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BRIEF COMMUNICATION

"Subcortical" cognitive impairment in patients with systemic lupus erythematosus

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Abstract

Studies of cognitive functioning in patients with systemic lupus erythematosus (SLE) have found deficits even in patients without other evidence of neurologic involvement. The present study used scores on the 11 items of the Mini-Mental State Exam (MMSE) to classify the cognitive impairment of 93 SLE patients as suggestive of "cortical" or "subcortical" dysfunction using a validated statistical algorithm. Ninety-five percent of patients were categorized as having "subcortical" deficits, and 5% were categorized as having "cortical" deficits. When the analysis was limited to only those with total MMSE scores ≤ 24, 81% were classified as "subcortical" and 19% as "cortical." These results suggest that SLE patients can have psychomotor and mental tracking deficits of a type seen in patients with subcortical brain disease, even in the absence of gross neurologic involvement. (*JINS*, 2000, *6*, 821–825.)

Keywords: Systemic lupus erythematosus, Cognitive impairment, Subcortical brain disease

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disorder affecting multiple organ systems. A considerable proportion of SLE patients (14–75%, depending on study methods) develop central nervous system (CNS) complications, including stroke, seizures, delirium, or psychosis (Kozora et al., 1996). As might be expected, many patients with "CNS lupus" suffer cognitive impairment (Carbotte et al., 1986; Fisk et al., 1993). However, several studies also find cognitive deficits in SLE patients without signs of overt brain disease (Carbotte et al., 1986; 1995; Denburg et al., 1992; Hanly et al., 1992, 1994; Hay et al., 1992). The prevalence of cognitive disorder in non-CNS lupus has been estimated to range from 15 to 38% (Carbotte et al., 1986; Denburg et al., 1992; Hanly et al., 1992; Hay et al., 1992), suggesting significant, if subclinical, brain involvement.

The cognitive impairment associated with non-CNS SLE has typically been attributed to subcortical rather than cortical dysfunction. While cortical syndromes, such as seen in Alzheimer's disease and infarction of the major cerebral arteries, typically produce aphasia, visual–constructional deficits, and amnesia due to encoding and storage deficits, signs of subcortical pathology typically include dysarthria, bradyphrenia, attention and working memory deficits, and memory retrieval problems. Early in the course of disease, cortical dementias typically do not include slowed cognitive processing or problems with mental control, symptoms often seen in patients with subcortical brain disease (Cummings, 1990).

While the results of prior studies do not reveal a clear cognitive profile, it can be concluded that many of the deficits exhibited by non-CNS SLE patients implicate subcortical brain structures. For example, Ginsburg et al. (1992) found that SLE patients perform worse than rheumatoid arthritis patients on a task involving complex attention. Additionally, they found subtle impairments in simpler atten-

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tional tasks, visuospatial abilities, and motor coordination. While the results of this study are limited by the fact that 9 out of 49 patients had either past or concurrent neurologic symptoms, other researchers have also found deficits in attention, intellect, and verbal fluency in "neurologically normal" SLE patients (Kozora et al., 1996). Denburg et al. (1997) found that non-CNS SLE patients who tested positive for the presence of lupus-specific antibodies performed worse on tasks involving verbal memory, psychomotor speed, and cognitive flexibility than antibody-negative patients. The authors interpreted this constellation of deficits as consistent with subcortical brain pathology. Earlier, Denburg et al. (1987) found that non-CNS SLE patients demonstrated significant difficulty with neuropsychological tasks assessing immediate visual–spatial memory, verbal fluency, and general fund of verbal knowledge.

Brain imaging studies in SLE patients without signs and symptoms of neurologic involvement have often revealed subcortical brain pathology. Chinn et al. (1997) found a greater number of white matter lesions in non-CNS SLE patients compared to controls. In addition, a greater percentage of SLE patients had infarcts, hemorrhages, and generalized cerebral atrophy. Kozora et al. (1998) used magnetic resonance imaging (MRI) and neuropsychological tests to study structural abnormalities and cognitive deficits in non-CNS SLE patients. They found white matter hyperintensities and increased ventricle-to-brain ratios (VBR) in 35% of the patients, and 35% were classified as cognitively impaired. The finding of white matter abnormalities suggests subcortical involvement, and is consistent with previous structural MRI studies in patients with SLE (Emmi et al., 1993). While no relationship was found between neuropsychological test performance and either of the imaging measurements, the authors suggest that this may be due to the fact that the MRI measures were global measures of atrophy, rather than specific to particular cortical regions or subcortical nuclei. Gonzalez-Crespo et al. (1995) studied brain MRI scans in patients with CNS lupus and those with non-CNS lupus. They reported that a large number of patients in both groups had periventricular and subcortical white matter lesions, but there was no significant difference in the number or location of lesions between the groups. Taken together, these imaging results suggest that the observed cognitive deficits may be the result of vascular abnormalities in the subcortical white matter.

We tested the hypothesis that non-CNS SLE patients would exhibit a cognitive profile typical of patients with "subcortical dementia," albeit in a much milder form. In an effort to distinguish cortical from subcortical types of brain disease, Brandt et al. (1988) differentiated patients with Alzheimer's disease (the prototypic cortical dementia), and Huntington's disease (a prototypic subcortical dementia) based on their patterns of performance on individual items of the Mini-Mental State Examination (MMSE; Folstein et al., 1975). A discriminant equation was empirically derived and cross-validated that correctly classified patients 84% of the time. We predicted that when MMSE scores of non-CNS SLE patients are subjected to the same discriminant formula, the majority of patients would be categorized as having cognitive impairments of a subcortical nature.

METHODS

Research Participants

The data from 93 consecutive patients attending the SLE clinic at the Johns Hopkins University School of Medicine and who had been administered the MMSE as part of the Johns Hopkins Lupus Cohort Study were subjected to analysis. Written informed consent was obtained from all patients; there was no payment for participation. All patients were diagnosed with SLE according to American College of Rheumatology criteria (Tan et al., 1982). A thorough history was obtained from both the patient and from available medical records. Exclusion criteria included any past record of seizures, stroke, meningitis, organic brain syndrome, or psychosis. Patients with histories of head injury causing loss of consciousness, alcohol or drug abuse, or learning disabilities were likewise excluded. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI; Bombardier et al., 1992), and duration of disease was obtained based on patient report of symptom onset. Clinical disease information was available for 91 of the 93 patients (see Table 1).

Procedures

The MMSE was administered by the third author, who was trained and supervised by a board-certified neuropsychologist (J.B.). The raw scores on the 11 items of the MMSE were used to calculate a discriminant score for each patient. The discriminant equation, derived by Brandt et al. (1988) is $\phi = 0.398 \times (\text{date}) - 0.480 \times (\text{registration}) - 0.202 \times (\text{calculation}) + 0.650 \times (\text{recall}) + 0.648 \times (\text{naming}) - 0.659 \times (\text{writing}) - 0.618$. If $\phi \geq 0$, a participant is clas-

Table 1. Demographic and clinical characteristics

Variable	*M*	(*SD*)	Range	*N*
Age (years)	41.42	(14.55)	13–93	–
Education level (highest grade)	13.12	(3.04)	3–21	–
Disease duration (years)	11.47	(8.72)	0–56	–
Disease activity (SLEDAI score)*	3.18	(3.40)	0–22	–
Prednisone dosage (mg/day)	7.71	(8.65)	0–60	–
Total sample	–	–	–	93
Male	–	–	–	4
Female	–	–	–	89
Prednisone use	–	–	–	73
NSAID use	–	–	–	33
Cytotoxic use	–	–	–	25

Note. SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; NSAID = nonsteroidal anti-inflammatory drugs.

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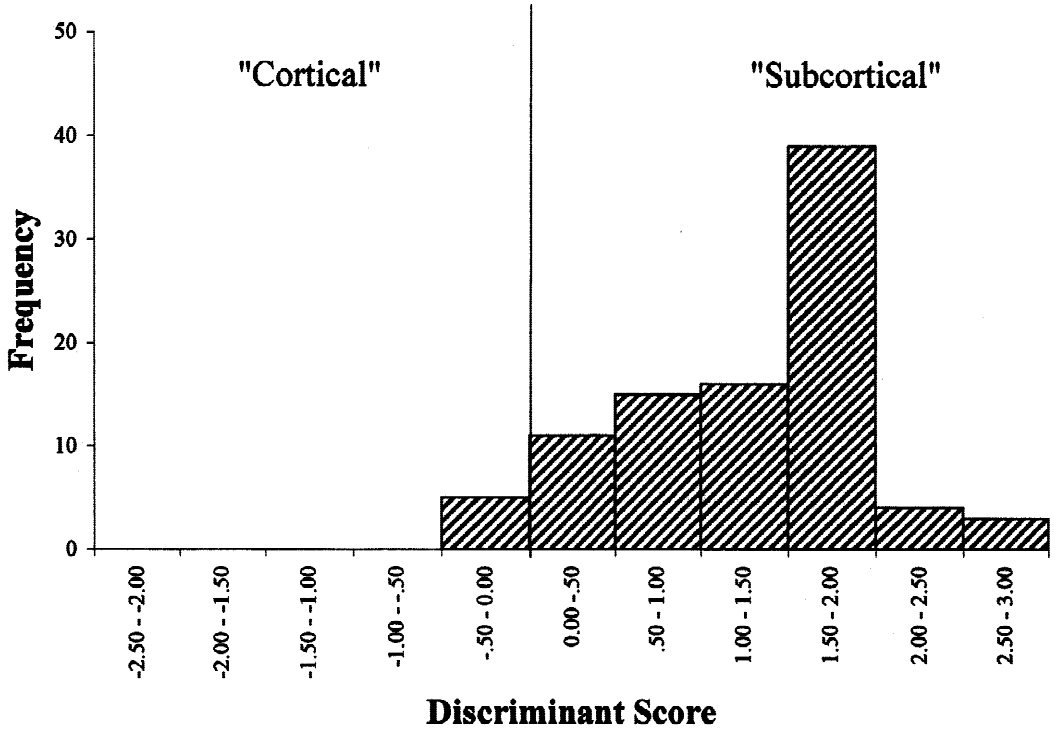

Fig. 1. Frequency distribution of discriminant scores for SLE patients. A score greater than zero indicates subcortical-type of impairment, a score less than zero indicates a cortical-type impairment.

sified as having "subcortical" deficits, while if $\phi < 0$, the participant is classified as having "cortical" deficits.[1]

RESULTS

MMSE scores ranged from 20 to 30 ($M = 27.46$, $SD = 2.64$). Discriminant scores (ϕ) ranged from -0.239 to $+2.519$ ($M = 1.186$, $SD = .625$) and are presented in Figure 1. Eighty-eight of the SLE patients (94.6%) were classified as having subcortical deficits, whereas only 5 (5.4%) were classified as having cortical deficits.

The correlation between discriminant score and total MMSE score was not significant (Pearson $r = .19$, $p > .05$). The correlations between disease severity (SLEDAI score) and MMSE score ($r = -.16$, $p > .05$), and between duration of disease and MMSE score ($r = -.19$, $p > .05$) were not significant. Finally, the correlations between SLEDAI score and discriminant score ($r = .012$, $p > .05$), and between duration of disease and discriminant score ($r = -.037$, $p > .05$) were not significant.

The analysis was then restricted to only those patients with total MMSE scores ≤ 24. The mean MMSE score of patients in this group was 22.22 ($SD = .786$). Discriminant scores ranged from $-.239$ to $+ 2.758$ ($M = 1.038$, $SD = .946$). Thirteen of the 16 SLE patients who fell in this range (81%) were classified as having a subcortical profile and 3 (18.8%) had a cortical profile. The individual item scores of these patients are displayed along with those of the HD and AD patients from Brandt et al. (1988) in Figure 2. It is clear that the SLE profile is more similar to the HD than the AD profile.

DISCUSSION

Almost every patient in this study received a negative discriminant score using the MMSE classification formula. Such scores are characteristic of patients with HD and unlike patients with Alzheimer's disease. Similar results were obtained when the sample was limited to those patients with total MMSE scores ≤ 24. SLE patients with scores in this range obtained particularly low scores on serial sevens, a task that requires attention, working memory, and mental tracking, all processes that have been linked to connections between basal ganglia and prefrontal cortex. In addition, SLE patients had difficulty articulating "no ifs, ands, or buts." Overall, they performed more like HD patients than AD patients on the majority of individual items.

Neuropsychological and neuroimaging studies suggest that patients with SLE who have never had a clinically significant neurologic event may nonetheless have subtle cognitive disturbances of a subcortical variety. Although the MMSE is only a brief cognitive screening test, and may be relatively insensitive to subcortical dementia (Rothlind & Brandt, 1993), it nonetheless distinguishes cortical and sub-

[1] There is an error in the original article (Brandt et al., 1988) with regard to the classification criteria. A score of less than zero indicates cortical dementia, while a score of zero or more indicates subcortical dementia.

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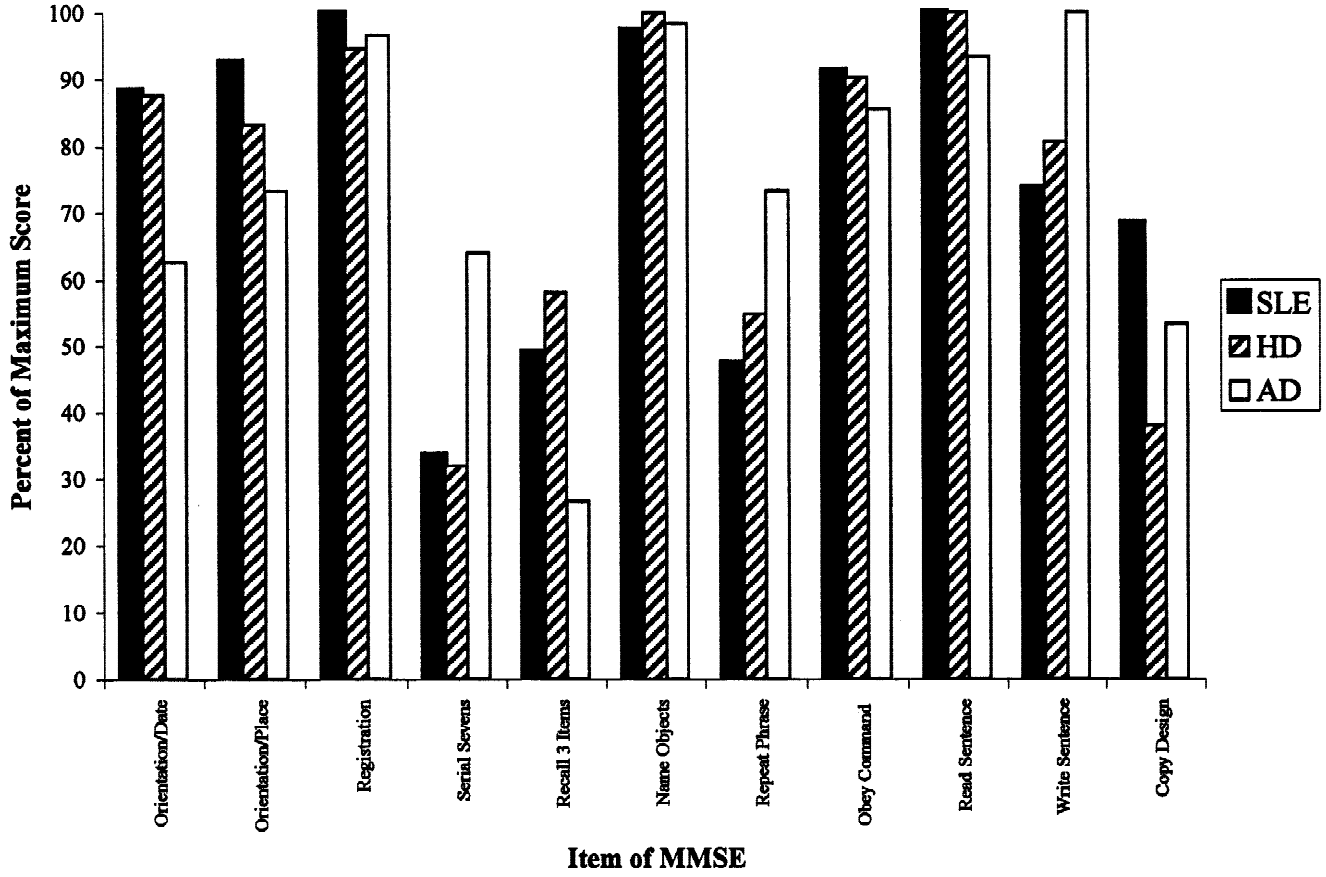

Fig. 2. MMSE individual item scores expressed as a percent of maximum score for SLE patients, and the HD and AD patients from the original sample.

cortical subtypes with reasonable accuracy. In our sample, correlation of total MMSE score with discriminant score was not significant, demonstrating that our algorithm is not distinguishing groups based on severity of impairment. Rather, the groups differ in the pattern of task failures.

SLE is a complicated disease, with many potential symptoms. It is likely that the level and pattern of cognitive function in SLE is influenced by factors such as disease severity, disease duration, comorbid depression, and medication use. However, the absence of a significant correlation between total MMSE score and duration of disease or an index of disease activity suggests that at least these factors were inconsequential in the present sample. In addition, previous research has demonstrated that corticosteroid use, disease activity, and general psychological distress are not related to cognitive impairment (Carbotte et al., 1986, 1995; Denburg et al., 1994).

Our data demonstrates that the cognitive dysfunction of non-CNS lupus patients tends to be of the type seen in patients with subcortical pathology. Future studies that employ more sensitive and specific neuropsychological measures of attention, tracking, and speed of processing, would be necessary to obtain a clearer picture of the particular cognitive deficits associated with non-CNS SLE. In addition, the potential roles of comorbid depression and medication use should be more thoroughly explored.

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REFERENCES

Bombardier, C., Gladman, D.D., Urowitz, M.B., Caron, D., Chang, C.H., & the Committee on Prognosis Studies in SLE. (1992). Derivation of the SLEDAI: A disease activity index for lupus patients. *Arthritis and Rheumatism*, *35*, 630–640.

Brandt, J., Folstein, S.E., & Folstein, M.F. (1988). Differential cognitive impairment in Alzheimer's disease and Huntington's disease. *Annals of Neurology*, *23*, 555–561.

Carbotte, R.M., Denburg, S.D., & Denburg, J.A. (1986). Prevalence of cognitive impairment in systemic lupus erythematosus. *Journal of Nervous and Mental Disease*, *174*, 357–364.

Carbotte, R.M., Denburg, S.D., & Denburg, J.A. (1995). Cognitive dysfunction in systemic lupus erythematosus is independent of active disease. *Journal of Rheumatology*, *22*, 863–867.

Chinn, R.J.S., Wilkinson, I.D., Hall-Cragge, M.A., Paley, M.N.J., Shortall, E., Carter, S., Kendall, B.E., Isenberg, D.A., New-

man, S.P., & Harrison, M.J.G. (1997). Magnetic resonance imagine of the brain and cerebral proton spectroscopy in patients with systemic lupus erythematosus. *Arthritis and Rheumatism*, *40*, 36–46.

Cummings, J.L. (1990). *Subcortical dementia*. New York: Oxford University Press.

Denburg, S.D., Carbotte, R.M., & Denburg, J.A. (1987). Cognitive impairment in Systemic Lupus Erythematosus: A neuropsychological study of individual and group deficits. *Journal of Clinical and Experimental Neuropsychology*, *9*, 323–339.

Denburg, S.D., Carbotte, R.M., & Denburg, J.A. (1992). Cognitive deficits in non-neuropsychiatric SLE (fact or fiction?) [Abstract]. *Arthritis and Rheumatism*, *35*, 5208.

Denburg, S.D., Carbotte, R.M., & Denburg, J.A. (1994). Corticosteroids and neuropsychological functioning in patients with systemic lupus erythematosus. *Arthritis and Rheumatism*, *9*, 1311–1320.

Denburg, S.D., Carbotte, R.M., Ginsberg, J.S., & Denburg, J.A. (1997). The relationship of antiphospholipid antibodies to cognitive function in patients with systemic lupus erythematosus. *Journal of the International Neuropsychological Society*, *3*, 377–386.

Emmi, L., Bramati, M., De Cristofaro, M.T.R., Mascalachi, M., Dal Pozzo, G., Marconi, G.P., Massai, G., & Passaleva, A. (1993). MRI and SPECT investigations of the CNS in SLE patients. *Clinical and Experimental Rhematology*, *11*, 13–20.

Fisk, J.D., Eastwood, B., Sherwood, G., & Hanly, J.G. (1993). Patterns of cognitive impairment in patients with systemic lupus erythematosus. *British Journal of Rheumatology*, *32*, 458–462.

Folstein, M.F., Folstein, S.E., & McHugh P.R. (1975). "Mini-Mental State." A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*, 189–198.

Ginsburg, K.S., Wright, E.A., Larson, M.G., Fossel, A.H., Albert, M., Schur, P.H., & Liang, M.H. (1992). A controlled study of the prevalence of cognitive dysfunction in randomly selected patients with systemic lupus erythematosus. *Arthritis and Rheumatism*, *35*, 776–782.

Gonzalez-Crespo, M.R., Blanco, F.J., Ramos, A., Ciruelo, E., Mateo, I., Lopez Pino, M.A., & Gomez-Reino, J.J. (1995). Magnetic resonance imaging of the brain in systemic lupus erythematosus. *British Journal of Rheumatology*, *34*, 1055–1060.

Hanly, J.G., Fisk, J.D., Sherwood, G., Jones, E., Verrier Jones, J., & Eastwood, B. (1992). Cognitive impairment in patients with systemic lupus erythematosus. *Journal of Rheumatology*, *19*, 562–567.

Hanly, J.G., Fisk, J.D., Sherwood, G., & Eastwood, B. (1994). Clinical course of cognitive dysfunction in systemic lupus erythematosus. *Arthritis and Rheumatism*, *35*, 411–416.

Hay, E.M., Black, D., Huddy, A., Creed, F., Tomenson, B., Bernstein, R.M., & Lennox Holt, P.J. (1992). Psychiatric disorder and cognitive impairment in systemic lupus erythematosus. *Arthritis and Rheumatism*, *35*, 411–416.

Kozora, E., Thompson, L.L., West, S.G., & Kotzin, B.L. (1996). Analysis of cognitive and psychological deficits in systemic lupus erythematosus patients without overt central nervous system disease. *Arthritis and Rheumatism*, *39*, 2035–2045.

Kozora, E., West, S.G., Kotzin, B.L., Julian, L., Porter, S., & Bigler, E. (1998). Magnetic resonance imaging abnormalities and cognitive deficits in systemic lupus erythematosus patients without overt central nervous system disease. *Arthritis and Rheumatism*, *41*, 41–47.

Rothlind, J.C. & Brandt, J. (1993). A brief assessment of frontal and subcortical functions in dementia. *Journal of Neuropsychiatry and Clinical Neurosciences*, *5*, 73–77.

Tan, E.M., Cohen, A.S., Fries, J.F., Masi, A.T., McShane, D.J., Rothfield, N.F., Schaller, J.G., Talal, N., & Winchester, R.J. (1982). The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis and Rheumatism*, *25*, 1271–1277.