

# Cognitive Deficit in Patients with Systemic Lupus Erythematosus

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**SUMMARY** This study aims to determine the prevalence of and variation in cognitive deficits in systemic lupus erythematosus (SLE) patients with a prior history of central nervous system involvement (+Hx CNS), and without (-Hx CNS); and the relationship of SLE-related cognitive deficits to medication dosage and disease activity. Ninety-four participants, 62 SLE and 32 controls, were screened for anxiety and depression before being tested for cognitive functioning. Subjects scoring >17 on the Hamilton anxiety score (HAM-A) and >10 on the Hamilton depressive score (HAM-D) were excluded from the study. After screening, 30 SLE patients, +Hx CNS (n = 11) and -Hx CNS (n = 19), and 22 healthy control subjects remained in the study. Cognitive impairment was identified in 9 (30.0%) SLE patients [5 (45.5%) SLE +Hx CNS patients and in 4 (21.1%) SLE -Hx CNS patients] compared with 0 (0%) control subjects ( $p = 0.003$ ). The SLE +Hx CNS patients had a higher degree of cognitive impairment than SLE -Hx CNS patients in the area of attention/calculation, auditory comprehension, visuospatial ability, and executive function. Cognitive scores significantly correlated with total disease activity at the onset of SLE ( $p = 0.005$ ,  $r = -0.500$ ). Further evaluation of both disease activity and cognitive function in SLE patients is needed to better anticipate and provide for the social care needs of these patients in the activities of daily living.

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Systemic lupus erythematosus (SLE) is an autoimmune-mediated collagen disease that can result in multiple organ failure. SLE is the collagen disease most frequently associated with neuropsychiatric symptoms, which have been hypothesized to be associated with specific patterns of cognitive dysfunction.<sup>1</sup> Prevalence of cognitive impairment in SLE cases in clinical settings has been found to range from 13% to 81%, depending on the methodology used.<sup>2-5</sup> Some studies have found that these cognitive deficits (especially in areas of memory, complex attention, visuospatial function, and psychomotor speed) are more prevalent and severe in SLE patients with neuropsychiatric complication than in other groups.<sup>6-8</sup>

Most studies have used comprehensive neuropsychological tests that cannot be routinely

used in clinical practice due to complexity and time requirements.<sup>2,4,6-8</sup> In addition, many researchers<sup>3,7,8</sup> did not exclude subjects with anxiety and/or depression from their studies, which could present as confounding variables,<sup>7,9-13</sup> making determination of cognitive function more difficult. These methods appear to offer the advantage of facilitating easy-to-understand generalizations about the disease, but they do not offer a clear understanding of the effects of prior central nervous system involvement on SLE symptom expression.

This study aims to determine the prevalence

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of and variation in cognitive deficits in systemic lupus erythematosus (SLE) patients with a prior history of central nervous system involvement (+Hx CNS), and without (-Hx CNS). A secondary purpose was to identify risk factors of cognitive deficits in SLE patients.

## MATERIALS AND METHODS

SLE patients and their relatives (controls), aged 18-60 years, with at least 6 years of formal education and good verbal communication skills who visited the Rheumatology Clinic of Maharaj Hospital, Chiang Mai University, Thailand, from December 2004 to December 2005 were invited to participate. A total of 62 SLE patients and 32 control subjects participated in the study. All patients met the revised American College of Rheumatology (ACR) diagnostic criteria for SLE.<sup>14</sup> All patients had been diagnosed with either inactive or active SLE, but did not have active CNS involvement. Participants were excluded if they were: unstable or confused, had significant hearing impairment, had any degree of visual impairment, or lacked the necessary communication skills to ensure the reliability of test scores. This study was approved by the Ethics Committee of Chiang Mai University, and all subjects provided informed consent.

An experienced rheumatologist (W.L.), blinded to patients' psychiatric condition and cognitive function, performed the following clinical assessments: detailed medical history including clinical and pharmaceutical treatments, physical examination, complete blood count, urinalysis, erythrocyte sedimentation rate, serum creatinine, and liver function test. The diagnostic assessment of any history of CNS involvement such as a history of seizures and any episode of an acute confusional state was recorded. SLE patients were divided into two groups based on the presence (+) or absence (-) of a history of central nervous system involvement (Hx CNS). Disease activity was assessed at the time of SLE diagnosis and later during cognitive testing with the Mexican-SLE Disease Activity Index (Mex-SLEDAI), a standardized index derived from clinical and serological variables.<sup>15</sup>

Two psychiatrists performed the neuropsychiatric assessment. The first psychiatrist (N.M.), blinded to patient's disease activity and cognitive

function, evaluated for levels of anxiety and depression in all patients using the Hamilton Anxiety Rating Scale (HAM-A),<sup>16</sup> and the Hamilton Depression Rating Scale (HAM-D).<sup>17</sup> The second psychiatrist (B.M.), blinded to patient's disease activity and psychiatric condition, performed three standardized neuropsychological tests to assess cognitive impairment. Approximately 20 minutes were needed to complete the neuropsychological tests. The tests administered were: the Mini-Mental State Examination (MMSE),<sup>18,19</sup> the Clock drawing test (CDT),<sup>20,21</sup> and the 5-item version of Instrumental Activities of Daily Living Modified Lawton's Scale (5-IADL).<sup>22</sup>

The Mini-Mental State Examination (MMSE) is widely used to screen for global cognitive impairment and has a maximum score of 30 points, classified on 11 items assessing the domains of: orientation to time and place (assessed cerebral hemisphere and brainstem = 10 points), short-term memory (registration and recall of three words = 6 points), attention and calculation (5 points), language (8 points), and visual construction (1 point). It was the longest test in the series, requiring about 10 minutes. The cutoff point for MMSE scores was  $\leq 24$ .

The Clock Drawing Test (CDT) is easy to perform and reflects frontal and temporo-parietal functioning by drawing on several skills: auditory comprehension, visuospatial ability, and constructional praxis. The CDT has a maximum score of 10 points. The cutoff point was a score below the 5th percentile according to age, gender and education level.

The 5-item version of Instrumental Activities of Daily Living (5-IADL) Modified Lawton's Scale is a functional assessment tool which rates five basic activities of daily living: the patient's ability to use a telephone, take transportation, take medication, handle finances, and attend social and recreational activities that reflect executive functioning. The 5-IADL scores above the 5th percentile indicate cognitive impairment.

## Statistical analysis

Results are presented as mean and standard deviation. The two-tailed paired t-test, Mann-

Whitney U test, One-way ANOVA, and Kruskal-Wallis test were used to assess differences of cognitive functioning between each group. Patients were considered cognitively impaired at raw scores  $\leq 24$  on the MMSE, a score in or below the 5th percentile on the CDT, or in or above the 5th percentile on the 5-IADL. Patients who were rated impaired on one or more tests were defined as having cognitive deficiencies. The numbers of impaired and unimpaired patient were compared by means of a contingency table (Fisher's exact test). The raw scores of MMSE, CDT, and 5-IADL were computed to T-scores (t) for each patient, which were then added to produce the patient's cumulative cognitive score; (CS) = (MMSEt) + (CDTt) - (5-IADLt). Pearson's correlation coefficient analyses were performed to identify factors associated with cognitive deficits, such as: disease duration, current daily dosage of anti-SLE drugs, and disease activity (SLEDAI). The statistically significant cutoff value was set at  $p < 0.05$ .

## RESULTS

Sixty-two patients and 32 control subjects were screened for this study. Thirty-two SLE patients [+Hx CNS, n=20; -Hx CNS, n=12] and 10

control subjects were excluded because of anxiety and/or depression [HAM-A score  $> 17$ , HAM-D score  $> 10$ ]. Thirty SLE patients [+Hx CNS, n=11; -Hx CNS, n=19] were evaluated in this study. Twenty-two healthy subjects (female first-degree relatives of the patients) matched for age, education, and social background were used as controls. Demographic data (age, sex, mean years of formal education, occupation) were recorded. The statistical analyses did not show significant differences among SLE patients and control subjects with regard to age, mean education, occupational history, anxiety, and depressive scores (Table 1).

Regarding clinical variables, there was a difference between SLE +Hx CNS patients and SLE -Hx CNS in prednisolone dosage at the time of the study and SLE disease activity at the time of SLE diagnosis (Table 2). An independent sample T-test revealed that SLE +Hx CNS patients showed significantly higher scores on the Mex-SLEDAI than SLE -Hx CNS patients at the time of SLE diagnosis ( $p = 0.001$ ). Thirty percent of SLE [5 SLE +Hx CNS patients (45.5%) and 4 SLE -Hx CNS patients (21.1%)], were classified as having cognitive abnormality, while the control group had no cognitive deficits (0%), ( $p = 0.003$ ), as shown in Table 3.

**Table 1** Patient characteristics

	CNS involvement (n = 11)	No CNS involvement (n = 19)	Control (n = 22)	Three group comparison ( $p^*$ )
<b>Age</b>	36.1 $\pm$ 12.0	31.3 $\pm$ 8.2	32.5 $\pm$ 11.7	0.483 <sup>a</sup>
<b>Sex (female)</b>	11	19	22	
<b>Mean education (years)</b>	9.9 $\pm$ 2.9	10.6 $\pm$ 2.8	11.2 $\pm$ 2.3	0.443 <sup>b</sup>
<b>Occupational history</b>	3	5	7	0.588 <sup>c</sup>
<b>Unemployed</b>	4	8	7	
<b>Labor</b>	2	1	2	
<b>Secretary</b>	1	2	1	
<b>Teacher</b>	0	1	5	
<b>Administrator</b>	1	2	0	
<b>Other</b>				
<b>Disease duration (years)</b>	5.5 $\pm$ 4.3	8.1 $\pm$ 5.9	-	0.213 <sup>d</sup>
<b>Hamilton Anxiety Rating Scale</b>	5.6 $\pm$ 3.3	5.4 $\pm$ 2.6	5.2 $\pm$ 3.6	0.521 <sup>b</sup>
<b>Hamilton Depression Rating Scale</b>	3.4 $\pm$ 2.2	3.7 $\pm$ 2.7	2.9 $\pm$ 2.5	0.578 <sup>b</sup>

<sup>a</sup>One-way ANOVA, <sup>b</sup>Kruskal-Wallis test, <sup>c</sup>Fisher's exact test, <sup>d</sup>Independent-sample t-test

There were significant differences between the three groups in scores on the MMSE, CDT, 5-IADL, and cognitive score ( $p = 0.009, 0.003, 0.022, \text{ and } 0.002$  respectively), as shown in Table 4. SLE +Hx CNS patients had lower scores on the MMSE and CDT than SLE -Hx CNS patients and control subjects. Mann-Whitney U test revealed that SLE patients showed significantly lower levels than control subjects on the MMSE score (SLE +Hx CNS:  $25.7 \pm 2.1$  vs. control:  $28.1 \pm 1.7, p = 0.003$ ), especially in the attention subscale (SLE +Hx CNS:  $2.6 \pm 1.8$  vs. control:  $4.2 \pm 1.4, p = 0.007$ ; SLE -Hx CNS:  $2.8 \pm 1.9$  vs. control:  $4.2 \pm 1.4, p = 0.009$ ), whereas there was no difference between SLE  $\pm$  Hx CNS patients ( $p = 0.748$ ) in the attention subscale. Moreover, SLE +Hx CNS patients showed significantly lower levels than control subjects in the writing subscale ( $0.2 \pm 0.4$  vs.  $0.6 \pm 0.5, p = 0.028$ ), but there was no difference between SLE -Hx CNS patients and control subjects ( $0.5 \pm 0.5$  vs.  $0.6 \pm 0.5, p = 0.284$ ); and

SLE -Hx CNS vs. SLE +Hx CNS ( $p = 0.188$ ). Mann-Whitney U test revealed that SLE +Hx CNS patients showed significantly lower levels than control subjects on CDT score ( $8.5 \pm 3.0$  vs.  $10.0 \pm 0.0, p = 0.001$ ), but there was no significant difference on CDT score between SLE -Hx CNS patients and controls ( $9.8 \pm 0.5$  vs.  $10.0 \pm 0.0, p = 0.056$ ), and SLE  $\pm$  Hx CNS patients ( $p = 0.071$ ).

Correlation analyses were performed to identify factors associated with cognitive scores. Cognitive score significantly correlated with disease activity at the time of SLE diagnosis ( $p = 0.005, r = -0.500$ ). However, there was no significant correlation between cognitive scores and demographic factors. Cognitive score did not correlate with clinical parameters: disease duration, medication dosage, and disease activity on the day of physical and psychological examination.

**Table 2** Medication and disease activity

	CNS involvement	No CNS involvement	Two group comparison ( $p$ )
<b>Prednisolone dosage, mg/day</b>	$11.4 \pm 13.9$	$17.4 \pm 12.6$	$0.045^a$
<b>N</b>	11	17	
<b>Mean prednisolone for whole illness duration, g</b>	$16.3 \pm 15.4$	$14.4 \pm 11.2$	$0.653^b$
<b>N</b>	11	17	
<b>Methotrexate dosage, mg/day</b>	-	$5.0 \pm 0.0$	
<b>N</b>		1	
<b>Mean methotrexate for whole illness duration, mg</b>	-	$180.0 \pm 0.0$	
<b>N</b>		1	
<b>Chloroquine dosage, mg/day</b>	$206.3 \pm 59.1$	$155.0 \pm 118.1$	$0.662^a$
<b>N</b>	4	15	
<b>Mean chloroquine for whole illness duration, g</b>	$147.4 \pm 84.9$	$132.2 \pm 104.8$	$0.793^b$
<b>n</b>	4	15	
<b>Endoxan dosage, mg/day</b>	$21.4 \pm 26.7$	$40.0 \pm 22.4$	$0.218^a$
<b>n</b>	7	5	
<b>Mean endoxan for whole illness duration, g</b>	$25.2 \pm 26.6$	$15.3 \pm 13.2$	$0.685^a$
<b>n</b>	7	5	
<b>Mex-SLEDAI (at the time of diagnosis of SLE)</b>	$16.6 \pm 4.1$	$10.6 \pm 3.9$	$0.001^b$
<b>n</b>	11	19	
<b>Mex-SLEDAI (at the time of examination cognitive test)</b>	$1.6 \pm 2.8$	$4.0 \pm 4.0$	$0.054^a$
<b>n</b>	11	19	

<sup>a</sup>Mann-Whitney U test, <sup>b</sup>T- test

## DISCUSSION

These results show that the prevalence of cognitive impairment was higher in SLE patients, especially in + Hx CNS patients. The SLE +Hx CNS patients had a higher degree of cognitive impairment than SLE -Hx CNS patients in the areas of attention/calculation, auditory comprehension, visu-

ospatial ability, and executive function. Cognitive scores were significantly correlated with total disease activity at the onset of SLE.

Based on these findings, it would be useful to know whether physicians are aware of this group of patients. Simple, short, and valid instruments such as MMSE, CDT, and 5-IADL may be benefi-

**Table 3** Prevalence of cognitive impairment with neuropsychological variables in SLE patients with and without CNS involvement and controls

Number of impairments in cognitive test	CNS involvement (n = 11)	No CNS involvement (n = 19)	Controls (n = 22)	p
Not impaired	6 (54.5%)	15 (78.9%)	22 (100%)	0.003 <sup>a</sup>
Impaired 1 test	3 (27.3%)	4 (21.1%)	0 (0%)	
Impaired 2 tests	1 (9.1%)	0 (0%)	0 (0%)	
Impaired 3 tests	1 (9.1%)	0 (0%)	0 (0%)	
Summary of cognitive impairment	5 (45.5%)	4 (21.1%)	0 (0%)	

<sup>a</sup>. Fisher's exact test

**Table 4** Neuropsychological performance of SLE patients with and without CNS involvement and controls

	CNS involvement (n = 11)	No CNS involvement (n = 19)	Controls (n = 22)	Three group comparison (p*)
<b>MMSE (30 points)</b>	25.7 ± 2.1	26.8 ± 2.3	28.1 ± 1.7	0.009 <sup>a</sup>
Orientation (10 points)	9.7 ± 0.7	9.9 ± 0.3	9.9 ± 0.3	0.691 <sup>a</sup>
Registration and recall memory (6 points)	5.2 ± 0.6	5.7 ± 0.6	5.6 ± 0.5	0.051 <sup>a</sup>
Attention/calculation (5 points)	2.6 ± 1.8	2.8 ± 1.9	4.2 ± 1.4	0.008 <sup>a</sup>
Language (8 points)	7.2 ± 0.4	7.4 ± 0.5	7.6 ± 0.5	0.085 <sup>a</sup>
- Naming (2 points)	2.0 ± 0.0	2.0 ± 0.0	2.0 ± 0.0	-
- Repeat command (1 points)	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	-
- Obey command (3 points)	3.0 ± 0.0	3.0 ± 0.0	3.0 ± 0.0	-
- Reading (1 points)	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	-
- Writing (1 points)	0.2 ± 0.4	0.5 ± 0.5	0.6 ± 0.5	0.088 <sup>a</sup>
<b>Visuoconstruction (1 points)</b>	1.0 ± 0.0	0.9 ± 0.3	0.9 ± 0.4	0.457 <sup>a</sup>
<b>CDT</b>	8.5 ± 3.0	9.8 ± 0.5	10.0 ± 0.0	0.003 <sup>a</sup>
<b>5-IADL</b>	0.5 ± 1.0	0	0	0.022 <sup>a</sup>
<b>Cognitive score</b>	27.2 ± 43.8	49.7 ± 11.0	57.4 ± 7.8	0.002 <sup>a</sup>

All scores are raw scores and data are expressed as mean ± S.D., <sup>a</sup>Kruskal-Wallis test

cial in clinical practice for assessing cognitive function in these patients.

Prevalence of cognitive deficit in this study was 30% which is lower than in other studies. Some studies have reported prevalence of cognitive deficit between 35% to 80%.<sup>3-5,23</sup> In this study, the criterion for diagnosis patients with cognitive impairment consisted of an impairment in one or more cognitive tests, which is not much different from other studies.<sup>3-5,23</sup> Hence the low prevalence rate of cognitive impairment in this study may have been caused by prior excluding SLE patients with anxiety and/or depression from the study, these are possibly confounding factors of cognitive impairment.<sup>7,9-13</sup> From this point of view, screening and excluding anxiety and depression before cognitive assessment in SLE patients may be useful.

Regarding to the degree of cognitive impairment, SLE patients with a prior history of CNS involvement tended to have more severe impairment than other patients. These findings support the idea of a spectrum of cognitive impairment present among SLE patients and increasing severity in those with clinically overt CNS involvement.<sup>5-7,24</sup>

In addition, this study found a correlation between cognitive impairment and disease activity at the onset of SLE, which agrees with previous studies.<sup>25,26</sup> However, cognitive deficits in SLE patients in this study were not correlated with current steroid usage nor past usage of steroid medication. There are some discrepancies in the prior studies regarding the association between cognitive impairments and steroid use.<sup>5,7,25,27-31</sup> One study demonstrated correlations between steroid use and cognitive impairment in SLE patients,<sup>28</sup> while other studies found no relationship between these factors.<sup>5,7,25,27,29-31</sup> This is an important area that deserves further study.

The strengths of this study were: excluding patients who presented with anxiety and/or depression; using simple cognitive tests, performed by the rating physician in a reasonable amount of time; using a control group whose subjects had no cognitive impairment; and sampling a population with similar social demography. The study could have been improved with the use of neuroimaging, but the ab-

sence of this investigation does not decrease its potential clinical predictive validity.

The limitations of this study were: a small sample size, and test selection. The MMSE was used mainly for assessment of cognitive function, but this test does not cover all domains of cognition and is less sensitive in some domains than other assessment tools. More sensitive and comprehensive cognitive testing should be administered to these patients.

In summary, the prevalence of cognitive deficits in SLE patients in the test group, which excluded those exhibiting anxiety and depression, was 30%. SLE patients with a prior history of CNS involvement had more severe cognitive impairment in the areas of attention/calculation, auditory comprehension, visuospatial ability, and executive function. Further evaluation of disease activity, anxiety and depression, and cognitive function in SLE patients is needed to better anticipate and provide for the social care needs of these patients in daily life activities.

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