Cognitive Dysfunction in Systemic Lupus Erythematosus Patients at Siriraj Hospital

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Abstract :

***Objectives*:** **To determine the prevalence of cognitive dysfunction in SLE patients with overt neuropsychiatric manifestations (NPSLE) or without overt neuropsychiatric manifestations (nSLE) and its association with disease duration, disease activity, previous neuropsychiatric involvement and medications.**

***Methods*:** **A cross-sectional study of 33 SLE patients, 33 rheumatoid arthritis (RA) patients and 32 healthy subjects (age, sex and education matched) were evaluated using the standardized neuropsychological battery tests recommended by the American College of Rheumatology Ad HOC Committee on neuropsychiatric lupus nomenclature and the Thai Mental State Examination (TMSE). Disease activity was measured by the SLE Activity Measure (SLAM). Current medications and previous NPSLE syndrome were documented.**

***Results*:** **Cognitive dysfunction in SLE patients (51.5%) and RA patients (48.5%) was significantly more than that in control subjects (18.8%). Cognitive dysfunction was not associated with disease duration, disease activity, previous NPSLE syndrome and current medications.**

***Conclusion*:** **The results suggest that cognitive dysfunction is common in Thai SLE patients even when there is no overt evidence of neuropsychiatric involvement.**

***Key words*:** cognitive dysfunction, neuropsychiatric SLE

เรื่องย่อ : **ภาวะสมรรถภาพทางสมองบกพร่องของผู้ป่วย SLE ในโรงพยาบาลศิริราช**

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งานวิจัยฉบับนี้ได้นำเสนอผลงานในงานประชุมวิชาการประจำปีสมาคมรูมาติสซั่มแห่งประเทศไทย ณ อาคารเฉลิมพระบารมี 50 ปี กรุงเทพมหานคร เมื่อเดือนมีนาคม 2546 และงาน Asia-Pacific League Againat Rheumatology (APLAR) 2004 เมื่อเดือนกันยายน 2547 ที่ประเทศเกาหลี (Abstract)

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วัตถุประสงค์ เพื่อศึกษาความชุกของภาวะสมรรถภาพทางสมองบกพร่องของผู้ป่วย SLE ที่มีและไม่มีอาการและอาการแสดงทางระบบประสาทและจิตใจ รวมทั้งศึกษาความสัมพันธ์ระหว่างภาวะสมรรถภาพทางสมองบกพร่องกับระยะเวลาที่เป็นโรค, disease activity, การมีอาการทางสมองและจิตใจเนื่องจากโรค SLE มาก่อนรวมทั้งยาที่ได้รับ

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วิธีการ ผู้ป่วย SLE, ข้ออักเสบรูมาตอยด์ กลุ่มละ 33 คน และกลุ่มควบคุม 32 คน (โดยมีอายุ, เพศและการศึกษาใกล้เคียงกัน) ได้รับการทดสอบสมรรถภาพทางสมองโดยใช้แบบทดสอบสมรรถภาพทางสมองมาตรฐานที่แนะนำโดย American College of Rheumatology Ad HOC Committee และแบบทดสอบสมรรถภาพทางสมองของไทย (TMSE) ประเมิน disease activity โดยใช้ SLE Activity Measure (SLAM) รวมทั้งเก็บข้อมูลทางด้านยาที่ได้รับในปัจจุบันและประวัติการมีอาการและอาการแสดงทางระบบประสาทและจิตใจเนื่องจากโรค SLE

ผลการศึกษา พบภาวะสมรรถภาพทางสมองบกพร่องพบในผู้ป่วย SLE และผู้ป่วยโรครูมาตอยด์ร้อยละ 51.5 และ 48.5 ตามลำดับ ส่วนในกลุ่มควบคุมพบร้อยละ 18.8 ภาวะสมรรถภาพทางสมองบกพร่องในผู้ป่วย SLE ไม่สัมพันธ์กับ disease activity, ระยะเวลาที่เป็นโรค, ยาที่ได้รับ รวมทั้งการมีอาการทางสมองและจิตใจเนื่องจากโรค SLE มาก่อน

สรุป ภาวะสมรรถภาพทางสมองบกพร่องในผู้ป่วย SLE พบได้บ่อยในคนไทย และอาจจะมีภาวะสมรรถภาพทางสมองบกพร่องได้โดยที่ไม่มีอาการทางสมองและจิตใจเนื่องจากโรค SLE มาก่อน

INTRDOUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune, multi-systemic disease with diverse manifestations. The nervous system is one of the most common major systems involved. Neuropsychiatric SLE (NPSLE) has been defined as a poor prognostic marker for survival and long-term morbidity. The prevalence of neuropsychiatric manifestations has varied widely from 9 to 75% in various series[1-4]. The definition criteria for a diagnosis of NPSLE was lacking until the American College of Rheumatology (ACR) Nomenclature for neuropsychiatric SLE was published in 1999. This nomenclature provided case definitions for 19 neuropsychiatric syndromes in SLE with reporting standards and recommendations for laboratory and imaging studies[5]. Using these new case definitions, the reported prevalence of NPSLE has been extremely high, up to 91% of patients[6-9]. Common clinical syndromes have included headaches, cognitive dysfunction and psychiatric disorders[6]. Since the standardized neuropsychological tests for cognitive evaluation are time-consuming procedures, the reported prevalence of cognitive dysfunction in SLE is still limited and controversial. The estimated frequency has been previously documented at 12-78% of patients[10-19]. This variability has largely reflected differences in classifications, subject selection, neuropsychological tests and methods for data analysis. To our knowledge, there have been no previous data reported from Thailand or other countries in Southeast Asia. Thus, we conducted this study emphasizing the prevalence and pattern of cognitive impairment in Thai SLE patients. The mechanisms underlying cognitive dysfunction are also not clear. It may be caused by the lupus immunological process or non-specific chronic inflammatory process; consequently, we compared the neuropsychological performance of SLE patients with that of rheumatoid arthritis patients (RA). Rheumatoid arthritis is the one chronic inflammatory rheumatic disease that does not involve the central nervous system. An unselected group of patients were recruited to our study. Cognitive functions were systematically evaluated by the standardized neuropsychological battery tests recommended by the ACR Ad HOC Committee. The association among cognitive dysfunction and disease activity, previous episodes of overt NPSLE, disease duration and current medications were also statistically determined.

MATERIALS AND METHODS

Patients

Patients enrolled in this study included 33 SLE and RA patients, and 32 healthy controls. All SLE patients fulfilled the revised 1982 American College of Rheumatology criteria for SLE[20] and the 1987 revised criteria for the classification of RA[21], respectively. The SLE and RA patients were outpatients in the Rheumatologic Clinic at Siriraj Hospital. The healthy controls were relatives of

inpatients in the medicine ward. The 3 groups were similar in age and educational level. The study was restricted to women to ensure a homogenous population and to facilitate interpretation of neuropsychiatric performance. The study was approved by the Ethics Committee of the Faculty of Medicine at Siriraj Hospital, and all subjects gave informed consent. Standard demographic data, education and previous NPSLE syndrome were recorded. Disease duration was defined as the interval between the time of onset of symptoms attributable to SLE and the time of assessment. The diagnosis of NPSLE was carried out according to the ACR criteria[5]. All current medications, including aspirin, NSAIDS, DMARDS, and prednisolone, were recorded.

Laboratory investigations included complete blood cell count, the erythrocyte sedimentation rate, renal function and urinary analysis.

Disease activity was assessed by the Systemic Lupus Erythematosus Activity Measure (SLAM)[22], a standardized index derived from clinical and serologic variables.

Neuropsychological assessments

Patients and controls were submitted to a battery of neuropsychological tests by the same physician (WK). The tests explored 7 domains, including simple attention, complex attention, executive function, memory, visual-spatial processing, language and psychomotor speed. The tests were completed within approximately 60 minutes. The Thai Mini-mental State Examination (TMSE)[23] was administered first and the following tests were used:

- Simple attention: Digit span (Forward) from the Wechsler Adult Intelligence Scale (WAIS).
- Complex attention/Executive function: Trail making test (part B)
- Memory: Rey-Auditory Verbal learning test, immediate and 30-minute recall. The former was used as a measure of immediate verbal memory; the latter evaluated long term memory.
- Visual-spatial processing: Rey-Osterieth's Complex Figure test
- Language: Word fluency test
- Psychomotor speed: Trail making test (part A)

A pathologic range was considered if a score of any test was below the 5th percentile of the healthy controls. The criterion for the presence of cognitive impairment was a score in the pathologic range in one or more tests.

Statistical analysis

Neuropsychological performances were analyzed by direct comparison of the raw scores among the two groups using one-way ANOVA. Multiple comparisons between groups were examined by the Post Hoc test (Tamhane). The differences were significant when $p < 0.05$.

A score in the pathological range (performance below the 5th percentile of the healthy controls) in one or more tests was considered a criterion for cognitive dysfunction. The number of patients fulfilling this criterion in each group was compared by the Chi-square test.

The possible effects on cognitive function were examined by the t-test in quantitative data (i.e. disease duration, disease activity SLAM), the Chi-squared test and Fisher's exact test in qualitative data (i.e. previous NPSLE, medication). The differences were significant if $p < 0.05$.

RESULTS

Demographic data and clinical characteristics of the study groups

Demographic and clinical characteristics of the SLE, RA and healthy control groups are shown in Table 1. There were no significant differences between the groups in terms of mean age ($p=0.533$), educational level ($p=0.847$) and disease duration ($p=0.828$). Medications taken at the time of the study included non-steroidal anti-inflammatory drugs (NSAIDS) (3% in SLE patients, 72% in RA patients), disease modifying anti-rheumatic drugs (DMARDS) (33% in SLE patients, 64% in RA patients) and prednisolone (79% in SLE patients, 21% in RA patients). The use of these medications was significantly different between the SLE and the RA groups, but aspirin use (30% in SLE patients, 9% in RA patients) and antimalarial drugs (90% in SLE patients, 88% in RA patients) showed no differences between the SLE and

Table 1. Demographic and clinical characteristics of the SLE, RA and healthy controls.

	SLE (n = 33) n (%)	RA (n = 33) n (%)	Control (n = 32) n (%)	P value
Age (years)	32.15	32.55	30.19	0.533
Education (years)	11.03	10.73	11.34	0.847
Disease duration				
< 10 y	23 (70)	25 (76)	-	0.828
> 10 y	10 (30)	8 (24)	-	
Medications				
ASA	10 (30)	3 (9)*	1 (3)	0.004
NSAIDS	1 (3)	24 (72)♣	0 (0)	< 0.0001
Antimalarials	30 (90)	29 (88)*	0 (0)	< 0.00001
DMARDS	-	21 (64)♣	0 (0)	
immunosuppressive	11 (33)	-	0 (0)	
Prednisolone	26 (79)	7 (21)♣	0 (0)	< 0.000001

* $p \geq 0.05$ SLE vs. RA after Chi-square analysis
♣ $p < 0.05$ SLE vs. RA, SLE or RA vs. control after Chi-square analysis

RA groups. In the SLE group, 9 patients (27.3%) had a history of at least one NPSLE syndrome. The mean disease activity score (SLAM) was 6.24.

Evaluation for cognitive deficits

Regarding cognitive function, the mean raw score for 7 cognitive domains are shown in Table 2. The inter-group comparison using post hoc analysis (Tamhane's method) indicated no differences between SLE vs. RA and SLE vs. control in all domains of cognitive function. For the Trial making B, RA were significantly more impaired than controls. (RA vs. Control, P=0.016)

The percentage of subjects in each group who had a cognitive dysfunction on specific domains was calculated (Figure 1). Fifty-one and a half percent (51.5%) of SLE patients and 48.5% of the RA patients were impaired in overall cognitive function, compared with 18.8 % of the healthy controls (p=0.012). SLE patients were significantly more impaired in short term memory than the control group (p=0.02). RA patients were significantly more impaired in executive functions than the control group (p=0.02).

SLE patients with NPSLE had more cognitive impairments in long term memory, psychomotor speed and executive function than those without neuropsychiatric problems (nSLE) ($p < 0.05$). Eight percent (8%) of nSLE showed an impairment of language and 16% of nSLE showed impairment in visual-spatial processing, while no NPSLE showed impairment in those domains (Table 3). Global cognitive dysfunction was found to be 55.6% in NPSLE and 50 % in nSLE.

Correlation among clinical characteristics

In evaluating the extent to which clinical variables were associated with cognitive dysfunction, using the Pearson Chi-square method, we found no significant correlation between cognitive dysfunction and disease duration (p=0.482), previous history of neuropsychiatric syndrome (p=0.776), NSAID use (p=0.48), prednisolone use (p=0.68), antimalarial drug use (p=1), and disease activity (p=0.269). The mean SLAM score in those with cognitive dysfunction was 7.12 and those without cognitive dysfunction was 5.31.

TMSE and Cognitive dysfunction

TMSE was not different between the cognitive dysfunction and non cognitive dysfunction scores (mean 27.53 vs. 28.56, $p = 0.096$). In regard to

Table 2. Neuropsychological performances of SLE, RA and healthy controls.

	SLE (n = 33) n (%)	RA (n = 33) n (%)	Control (n = 32) n (%)	P*
TMSE	28.03	28.64	28.75	0.152
Memory				
Immediate recall	50.82	53.36	54.22	0.146
Remote recall	11.06	12.03	12.38	0.052
Recognition	14.36	14.79	14.66	0.065
Simple attention				
Digit span (forward)	12.15	11.70	11.84	0.45
Language				
Word fluency	11.00	10.80	11.06	0.955
Psychomotor speed				
Trail Making A	40.79	43.15	34.41	0.051
Complex attention / Executive function				
Trail Making B	98.12	102.24**	77.98	0.017*
Visual-spatial function				
Rey-Osterieth's complex figure	29.92	30.42	31.16	0.494

*One-way analysis (ANOVA) significant at $p < 0.05$.
**p 0.016 vs. control after Tamhane's post hoc analysis.
Trail making A, B are evaluated by time (minutes). Poor performance takes more time than good performance.

Table 3. Prevalence of cognitive impairment for each neuropsychological variable in NPSLE patients vs. nSLE patients.

	NPSLE (n = 9)	nSLE (n = 24)	P
Immediate recall	2 (22)	7 (29)	0.69
Remote recall	4 (44)	3 (12)	0.046*
Recognition	1 (11)	3 (12)	0.913
Digit span (forward)	-	-	-
Word fluency	-	2 (8)	0.372
Trail making A	3 (33)	1 (4)	0.022*
Trail making B	4 (44)	3 (12)	0.046*
Rey-Ostereith figure	-	4 (16)	0.191
Global	5 (55)	12 (50)	1

*Significant $p < 0.05$ by Chi-square analysis Cognitive Domain

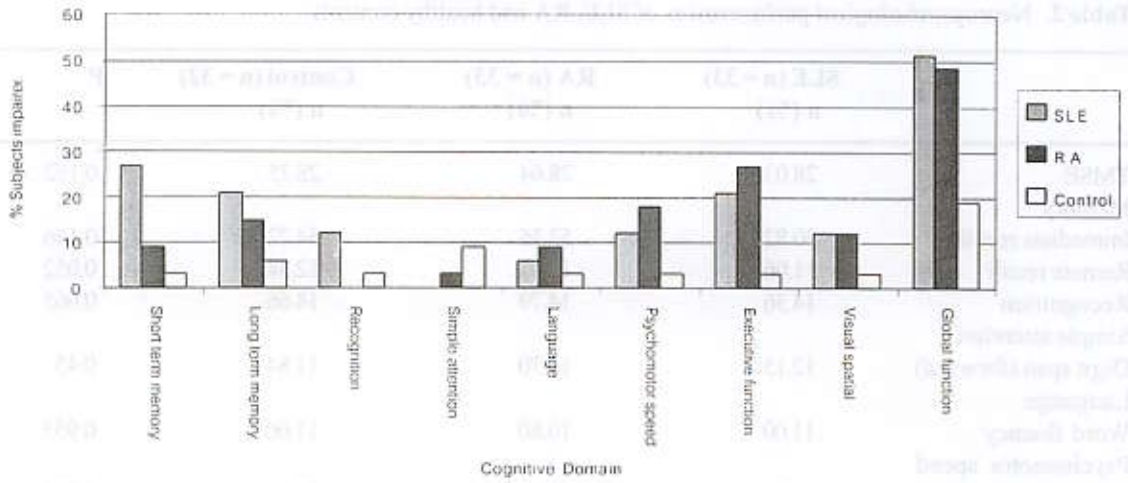

Figure 1. Percentage of individuals with cognitive impairment in SLE, RA and healthy controls.

global cognitive dysfunction, we found that 3 in 17 (17.6%) SLE patients, 2 in 16 (12.5%) RA patients and 1 in 6 (16.7 %) controls with cognitive dysfunction had TMSE in the pathologic range.

DISCUSSION

This study indicated that 51.5% of unselected patients with SLE, 48.5% in RA patients and 18.8% in healthy controls, had evidence of cognitive dysfunction when assessed by standardized neuropsychological tests in a single cross sectional analysis. Prevalence of cognitive dysfunction has been previously estimated to vary from 12 to 87%[11-19]. This variability was due to diverse demographic and SLE disease characteristics, the differences in neuropsychological tests and definitions of cognitive dysfunction. According to the ACR nomenclature, individual patients have been defined as having cognitive impairment if they demonstrated impairment in one or more of eight areas of cognitive ability. This may include mild cognitive dysfunction, whereas in other studies[13,15,24-26], patients were defined as having cognitive impairment if they demonstrated impairment in two or more areas of cognitive ability. Based on the definition of cognitive dysfunction in other studies, only 33.3% of SLE patients, 21.2% of RA patients and 6.3% of healthy controls in our study would have been classified as having a cognitive impairment. This figure was consistent with previous studies[13,15, 24-26]. The variety of neuropsychological tests might create different abilities to explore cognitive dysfunction. Some tests had more ability in demonstrating subtle impairments.

The prevalence of cognitive dysfunction in our study is lower than that reported by Ainiala H, et al[27]. In that study, cognitive dysfunction was classified according to the recently developed ACR nomenclature and case definitions for NPSLE, similar to our study. This study reported overall cognitive dysfunction at 81% of unselected SLE patients and 24% had cognitive dysfunctions based on the definition of previous criterion. There were 4 main reasons for this difference. The first is the difference between the neuropsychological tests used. The battery of neuropsychological tests carried out by Ainiala, et al.[27] were more extensive, requiring up to 3-4 hours for completion, compared to 45 to 60 minutes in our study. This might result in better identification of more subtle defects in cognitive function. However, the neuropsychological tests which required abundant time might cause more fatigue, worse performance and might result in false positive outcomes. Secondly, there was a difference in the prevalence of NPSLE in the two study populations. In Ainiala's study[9], at least 46% of patients were judged

to have had NPSLE (excluding anxiety, headache, mild cognitive dysfunction and unconfirmed polyneuropathy). In our study, only 27% of patients had a history of NPSLE. Thirdly, there was no normative data for our neuropsychological test in the Thai population; thus we used data of healthy controls as a cut-off value for defining the pathologic range for each test. This simplified method might not represent the norm in our general population. Lastly, Ainiala's SLE patients had a more prolonged disease duration than our patients, with a mean duration 14 $\pm$ 8 years, whereas it was less than 10 years in 80% of our SLE patients. Prolonged disease duration might cause chronic inflammation, hormonal disturbance, fatigue, depression and anxiety, all of which might affect cognitive functioning.

The analysis of raw scores between groups revealed that SLE patients had no significant impairment in all domains when compared to that of controls. However, if we calculated the percentage of impaired subjects, we found that up to 30 % of SLE patients had global cognitive dysfunctions. This finding was not compatible with the most recent data from Monasstero et al[26]. Monasstero proposed that the utilization of corrected raw scores was a more sensitive method than using the percentage of impaired subjects on each test to identify cognitive function in a population.

Regarding the pattern of cognitive dysfunction, Thai SLE patients showed impairment only in short-term memory. Many previous studies showed similar frequencies of impairment in both short and long-term memory, visual-spatial function, psychomotor speed[6,13,24,26-27], language[13] and attention [6,24,27]. Most studies revealed impairment in one or two domains categorized as mild cognitive dysfunction.

Cognitive dysfunction also occurred in SLE patients without overt NPSLE, which is similar to that reported in other studies[15,24] However, cognitive dysfunction occurred more frequently in SLE patients with NPSLE than those without neurolopsychological involvement.

RA patients had a worse performance in Trail making A, B and Rey-Osterieth's complex figure test (psychomotor speed, executive function and visual-spatial function) in comparison. This might be due to motor limitations from wrist and finger deformities and pain. However, motor limitation and pain scores in our SLE and RA subjects were not directly measured. Other factors, which might also have had effects on cognitive dysfunction, such as systemic inflammation, fatigue, depression and anxiety, were not evaluated in this study.

We found no association between systemic disease activity, corticosteroid use and cognitive dysfunction. The result was consistent with that reported in other studies[13,15,24-26].

The use of TMSE to identify cognitively impaired patients had substantial rates of false-negative findings. Screening tests cannot be substituted for detailed neuropsychological assessment when milder (but potentially clinically important) deficits are suspected.

Our study was consistent with other studies in that mild cognitive dysfunction was frequently found and not specific for NPSLE. Mild cognitive dysfunction was also found in up to 18 % of healthy controls. According to the ACR case definition, documented impairment in one of the cognitive domains is sufficient for a diagnosis of cognitive dysfunction. Our results suggested that the criteria for clinically significant cognitive impairment and the most sensitive neuropsychological tests for practical use in SLE and RA patients are essentially required.

CONCLUSION

The results suggest that cognitive dysfunction is common in Thai SLE patients. Marked cognitive dysfunction is present even when there is no overt evidence of neuropsychiatric involvement.

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