):Central Nervous System Affection in SLE Patients

Patient No.	Major Neuropsychiatric		Minor Neuropsychiatric		NOTES
	Major Neurological	Major Psychiatric	Minor Neurological	Minor Psychiatric	
1	Yes	Yes		Yes	Cerebrovascular accident, seizures, and organic mood (affective) disorder, organic depressive disorder (moderate depression) as well as cognitive impairment
2	Yes	Yes		Yes	Cerebrovascular accident and organic mood (affective) disorder, organic depressive disorder (severe depression) as well as cognitive impairment
3	Yes	Yes		Yes	Cerebrovascular accident, seizures, and organic mood (affective) disorder, organic depressive disorder (moderate depression) as well as cognitive impairment. Patient started by coma and recovered
4	Yes	Yes		Yes	Cerebrovascular accident, seizures, and organic mood (affective) disorder, organic depressive disorder (severe depression) as well as cognitive impairment. Patient developed coma and died before the first SPECT scanning
5		Yes		Yes	Organic delusional (schizophrenia-like) disorder as well as cognitive impairment.
6	Yes	Yes		Yes	Cerebrovascular accident and organic mood (affective) disorder, organic depressive disorder (severe depression) as well as cognitive impairment. Patient developed coma and died before the second SPECT scanning
7		Yes		Yes	Organic delusional (schizophrenia-like) disorder as well as cognitive impairment. Patient developed coma and died before the second SPECT scanning
8				Yes	Organic anxiety disorder (moderate to severe)
9			Yes	Yes	Migraine and cognitive impairment
10			Yes	Yes	Migraine and cognitive impairment
Total	5	7	2	10	

Table (2): Comparison between SLE Patients and the Control Group Regarding Laboratory Findings

LABORATORY FINDINGS	SLE Mean±SD	Control Mean±SD	T-Test	P
Hb (gm%)	9.5 ± 2.3	14.1 ± 1.1	-8.64	< 0.05*
RBCs (106/UL)	3.5 ± 0.8	4.7 ± 0.5	-4.57	> 0.05
WBCs (103/UL)	5.98 ± 3.3	6.64 ± 1.1	-0.95	< 0.05*
Platelets (103/UL)	240.1 ± 79.6	252.9 ± 77.9	-0.44	> 0.05
ESR (mm/hr)	61.0 ± 34.9	9.2 ± 4.5	7.94	< 0.001**
S. Creatinine (mg/dl)	1.01 ± 5.3	0.59 ± 0.14	2.45	> 0.05
ALT (U/L)	20.2 ± 6.8	17.4 ± 2.3	3.32	> 0.05
AST (U/L)	19.3 ± 4.9	16.0 ± 2.0	2.03	> 0.05

* = significant

**= highly significant

Table (3): Association of SPECT Findings with the Different Disease Manifestations

Disease Features	No. of Patients	Spect +Ve (N=11)	Spect -Ve (N=16)	P (Fisher's Exact Test)
CNS	7	5	1	< 0.05*
-major	3	1	2	
-only minor	18	5	13	
-No CNS	24	10	14	> 0.05
Arthritis	3	1	2	
No arthritis	5	3	2	> 0.05
Renal disorder	22	8	14	
No renal disorder	9	5	4	> 0.05
Chest disorder	18	6	12	
No chest disorder	1	1	0	> 0.05
Cardiac disorder	26	10	16	
No cardiac disorder	10	6	4	> 0.05
Hematological disorder	17	5	12	
No hematological disorder				

* = significant

NB: one of the patients with major NPSLE died before doing the first SPECT scanning

Table (4): Association of SPECT Findings with the Different Disease Parameters

Disease Parameter	SPECT +VE (N=11) Mean ± SD	SPECT -VE (N=16) Mean ± SD	T-Test	P
ESR	65.4 ± 33.2	58.8 ± 37.2	- 0.47	> 0.05
Hb%	9.4 ± 1.8	9.8 ± 2.6	0.49	> 0.05
RBCs	3.4 ± 0.6	3.6 ± 0.9	0.53	> 0.05
WBCs	5.7 ± 3.5	6.4 ± 3.3	0.57	> 0.05
Platelets	260.9 ± 54.5	241.9 ± 89.1	- 0.63	> 0.05
S. Creatinine	0.9 ± 0.2	0.9 ± 0.2	-0.70	> 0.05
ALT	19.7 ± 6.3	21.7 ± 7.2	0.73	> 0.05
AST	18.5 ± 3.8	19.1 ± 5	0.34	> 0.05
Prolactin	13.8 ± 7.4	10.7 ± 5.1	-1.21	< 0.05*
Anti-P	6.8 ± 3.2	4.5 ± 1.6	-2.18	< 0.05*
Activity score	12.6 ± 7.5	9.3 ± 4.8	-1.40	> 0.05

* = significant

Table (5): SPECT, CT scan and EEG results in 30 SLE patients according to Neuropsychiatric Manifestations

PATIENT GROUP	PT NO	SPECT	CT SCAN	EEG
<i>Major NPSLE</i>	1	Diffuse uptake defects	Normal	Background activity
	2	Diffuse uptake defects	Normal	Normal
	3	Normal	Normal	Epileptogenic focus
	4	Not done	Right and left parietal infarctions	Normal
	5	Focal left frontal region defect	Normal	Normal
	6	Diffuse uptake defects	Right parietal infarction	Normal
	7	Diffuse uptake defects	Normal	Normal
<i>Only minor NPSLE</i>	8	Normal	Normal	Normal
	9	Diffuse uptake defects	Normal	Normal
	10	Normal	Normal	Normal
<i>No NPSLE (Long disease duration, i.e., > 5 years)</i>	11	Normal		Normal
	12	Diffuse uptake defects		Normal
<i>No NPSLE</i>	13	Diffuse uptake defects		Normal
	14	Normal		Normal
	15	Normal		Normal
	16	Normal		Normal
	17	Diffuse uptake defects		Epileptogenic focus
	18	Focal right parietal region defect		Normal
	19	Focal left frontal region defect		Normal
	20	Normal		Normal
	21	Normal		Normal
	22	Not done		Normal
	23	Normal		Normal
	24	Normal		Normal
	25	Normal		Normal
	26	Normal		Normal
	27	Not done		Normal
	28	Normal		Normal
	29	Normal		Normal
	30	Normal		Normal

PT NO= patient number

Table (6): SPECT Scan Findings Six Months after the Initial SPECT

	PATIENT NO.	1 ST SPECT	2 ND SPECT	NOTES
Major NPSLE	1	Diffuse uptake defects	Same findings	Both uptake defects noted on SPECT and neuropsychiatric symptoms noted clinically unchanged despite intensification of immunosuppressive therapy.
	2	Diffuse uptake defects	Same findings	
	3	Normal	Normal	Patient symptoms controlled.
	5	Focal left frontal region defect	Improvement (normal)	Improvement of neuropsychiatric symptoms after the patient received high dose of steroids.
Only minor NPSLE	8	Normal	Worsened, it showed small perfusion defect in left frontal cortex	Persistence of neuropsychiatric symptoms, patient received steroids.
	9	Diffuse uptake defects	Same findings	Both uptake defects and neuropsychiatric symptoms were unchanged.
	10	Normal	Worsened, it showed diffuse uptake defects	Persistence of neuropsychiatric symptoms, patient received steroids.
No NPSLE (Long disease duration, i.e., > 5 years)	11	Normal	Normal	Neither developed NPSLE nor changes in their conditions.
	12	Diffuse uptake defects	Improvement in perfusion right frontal, left frontal and left parietal	Patient received cyclophosphamide during the six months period between the two SPECT scanning events.
No NPSLE	13, 17	Diffuse uptake defects	Same findings	Neither developed NPSLE nor changes in their conditions.
	14,16	Normal	Normal	
	18	Focal right parietal region defect	Same findings	
	19	Focal left frontal region	Same finding	
	20 – 30 (except for the 22 nd and 27 th patients)	Normal	Normal	

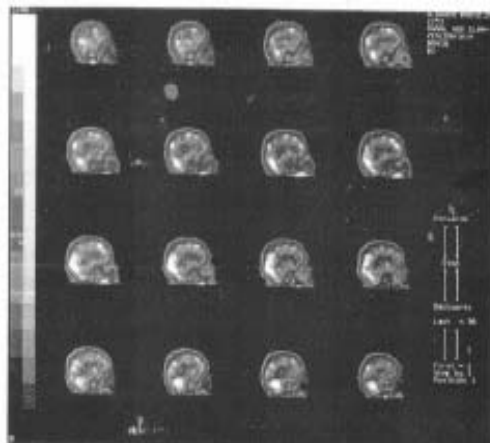


Plate (1): Sagittal view of the brain, normal cerebral SPECT scan.

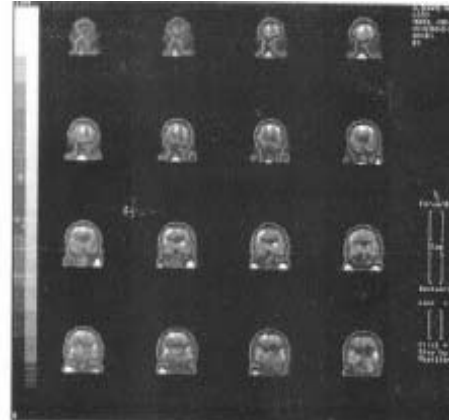


Plate (2): Coronal section through the cerebrum, normal cerebral SPECT scan.

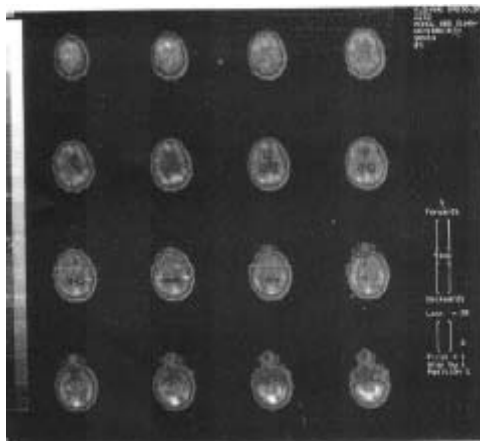


Plate (3): Transaxial view of the brain, normal cerebral SPECT scan

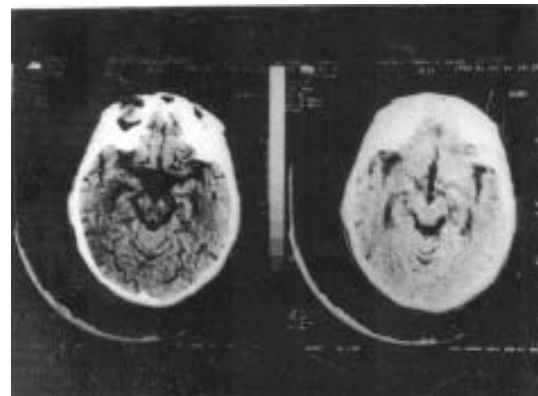


Plate (4): Patient no. (5): Normal CT scan.

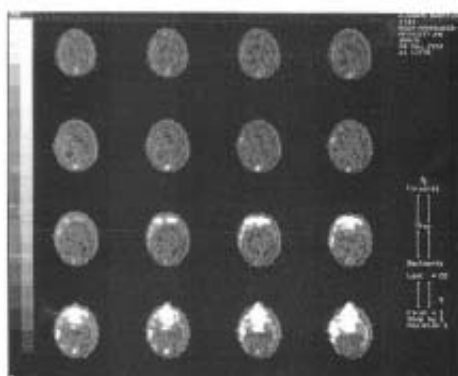


Plate (9): Patient no. (12): SPECT scanning showed perfusion defects in both frontal, left parietal and left occipital cortex, hypo perfusion of cerebellum and deep sub cortical structures (transaxial view).

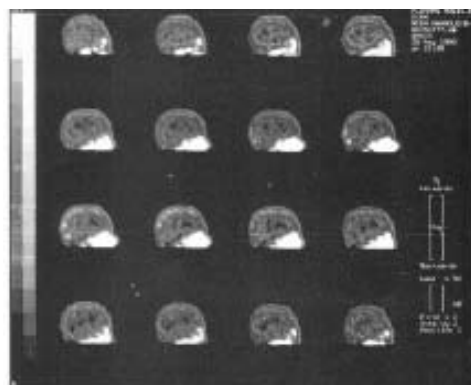


Plate (10): Patient no. (12): SPECT scanning showed perfusion defects in both frontal, left parietal and left occipital cortex, hypo perfusion of cerebellum and deep subcortical structures (sagittal view).

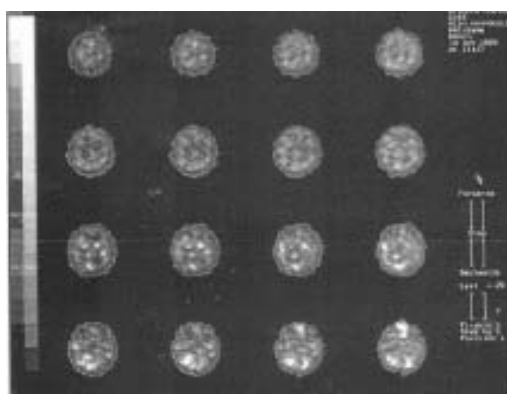


Plate (11): Patient no. (12): Follow up after 6 months, SPECT scan showed perfusion defects in right frontal and left occipital cortex. Rest of the brain fairly perfused (transaxial view).

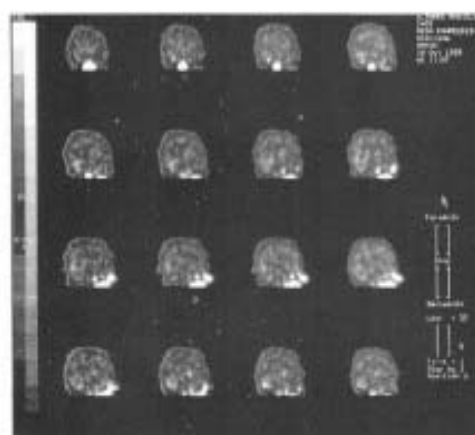


Plate (12): Patient no. (12): Follow up after 6 months, SPECT scan showed perfusion defects in right frontal and left occipital cortex. Rest of the brain fairly perfused (sagittal view).

Discussion

Although involvement of the brain is one of the most important complications of systemic lupus erythematosus (SLE), yet its pathophysiology remains obscure and our understanding of NPSLE is still far from clear. First, it is difficult to distinguish between events resulting from the direct effect of active SLE on the CNS and events attributed to SLE-induced dysfunction of other organs or to side-effects of drug therapy (*Bresnihan, 1982*). Second, specific diagnostic methods have not been established (*Oku et al., 2003*).

We studied 30 Egyptian SLE female patients and 10 controls. Central nervous system affection was present in 10 (33.3%) of our patients. Our results are similar to an Egyptian study done earlier by *Aref et al., 1992* who reported CNS manifestations to be 33%. Also, *Jonsen et al. (2002)* found that NPSLE occurs in 38% of SLE patients in a Swedish sample. Other studies reported higher percentage of CNS affection in patients with SLE. *Gibson & Myers (1976)*; *Feinglass et al. (1976)* and *Grigor et al. (1978)*, suggested that CNS involvement occurs in up to 50% of SLE patients. Also, *Bluestein (1987)*; *McCune & Globus (1988)* reported CNS involvement to be 75% and 66% respectively. The highest reported rate of NPSLE was by *Ainiala et al. (2001)* in a Finnish population, who found that 91% SLE patients had at least one NP syndrome. However, when minor manifestations were excluded, the prevalence of NPSLE dropped to 46%.

On the other hand, another study reported CNS involvement to occur in only 12%, which was lower than our study (*Abdel-Galil et al., 1996*). The difference in the results may be due to marked variation in the presentation, the severity and the often-

transient nature of CNS affection in SLE (*Teh et al., 1993*). Also, the differences in methods and criteria used to define CNS affection are likely to be a major contributor to the controversial results reported (*Bruyne, 1995*).

One aim of our study was to detect the diagnostic value of SPECT in CNS affection in SLE patients. Also, we compared SPECT findings with findings from clinical, neuropsychiatric, neuropsychological, laboratory, electroencephalographic (EEG) and CT scan evaluation and we studied the value of SPECT as a prognostic tool in these patients. We used SPECT scan in this situation for two reasons: the first reason is that the most consistent cerebral pathologic finding at autopsy of SLE patients has been vasculopathy (*Johnson & Richardson, 1968*). Because vasculitic processes are the mechanisms of cerebral symptoms in SLE, determination of rCBF as an indicator of early CNS involvement seems promising. SPECT scanning provides information on regional brain perfusion, which is closely linked to cerebral metabolism (*Stefan et al., 1990*). The second reason for using SPECT scan is that the diagnosis of CNS involvement is hampered by relative insensitivity of conventional imaging techniques applied in the past. MRI has been used in the diagnosis of cerebral lupus (*Jacobs et al., 1988*). Although it seems more sensitive than CT scan findings, both MRI and CT scan mainly correspond to structural and not functional abnormalities (*Nossent et al., 1991*). So, CT or MRI can reveal morphologic alteration in a substantial proportion of patients with overt neurological symptoms but it would be desirable to identify changes before structural damage occur. Functional

neuroimaging by SPECT should be able to demonstrate brain perfusion abnormalities early (*Rubbert et al., 1993*). Also, in psychiatric disease, no MRI or CT defect was consistently demonstrated (*Vermess et al., 1983*).

SLE patients were categorized into 3 groups; group I with major neuropsychiatric disorders (n=7), group II with minor neuropsychiatric symptoms (n=3) and group III without neuropsychiatric symptoms (n=20). It is also worth mentioning that all patients with NPSLE in this study, whether major or minor, had both neurological as well as psychiatric disorders except for the two patients who had organic delusional (schizophrenia-like) disorder and one of them developed coma and died. Thus, an organic cause for the psychiatric disorders can be suggested and this explains the abnormal SPECT findings in these cases.

Our results revealed that 5 out of 6 patients (83%) with major NPSLE showed abnormal SPECT scan, with predominately diffuse uptake defects (in four patients out of the five, i.e., 80%). Other studies has shown SPECT to be highly sensitive, detecting abnormalities in up to 100%, 93%, and 90% of patients with clinical neuropsychiatric involvement (*Kao et al., 1999a; Kikukawa et al., 2000; Kovacs et al., 1995* respectively). However, SPECT has low specificity and comparable abnormalities have been described in patients with acute stroke, transient ischemic attacks, epilepsy and other neurological conditions (*Rubbert et al., 1993*). Thus, SPECT scanning may be used mainly to support a clinical diagnosis of neuropsychiatric involvement.

As regards SPECT as a prognostic tool for NPSLE, it was found that all patients with

major NPSLE who had diffuse defects either remained unchanged or became worse clinically as well as on follow-up SPECT (two out of four, i.e., 50% died on follow-up), despite the treatment with steroids and/or immunosuppressive agents. This was in contrast to the patient with a focal defect who showed clinical improvement over time associated with improvement on her rCBF as shown on her second SPECT scanning.

Interestingly (33%) of patients with only minor NPSLE showed abnormal SPECT scan. This result is in agreement with *kao et al. (1999a)* who found that 33% of patients with minor manifestations of NPSLE had hypoperfusion. Moreover, in our study, all of them (100%) showed abnormal SPECT scan on follow up. This means that rCBF abnormalities are present in a substantial proportion of SLE patients with mild neuropsychiatric symptoms.

However, 15 out of 18 (72%) of patients without NPSLE showed normal SPECT scan. None of the healthy controls demonstrated perfusion defects. Our results are similar to that of *Handa et al., 2003* who found perfusion defects on SPECT in 8/10 patients with NPSLE, while only 1/10 lupus patients without clinical NP involvement and none of the healthy controls demonstrated perfusion defects. Abnormalities in cerebral perfusion in SLE patients without NPSLE may be due to the long-term use of steroids and/or SPECT may be a very sensitive detector of subclinical NPSLE (*Nossent et al., 1991; Falcini et al., 1998 and Sabbadini et al., 1999*) that could progress to severe NPSLE (*Falcini et al., 1998*), however this needs a follow-up study of longer duration for a larger number of patients to conclude.

Since the territory of middle cerebral artery (MCA) is at higher risk of cerebral vasculopathy than other territories (*Mitchell et al., 1994*), the 3 most common hypoperfusion areas found on SPECT scan in our study were frontal (10 out of 11, 91%), parietal (7 out of 11, 64%) and temporal (6 out of 11, 55%) lobes which are under territory of MCA. Our results are similar to *Colamussi et al. (1995)* and *Kao et al. (1999b)*, who found multiple areas of hypoperfusion especially in the territory of MCA, however with more involvement of the parietal lobes. Also, *Lin et al., 1997* found that parietal, frontal, and temporal lobes were the most common areas of CNS involvement, with 95.6%, 56.5% and 56.5% involvement respectively in patients with major NPSLE; and 80.7%, 65.3% and 46.1% involvement respectively in patients with minor NPSLE. Other studies found that hypoperfusion in the posterior cingulate gyrus and thalamus was associated with the severity of psychiatric symptoms (*Oda et al., 2005*). It is often suggested in these studies that correlations between anatomic location of perfusion defects or the pattern of uptake defect and clinical symptoms were not evident, due to limited number of patients (*Rubbert et al., 1993*). In our study, one of the two psychotic patients has shown focal left frontal region perfusion defect, this is in agreement with what *Kovacs et al. (1995)* suggested that SLE patients with psychosis displayed hypofrontality previously described with schizophrenia.

The observation of both diffuse and focal CNS involvement in SLE has led us, as other researchers, to hypothesize that there are several pathogenic mechanisms in NPSLE, such as microvascular damage, small-vessel vasculopathy and autoantibody-mediated neuronal cell injury

(*Devinsky et al., 1988; Hanly et al., 1992; Denburg & Behmann, 1994*).

It was found that SPECT documented subtle and multiple abnormalities not detected by conventional imaging technique (i.e., CT scan). This may be due to the fact that CT scan can reveal morphologic alteration in the brain but SPECT was able to detect functional changes before structural damage occur (*Reiff et al., 1997; Falcini et al., 1998*). On the other hand, SPECT was less sensitive than EEG in detecting seizures and this may be due to transient nature of NPSLE particularly when it comes to seizures evaluation (*Rubbert et al., 1993*). However, other studies found that SPECT in patients with focal EEG abnormalities showed more hypoperfused areas than did SPECT of patients with diffuse EEG abnormalities, although the difference was not statistically significant (*Colamussi et al., 1995*).

Especially when anti-neuronal antibodies are responsible for CNS involvement, usually there is no structural damage but only cellular dysfunction which is reversible and this may have specific predilection sites (*Aref et al., 1992*). The transient nature of CNS involvement may affect sensitivity of SPECT (*Falcini et al., 1998*), hence it is possible that sensitivity of SPECT depends on timing of scanning in relation to the onset and termination of seizure attacks. Unfortunately, true ictal studies with HMPAO are nearly impossible to obtain, because this compound is stable in vitro leading to delay between seizures onset and scanning of about 5 – 20 minutes (*Devous & Leroy, 1989*).

Impairment of cognitive function was present in 9 (30%) patients, 7 of them had major CNS affection and two (3.33%) had only minor NPSLE. These results are in

agreement with *Monastero et al. (2001)*, who found cognitive dysfunction in 26.9% of his sample. Also, *Waterloo et al. (2002)* suggested that cognitive dysfunction appears to be more common than previously thought, but its clinical significance and prognostic implications remain unclear. Other studies show a high prevalence of low-level cognitive dysfunctions, whose prevalence reaches 81% (*Ainiala et al., 2001*). More recently, *Denburg & Denburg (2003)* concluded that cognitive dysfunction has now been accepted as a bona fide manifestation of NPSLE.

Interestingly, (50%) of patients with long-standing disease (> 5 years) showed cerebral blood flow abnormalities, with diffuse uptake defects. This finding supports the notion that cerebral vasculopathy arises during the course of the disease and although it is often subclinical, it leads to cerebral blood flow disturbances in a substantial proportion of patients (*Rubbert et al., 1993*). These findings are consistent with data from autopsy studies suggesting that subclinical CNS disease may occur in a considerable proportion of SLE patients. So, cerebral lesions have been detected in absence of previous neuropsychiatric symptoms (*Harris & Huges, 1985*).

Major psychiatric manifestations were common in our sample. Depression was found in five patients (16.67%), however, other studies found higher rates of mood disorders that reached 43% (*Ainiala et al., 2001*). It is worth mentioning that the three patients who developed coma and died had major psychiatric manifestations: one of the patients presenting with cerebrovascular accident, seizures as well as organic mood (affective) disorder, organic depressive

disorder (severe depression), another one with cerebrovascular accident as well as organic mood (affective) disorder, organic depressive disorder (severe depression), and the third had organic delusional (schizophrenia-like) disorder. On the other hand, one of the patients started by coma and recovered and she had cerebrovascular accident, seizures as well as organic mood (affective) disorder, organic depressive disorder (moderate depression). This can be explained by the negative effects of depression on the immune system which might lead to aggravation of SLE symptoms and/or death. *Karassa et al. (2003)* studied the files of 300 patients with SLE. They found that all those attempting suicide had a history of NPSLE presenting with depression, which forms another important cause for the increased mortality rate in these patients.

In general mortality was high in our sample of patients. So, three patients with major NPSLE (i.e., 42.86%) as compared to one patient without NPSLE (i.e., 5%) and none of the patients with minor NPSLE were dead by the end of the study. The difference was statistically significant ($P<0.05$) among the three groups. This is in agreement with what was suggested in earlier studies that NPSLE was a predictor of high mortality rate (*Jonsson et al., 1989*).

Several mechanisms including immunomedi-ated vasculopathy and neuron reactive autoantibodies (*How et al., 1985*) have been implicated in the pathogenesis of CNS involvement. In our study 100% of patients with CNS affection had anti-P antibodies, yet this proportion was not significantly different ($P>0.05$) in those with and without CNS affection. However, we found a significant correlation ($P<0.05$) between SPECT findings and anti-P-

antibodies. Data suggest a role for such antibodies might be presumed in CNS lupus. Also, *Kao et al., (1999a)* found that 5 patients out of the 12 with NPSLE had anti-P-antibodies and psychosis/depression. More recently, *Eber et al. (2005)* found that several autoantibodies may play a role in the pathogenesis of psychiatric complications of SLE, particularly antibodies against ribosomal P-proteins (anti-P). These autoantibodies have been suggested to be specific markers of the psychiatric manifestations of SLE. The reported prevalence of anti-P is highly variable in SLE patients and is dependent on different ethnic backgrounds, sensitivity, specificity of the assays employed for autoantibody detection, and the time at which sera were analyzed in relation to clinical events. Some studies have confirmed the hypothesis of an association of anti-P antibodies with psychiatric manifestations of neuropsychiatric SLE (NPSLE), while others have disputed this relationship. Other investigators studied anticardiolipin antibodies which had been related to various thrombotic events as well as cerebral abnormalities in SLE (*Levine & Welch, 1987*), they did not find any correlation between anti cardiolipin and SPECT scan findings (*Nossent et al., 1991; Kovacs et al., 1995; and Falcini et al., 1998*).

On the other hand, our study found no significant association between the occurrence of NPSLE and the overall disease activity. This supports the hypothesis that CNS involvement in SLE is not simply a reflection of systemic disease, and evidence of disease activity in other organs is not always present (*Sibley et al., 1992*). However, other studies found that cerebral hypoperfusion detected by SPECT is related to clinical activity (*Lopez-Longo*

et al., 2003). Thus, accurate diagnosis of NPSLE is an important clinical dilemma, as treatment with high-dose glucocorticoids with or without cyclophosphamide is appropriate in these conditions whether there is evidence of other systemic disease activity or not (*Navarrete & Brey, 2000*).

Prolactin serum hormone level was found to be ≥ 19.1 ng/ml (i.e., hyperprolactinemia) in 9 patients (30%). These results were found to be in agreement with other studies who found that 20-30% of SLE patients have hyperprolactinemia (*Jimena et al., 1998; Walker & Jacobson, 2000; Jara et al., 2001*). Also, hyperprolactinemia was found to have a significant statistical association ($P < 0.05$) with CNS manifestations as well as with SPECT findings in our study. The interrelationship between prolactin and the immune system have been elucidated in the last decade, opening new horizons in the field of immunoendocrinology. Prolactin is secreted not only by the anterior pituitary but also by many extra-pituitary sites including the immune cells. It serves as an immunomodulator involved in lymphocyte survival, activation, and proliferation, and is, in effect, a cytokine. Prolactin receptors are distributed throughout the immune system and are included as members of the cytokine receptor superfamily (*Vera-Lastra et al., 2002*). There is increasing data implicating prolactin in autoimmunity, and specifically in SLE. Hyperprolactinemia was found to be common in patients with SLE and several clinical reports have suggested that prolactin plays an important role in its pathogenesis (*Mendez et al., 2004; Takizawa et al., 2005*). Although, many studies found an increased level of prolactin in SLE patients (*Vera-Lastra et al., 2003; Kramer et al., 2005*), yet studies

on the relation of prolactin level to the NPSLE has been scarce to date.

Our longitudinal data showed clinical recovery and amelioration of perfusion deficits in some patients, improvement in those patients can be attributed to increasing the doses of steroids or starting immunosuppressive therapy. Also, some patients showed the same findings in their SPECT scan, other showed more deterioration in their SPECT scan. These results are in agreement with what was found by **Zhang et al. (2005)**, who has concluded that SPECT is more sensitive than MRI in revealing damage in diffuse CNS-SLE, and is useful in follow-up, especially for monitoring disease severity and guiding treatment. Also, **Sun et al., 2004** found that HMPAO-SPECT is a logical and objective tool for measuring the effects of methylprednisolone pulse therapy in SLE patients with brain involvement by determining changes in rCBF.

This difference in outcome may be explained by two different mechanisms involved in pathogenesis of CNS lupus; the first one is neuron reactive autoantibodies, which has a good prognosis and the other one is vasculitis which carries a bad prognosis usually with renal affection (**Aref et al., 1992**). So bad prognosis in those patients may not only be explained by CNS affection, but the affection of other systems especially renal affection.

Despite the fact that this study is one of the few that were longitudinal focusing on SPECT use as a diagnostic as well as a prognostic tool in NPSLE, yet it has some limitations: 1) its small sample size, this problem has faced most of the researchers who had worked on the same population; 2) although visual interpretation of SPECT results may sometimes be superior to semi-

quantitative analysis, yet some subtle changes may be overlooked; 3) the short duration of the follow-up study (only 6 months).

As it is crucial to exclude secondary causes of the presenting symptoms in any patient with suspected NPSLE, our results suggest that SPECT imaging is a sensitive tool for the diagnosis of CNS involvements in SLE. While the meaning of perfusion deficits in patients without neuropsychiatric symptoms remains to be clarified, the domain of SPECT as a diagnostic tool may lie in the early detection of brain perfusion defects in patients with clinical symptoms such as headache and cognitive dysfunction. SPECT scan could therefore be helpful in substantiating the clinician's suspicion of an incipient CNS involvement. It was also found that follow-up SPECT findings were correlated with changes in neuropsychiatric symptoms. So, it might be promising as a prognostic tool in NPSLE that can be used as an activity marker that represents the activity of cerebral involvement and its response to different treatments. Whether therapeutic decision should be based on our findings, additional larger, longitudinal studies to determine the significance of SPECT alteration over the long-term course of disease need to be performed. Last but not least, it can be suggested that the clinical presentation, serologic tests and neuroimaging techniques should be combined to support the diagnosis of NPSLE.

References

Abdel-Galil M, El-Kadery N, Ali N, Kamel N (1996): Role of anti-P antibodies in the pathogenesis of systemic lupus erythematosus and systemic sclerosis (MD Thesis, Ain Shams Faculty of Medicine).

Abdel Khalek A (1996): Beck Depression Inventory (Arabic Version). Cairo: Dar El Nahda Egyptian Press.

Ainiala H, Loukkola J, Peltola J, Korpela M, Hietaharju A (2001): The prevalence of neuropsychiatric syndromes in systemic lupus erythematosus. *Neurology*; 57(3): 496-500.

American College of Rheumatology (ACR) ad hoc Committee on Neuropsychiatric Lupus Nomenclature (1999): Case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum*; 42(4): 599-608.

Aref HMA, Fadli E, Tamara F, Sallam T (1992): The value of BAEP and BEAM in detection of subclinical central nervous system affection in patients with systemic lupus erythematosus (MD Thesis, Ain Shams Faculty of Medicine).

Beck AT & Steer RA (1993): Manual for the Beck Depression Inventory, San Antonio: Psychological Corporation.

Bluestein HG (1987): Neuropsychiatric manifestations of systemic lupus erythematosus. *N Engl J Med*; 317(5): 309-311.

Bombardier C, Gladman DD, Urowitz MB, Caron D, Change CH (1992): The development and validation of the SLE Disease Activity Index (SLEDAI). *Arthritis Rheum*; 35(6): 630 - 640.

Bresnihan B (1982): CNS lupus. *Clin Rheum Dis*; 8 (1): 183-195.

Brayne GAW (1995): Controversies in lupus: nervous system involvement. *Ann Rheum Disease*; 54(2): 159-167.

Colamussi P, Giganti M, Cittanti C, Dovigo L, Trotta F, Tola MR, et al. (1995): Brain single-photon emission

computed tomography with 99mTc-HMPAO in neuropsychiatric systemic lupus erythematosus: relations with EEG and MRI findings and clinical manifestations. *Eur J Nucl Med*; 22(1): 17-24.

Denburg JA & Behmann SA (1994): Lymphocyte and neuronal antigens in neuropsychiatric lupus. *Ann Rheum Dis*; 53(5): 304-308.

Denburg JA, Behman SA, Carbotte RM, Denburg SD (1994): Lymphocyte antigens in neuropsychiatric systemic lupus erythematosus. Relationship of lymphocyte antibody specificities to clinical disease. *Arthritis Rheum*; 37(3): 369-375.

Denburg SD & Denburg JA (2003): Cognitive dysfunction and antiphospholipid antibodies in systemic lupus erythematosus. *Lupus*; 12(12): 883-890.

Devinsky O, Petito CK, Alonso DR (1988): Clinical and neuropathological findings in systemic lupus erythematosus: the role of vasculitis, heart emboli, and thrombotic thrombocytopenia purpura. *Ann Neurol*; 23(4): 380-384.

Devous MD & Leroy RF (1989): Comparison of interictal and ictal regional cerebral blood flow findings with scalp and depth electrode focus localization. *J Cereb Blood Flow Metab*; 9(10): 891-897.

Eber T, Chapman J, Shoenfeld Y (2005): Anti-ribosomal P-antibody and its role in psychiatric manifestations of systemic lupus erythematosus: myth or reality? *Lupus*; 14(8): 571-575.

Falcini F, De Cristofaro MTR, Ermini M, Masi A, Meldolesi U (1998): Regional cerebral blood flow in Juvenile SLE. A Prospective SPECT study. *J Rheumatol*; 25(3): 583-588.

Fatim L (1992): Hamilton Anxiety Scale (Arabic Version). Cairo: Anglo Egyptian Press

Feinglass EJ, Arnett FC, Dorsch CA, Zizic TM (1976): Neuropsychiatric manifestations of systemic lupus erythematosus: Diagnosis, clinical spectrum and relationship to other features of the disease. *Medicine (Baltimore)*; 55(4): 323-339.

Ghanem M (1981): Cerebral hemispheric lateralization of cognitive deficits due to depressive or schizophrenic illnesses (MS Thesis, Ain Shams Faculty of Medicine).

Gibson T & Myers AR (1976): Nervous system involvement in systemic lupus erythematosus. *Ann Rheum Dis*; 35(5): 398-406.

Goldberg D & Williams P (1983): A user's guide to the General Health Questionnaire. Windsor, Berkshire: NFER-Nelsen.

Grigor R, Edmonds J, Huges GRV (1978): Systemic lupus erythematosus: a prospective analysis. *Ann Rheum Dis*; 31(2): 121-128.

Hamilton M (1976): "Hamilton Anxiety Scale", ECDEU Assessment Manual for Psychopharmacology, Guy W, ed, Rockville, MD: U.S. Department of Health, Education, and Welfare. p. 193-198.

Handa R, Sahota P, kumar M, Jagannathan NR, Bal CS, Gulati M, et al. (2003): In vivo proton magnetic resonance spectroscopy (MRS) and single photon emission computed tomography (SPECT) in systemic lupus erythematosus (SLE). *Magn Reson Imaging*; 21(9): 1033-1037.

Hanly JG, Walsh NM, Sangalang V (1992): Brain pathology in systemic lupus erythematosus. *J Rheumatol*; 19(5):732-741

Hanly JG, Walsh NM, Fisk JD, Eastwood B, Hong C, Sherwood G, et al. (1993): Cognitive impairment and autoantibodies in systemic lupus erythematosus. *Br J Rheumatology*; 32(4): 291-296.

Harris E & Hughes G (1985): Cerebral disease in systemic lupus erythematosus. *Semin Immunopathol*; 8(3): 251-266.

How A, Dent PB, Liao SK, Denburg JA (1985): Antineuronal antibodies in neuropsychiatric systemic lupus erythematosus. *Arth Rheum*; 28(7): 789-795.

Jacobs L, Kinkel PR, Costello PB, Alukal MK, Kinkel WR, Green FA (1988): Central nervous system systemic lupus erythematosus: The value of magnetic resonance imaging. *J Rheumatol*; 15(4): 601-606.

Janca A, Ustrin B, Isaac M, Van Drimmelen J, Dittmann V (1994): ICD-10 Symptom Checklist for Mental Disorders. Division of Mental Health, World Health Organization, Geneva.

Jara LJ, Vera-Lustra O, Miranda JM, Alcalá M, Alvarez-Nemegyei J (2001): Prolactin in human systemic lupus erythematosus. *Lupus*; 10 (10): 748-756.

Jimena P, Aguirre MA, Lopez-Curbalo A, de Andres M, Garcia-Courtay C, Cuadrado MJ (1998): Prolactin levels in patients with systemic lupus erythematosus: a case controlled study. *Lupus*; 7(6): 383-386.

Johnson RT & Richardson EP (1968): The neurological manifestations of systemic lupus erythematosus. *Medicine (Baltimore)*; 47(4): 337-369.

Jonsen A, Bengtsson AA, Nived O, Ryberg B, Sturfelt (2002): Outcome of neuropsychiatric systemic lupus

erythematosus within a defined Swedish population: increased morbidity but low mortality. *Rheumatol*; 41(11): 1308-1312.

Jonsson H, Nived O, Sturffelt G (1989): Outcome in systemic lupus erythematosus: a prospective study of patients from a defined population. *Medicine (Baltimore)*; 68(3): 141-149.

Kao CH, Ho Y, Lan JL, Changlai SP, Liao KK, Chieng PU (1999a): Discrepancy between regional cerebral blood flow and glucose metabolism of the brain in systemic lupus erythematosus patients with normal brain magnetic resonance imaging findings. *Arth Rheum*; 42(1): 61-68.

Kao CH, Lan JL, ChangLai SP, Liao KK, Yen RF, Chieng PU (1999b): The role of FDG-PET, HMPAO-SPET and MRI in the detection of brain involvement in patients with systemic lupus erythematosus. *Eur J Nucl Med*; 26(2): 129-134.

Karassa FB, Magliano M, Isenberg DA (2003): Suicide attempts in patients with systemic lupus erythematosus. *Ann Rheum Dis*; 62(1):58-60.

Kikukawa K, Toyama H, Katayama M, Nishimura T, Ejiri K, Minami K, et al. (2000): Early and delayed Tc-99m ECD brain SPECT in SLE patients with CNS involvement. *Ann Nucl Med*; 14 (1): 25-32.

Kovacs JA, Urowitz MB, Gladman DD, Zeman R (1995): The use of single photon emission computed tomography in neuropsychiatric SLE: a pilot study. *J Rheumatol*; 22(7): 1247-1253.

Kramer CK, Tourinho TF, Castro WP, da Costa Oliveira M (2005): Association between systemic lupus erythematosus, rheumatoid arthritis, hyperprolactinemia and thyroid autoantibodies. *Arch Med Res*; 36(1): 54-58.

Levine SR & Welch KM (1987): The spectrum of neurological disease associated with antiphospholipid antibodies. *Arch Neurol*; 44(8): 876-884.

Lewis SW, Ford RA, Syed GM, Revelly AM, Toone B (1992): A controlled study of 99mTc-HMPAO single-photon emission imaging in chronic schizophrenia. *Psychol Med*; 22(1):27-35.

Lin WY, Wang SJ, Yen TC and Lan JL (1997): Technetium - 99m HM PAO brain SPECT in systemic lupus erythematosus with CNS involvement. *J Nucl Med*; 38(5): 1112- 1115.

Lopez-Longo FJ, Carol N, Almoguera MI, Olazaran J, Alonso-Farto JC, Ortega A, et al. (2003): Cerebral hypoperfusion detected by SPECT in patients with systemic lupus erythematosus is related to clinical activity and cumulative tissue damage. *Lupus*; 12(11): 813-819.

McCune WJ & Golbus J (1988): Neuropsychiatric lupus. *Clin Rheum Dis Clin North Am*; 14(1): 149-167.

Mendez I, Alcocer-Varela J, Parra A, Lava-zavala A, de la Cruz DA, Alarcon-Segovia D, Larrea F (2004): Neuroendocrine dopaminergic regulation of prolactin release in systemic lupus erythematosus: a possible role of lymphocyte-derived prolactin. *Lupus*; 13(1):45-53.

Mitchell I, Webb M, Hughes R, Stewart J (1994): Cerebral lupus. *Lancet*; 343(8897):579-82.

Monastero R, Bettini P, Del Zotto E, Cottini E, Tincani A, Balestrieri G, et al. (2001): Prevalence and pattern of cognitive impairment in systemic lupus erythematosus patients with and without

overt neuropsychiatric manifestations. *J Neurol Sci*; 184(1): 33-39.

Navarrete MG & Brey RL (2000): Neuropsychiatric systemic lupus erythematosus. *Curr Treat Options Neurol*; 2(5):473-485.

Nossent JC, Hovestadt A, Schonfeld DH, Swaak AJ (1991): Single photon- emission computed tomography of the brain in the evaluation of cerebral lupus. *Arth Rheum*; 34(11): 1397-1403.

Oda K, Matsushima E, Okuba Y, Ohta K, Koike R, Miyasaka N, Kato M (2005): Abnormal regional cerebral blood flow in systemic lupus erythematosus patients with psychiatric symptoms. *J Clin Psychiatry*; 66(7): 907-913.

Okasha A, Kamel M, Fares R, Abdel Hakim (1988): An epidemiological study of depressive symptoms in rural and urban population in Egypt (MD Thesis, Ain Shams Faculty of Medicine).

Oku K, Atsumi T, Furukawa S, Horita T, Sakai Y, Jodo S, et al. (2003): Cerebral imaging by magnetic resonance imaging and single photon emission computed tomography in systemic lupus erythematosus with central nervous system involvement. *Rheumatol*; 42(6): 773-777.

Reiff A, Miller J, Shaham B, Bernstein B, Szer IS (1997): Childhood central nervous system lupus; longitudinal assessment using single photon emission computed tomography. *J Rheumatol*; 24(12): 2461-2465.

Rubbert A, Marienhagen J, Pirner K, Manger B, Grebmeier J, Engelhardt A, Wolf F, Kalden JR. (1993): Single-photon emission computed tomography analysis of cerebral blood flow in the evaluation of central nervous system involvement in

patients with lupus erythematosus. *Arth Rheum*; 36(9): 1253-1262.

Sabbadini MG, Manfredi AA, Bozzolo E, Ferrario L (1999): Central nervous system involvement in systemic lupus erythematosus patients without overt neuropsychiatric manifestations. *Lupus*; 8(1):11-19.

Sibley JT, Olszynski WP, Decoteau WE, Sundaram MB (1992): The incidence and prognosis of central nervous system affection in systemic lupus erythematosus. *J Rheumatol*; 19(1): 47-52.

Stefan H, Bauer J, Huk WJ (1990): Regional cerebral blood flow during focal seizures of temporal and frontocentral onset. *Ann Neurol*; 27(2): 162-166.

Sun SS, Huang WS, Chen JJ, Chang CP, Kao CH, Wang JJ (2004): Evaluation of the effects of methylprednisolone pulse therapy in patients with systemic lupus erythematosus with brain involvement by Tc-99m HMPAO brain SPECT. *Eur Radiol*; 14(7): 1311-1315.

Takizawa K, Kitani S, Takeuchi F, Yamamoto K (2005): Enhanced expression of CD69 and CD25 antigen on human peripheral blood mononuclear cells by prolactin. *Endocr J*; 52(5): 635-41.

Teh LS, Lee MK, Wang F, Manivasagar M, Charles PJ, Nicholson GD, et al. (1993): Antiribosomal P-protein antibodies in different populations of patients with systemic lupus erythematosus. *Br J Rheumatol*; 32(8): 663-665.

Vera-Lastra O, Jara LJ, Espinoza LR (2002): Prolactin and autoimmunity. *Autoimmun Rev*; 1(6): 360-364.

Vera-Lastra O, Mendez C, Jara LJ, Cisneros M, Medina G, Ariza R, Espinoza LR (2003): Correlation of prolactin serum

concentrations with clinical activity and remission in patients with systemic lupus erythematosus. Effect of conventional treatment. *J Rheumatol*; 30(10): 2140-2146.

Vermess M, Bernstein RM, Bydder GM, Steiner RE, Young IR, Hughes GR (1983): Nuclear magnetic resonance (NMR) of the brain in systemic lupus erythematosus. *J Comput Assist Tomogr*; 7(3): 461-467.

Walker SE & Jacobson JD (2000): Roles of prolactin and gonadotrophin-releasing hormone in rheumatic disease. *Rheum Dis Clin North Am*; 26(4): 713-736.

Waterloo K, Omdal R, Husby G, Mellgren SI (2002): Neuropsychological function in systemic lupus erythematosus: a five-year longitudinal study. *Rheumatol*; 41(4): 411-415.

Wechsler D (1945): Manual for the Wechsler Memory Scale. San Antonio, TX: The Psychological Corporation.

Zhang X, Zhu Z, Zhang X, Shu H, Li F, Dong Y (2005): Diagnostic value of single-photon-emission computed tomography in severe central nervous system involvement of systemic lupus erythematosus: a case-

control study. *Arthritis Rheum*; 53(6): 845-849.

Authors:

Kamel, AL-Gogary A, AL-Shishtawy H
Department of Physical Medicine & Rehabilitation
Faculty of Medicine
Ain Shams University

Khodeir A
Department of Radiology
Faculty of Medicine
Ain Shams University

Haroun El Rasheed A
Department of Neuropsychiatry
Faculty of Medicine
Ain Shams University

Youssof N
Department of Clinical Pathology
Faculty of Medicine
Ain Shams University

Address of Correspondence

Haroun El Rasheed A
Assistant Professor in Psychiatry
Faculty of Medicine
Ain Shams University
E-mail: amanyhelrasheed@yahoo.com

:

M M T

T ~ M Q

Δ í H

H

Δ Q T í

H . Q M M

M M

M

T M