Abnormal Regional Cerebral Blood Flow in Systemic Lupus Erythematosus Patients With Psychiatric Symptoms

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Objective: Single-photon emission computed tomography (SPECT) studies have demonstrated decreased regional cerebral blood flow (rCBF) in systemic lupus erythematosus (SLE) patients. However, no study has done voxel-based analysis using statistical parametric mapping (SPM) that can evaluate rCBF objectively, and the relationship between rCBF and psychiatric symptoms has not been well investigated. Using L,L-ethyl cysteinate dimer (^{99m}Tc ECD) SPECT and SPM, we aimed to clarify the association of rCBF changes with psychiatric symptoms in SLE patients whose magnetic resonance imaging (MRI) showed no morphological abnormalities.

Method: Twenty SLE patients and 19 healthy volunteers underwent ^{99m}Tc ECD SPECT. Data were collected from August 2000 to March 2003. SLE was diagnosed according to American College of Rheumatology criteria, and psychiatric symptoms were diagnosed according to ICD-10 criteria. On the basis of the modified Carbotte, Denburg, and Denburg method, the patients were classified into 3 groups: a group with major psychiatric symptoms (hallucinosis, delusional disorder, and mood disorder), a group with minor psychiatric symptoms (anxiety disorder, dissociative disorder, and emotionally labile disorder), and a group without psychiatric symptoms. Gross organic lesions were ruled out by brain MRI. Group comparisons of rCBF were performed with analysis using SPM99.

Results: SLE patients without MRI lesions showed decreased rCBF in the posterior cingulate gyrus and thalamus. The reduction in rCBF was overt in patients with major psychiatric symptoms.

Conclusion: Our study indicated that SLE patients may have dysfunction in the posterior cingulate gyrus and thalamus and that this may be associated with the severity of psychiatric symptoms.

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Systemic lupus erythematosus (SLE) is an autoimmune disease with a variety of clinical features including abnormalities of the skin, joints, lungs, heart, kidneys, and central nervous system (CNS). CNS involvement is one of the important manifestations of SLE and is variously reported to occur in 20% to 75% of SLE patients.[1–5] The features of neuropsychiatric symptoms vary from global to focal cerebral dysfunction,[5,6] and the occurrence of not only neurologic diseases such as cerebrovascular disease, seizures, headaches, dizziness, and cognitive disorders, but also psychiatric symptoms such as hallucination, delusion, mood disorder, anxiety disorder, dissociative disorder, emotionally labile disorder, etc., have been reported.[7,8] However, the pathophysiology underlying CNS diseases has remained elusive.[8] The observation of both diffuse and focal CNS involvements in SLE has led to the hypothesis that there are several pathogenic mechanisms in these patients such as microvascular damage, small vessel vasculopathy, and autoantibody-mediated neuronal cell injury.[9–12] Many studies have already been performed with neuroimaging technologies such as magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT). Several studies have reported that brain T2-weighted MRI is

sensitive for the detection of CNS lesions, i.e., a wide spectrum of MRI abnormalities has been described in such patients, including isolated and multiple ischemic lesions, dural sinus thrombosis, brain atrophy, and diffuse meningeal thickening.[13–21]

Cerebral blood flow (CBF) imaging techniques using ^{133}Xe blood flow or SPECT have also been applied,[22] proving to be highly sensitive in monitoring CNS involvement in patients with SLE.[23–25] The use of SPECT for studying blood flow can reveal disease progression and lesions most relevant at the time of evaluation and objectify neuropsychiatric manifestations without detectable MRI abnormalities.[26–30] Several CBF studies[12,23,25–30,32–36,37] have reported hypoperfusion in global or regional CBF. However, these past studies are not without shortcomings.

First, in spite of recent developments in neuroimaging data analysis using voxel-based analysis, most of the studies adopted the visual inspection method that is thought to have lower sensitivity, or the region of interest (ROI) method that only provides regional CBF (rCBF) data for a limited portion of the brain where the selected ROIs are located.[31] Second, although several studies have noticed the relationship between blood flow and neuropsychiatric symptoms and suggested that low global or regional CBF was associated with the severity of neuropsychiatric symptoms,[12,23,25–30,32–36,38] the subjects' symptoms included not only psychiatric but also neurologic ones at the same time, and their criteria for diagnosis were not well clarified. Third, morphological imaging such as computed tomography (CT) and MRI has been performed in past CBF studies, but its criteria for abnormalities were in disagreement. The manner of morphological imaging varied from the inclusion of ischemic infarction,[12,35–38] cortical atrophy,[23,34,37,38] dilatation of lateral ventricles,[33] and MRI-defined hyperintensity,[25,28–30,32,33,38] to excluding all morphological abnormalities.[26] That is to say, previous studies were not well controlled in respect to CT and MRI findings.

In the present study using statistical parametric mapping (SPM99), we investigated rCBF of SLE patients with and without psychiatric symptoms but without morphological abnormalities on MRI. We aimed to elucidate the rCBF changes in SLE patients and the pathophysiology for psychiatric symptoms.

METHOD

Subjects

We studied 20 patients (1 man, 19 women; mean ± SD age: 36.4 ± 10.8 years), both inpatients and outpatients, who had been diagnosed with SLE at the Tokyo Medical and Dental University Hospital, Tokyo, Japan. The patients fulfilled the American College of Rheumatology criteria for the diagnosis of SLE[39] with (N = 14; 1 male and 13 female patients; mean age: 37.3 ± 12.0 years) or without (N = 6; all female patients; mean age: 35.7 ± 8.6 years) psychiatric symptoms. Patients with a history of stroke, movement disorder, or dementia were excluded. MRIs were performed to rule out gross organic brain lesions (see MRI methods below). Data were collected from August 2000 to March 2003.

A psychiatrist (E.M.) and an accomplished psychologist investigated the psychiatric and mental states of the patients by clinical interview and diagnosed their psychiatric symptoms. Psychiatric symptoms were evaluated on the same day as the SPECT scanning. Then the patients' psychopathologic conditions were reviewed and diagnoses were made by E.M. according to the criteria of ICD-10[40]; patients met the code of F06 for other mental disorders due to brain damage and dysfunction and to physical disease. Patients with psychiatric symptoms were further differentiated into organic hallucinosis (N = 2; ICD-10 code: F06.0), organic delusional (schizophrenia-like) disorder (N = 1; code: F06.2), organic mood (affective) disorder (N = 4; code: F06.3), organic anxiety disorder (N = 4; code: F06.4), organic dissociative disorder (N = 1; code: F06.5), and organic emotionally labile (asthenic) disorder (N = 2; code: F06.6).

Further, on the basis of the modified Carbotte, Denburg, and Denburg method,[41–43] we categorized the patients into 2 groups according to the severity of psychiatric symptoms, i.e., those with major psychiatric symptoms corresponding to hallucinosis, delusional disorder, or mood disorder (N = 7; 1 man and 6 women; mean age: 42.1 ± 10.6 years; code: F06.0, F06.2, or F06.3) and those with minor psychiatric symptoms corresponding to anxiety disorder, dissociative disorder, or emotionally labile disorder (N = 7; all women; mean age: 31.1 ± 9.8 years; code: F06.4, F06.5, or F06.6).

SLE disease activity was evaluated by anti–double-stranded DNA (anti-dsDNA) antibody immunoglobulin G (IgG). The presence of anticardiolipin antibodies (aCL) of IgG and IgM isotypes was determined. If either IgG or IgM index was above 1.0, we considered the patient's aCL as positive. Age, sex, symptom grade, ICD-10 code, psychiatric symptoms, duration of illness, corticosteroid dosage, psychotropic drugs, anti-dsDNA, and aCL were recorded for each patient (Table 1). Age and anti-dsDNA were not significantly different between symptom grades, but duration of illness showed a significant difference between patients with major psychiatric symptoms and without psychiatric symptoms by analysis of variance. Although all but 1 of the patients were receiving corticosteroid treatment, there was no difference in dosage among patients with major psychiatric symptoms, those with minor psychiatric symptoms, and those without psychiatric symptoms.

We also examined 17 female and 2 male age-matched, right-handed, healthy volunteers (mean age: 37.9 ± 8.7 years). They were recruited from the general surrounding

Table 1. Clinical Characteristics of Patients With Systemic Lupus Erythematosus

Patient	Age, y	Sex	Symptom Grade	ICD-10 Code	Symptom	Duration of Illness, y	Steroid Dosage, mg/d	Psychotropic Drug (mg/d)	anti-dsDNA, IU/mL	aCL
1	23	Male	Major	F06.0	Visual hallucination	0	40		< 5	–
2	54	Female	Major	F06.0	Visual hallucination	30	30	Zopiclone (7.5)	64	–
3	53	Female	Major	F06.2	Delusion	40	5		35	–
4	32	Female	Major	F06.3	Major depression	13	12.5		< 5	+
5	39	Female	Major	F06.3	Major depression	0	40	Amoxapine (75)	< 5	+
6	45	Female	Major	F06.3	Bipolar disorder	16	10		11	+
7	49	Female	Major	F06.3	Major depression	1	30		< 5	+
8	16	Female	Minor	F06.4	Anxiety	0	20		< 5	+
9	27	Female	Minor	F06.4	Anxiety	1	35	Trazodone (75)	8	–
10	30	Female	Minor	F06.4	Anxiety	16	5	Milnacipran (50)	114	–
11	37	Female	Minor	F06.4	Anxiety	4	7.5	Estazolam (2)	< 5	–
12	22	Female	Minor	F06.5	Dissociative disorder	2	30	Levomepromazine (10)	6	+
13	39	Female	Minor	F06.6	Emotionally labile disorder	22	7.5	Milnacipran (100)	< 5	–
14	47	Female	Minor	F06.6	Emotionally labile disorder	16	17.5	Lorazepam (3)	< 5	–
15	27	Female	None			0	35		< 5	–
16	33	Female	None			0	30		64	+
17	30	Female	None			4	12.5	Brotizolam (0.25)	< 5	–
18	29	Female	None			2	4		< 5	–
19	48	Female	None			2	0		< 5	+
20	47	Female	None			0	40	Zopiclone (7.5)	7	–

Abbreviations: aCL = anticardiolipin antibodies, anti-dsDNA = anti–double-stranded DNA.
Symbols: – = negative, + = positive.

population, did not meet any criteria for neuropsychiatric disorders, and had no relatives with neuropsychiatric disorders on the basis of unstructured psychiatric screening interviews. Their Mini-Mental State Examination (MMSE)[44] scores were 28 or higher. The volunteers were free of any medication, and they underwent MRI to rule out the presence of any gross organic brain lesions (see MRI methods below).

The purpose and procedures of the study were explained to all subjects, and written informed consent was obtained. This study was approved by the Ethics Committee of Tokyo Medical and Dental University.

Image Acquisition and Analysis

^{99m}Tc ECD (technetium-99m L,L-ethyl cysteinate dimer) SPECT. The consciousness of all subjects at the time of SPECT scanning was clear. They were studied in a supine resting position with eyes closed and minimal sensory simulation in a silent room at the Nuclear Medicine Unit, Tokyo Medical and Dental University Hospital. Brain SPECT was performed using a triple-head gamma camera PRISM 3000 (Picker International, Cleveland, Ohio) with low-energy ultra–high-resolution fan beam collimators. Although most previous SPECT studies used ^{99m}Tc HMPAO (hexamethylpropyleneamineoxime), we used ^{99m}Tc ECD in the present study. The advantages of ^{99m}Tc ECD over ^{99m}Tc HMPAO include a faster blood disappearance rate and more rapid urinary excretion,[45] features resulting in a higher brain-to-background ratio and a lower total-body–absorbed radiation dose. In addition, ^{99m}Tc ECD has a shelf life of approximately 6 hours compared with less than 30 minutes for ^{99m}Tc HMPAO. A bolus of 800 MBq of ^{99m}Tc ECD was injected intravenously from the antecubital vein with a 20-mL saline flush. Scans were performed for 20 minutes, starting precisely 5 minutes after injection. Spatial resolution of the scanner was 3.8 mm full width at half maximum (FWHM). Projection data were acquired in a 128 × 128 matrix. All SPECT data were reconstructed with a 3D post filter (Butterworth) cutoff frequency of 0.24 cycles/pixel and order 4.0.

MRI. In patients, the whole brain was examined at the Tokyo Medical and Dental University Hospital using a GE 1.5-T MRI camera (General Electric Medical Systems, Milwaukee, Wis.) with a series of T1-weighted images, T2-weighted images, and fluid attenuated inversion recovery (FLAIR) images. MRI scans were assessed by radiologists, and then rechecked by 2 raters (K. Oda and E.M.). Patients with cerebral infarction, cortical atrophy, dilatation of lateral ventricles in their MRI, and hyperintensities of more than 2 mm in deep white matter regions or subcortical regions on T2-weighted or FLAIR images were excluded.

In control subjects, MRIs were acquired on a Phillips Gyroscan NT, 1.5-T MRI camera (Phillips, Eindhoven, the Netherlands) with a series of T1-weighted images, T2-weighted images, and proton images at the National Institute of Radiologic Sciences, Chiba, Japan. Their MRI findings were all normal, i.e., none showed cerebral infarction, cortical atrophy, dilatation of lateral ventricles, or even small hyperintensity areas.

Data Analysis

Statistical parametric mapping. We analyzed the data using MATLAB 5.3 (The MathWorks, Natick, Mass.) and SPM99 (Wellcome Department of Cognitive Neurology,

Institute of Neurology, London, U.K.). SPM99 is an increasingly recognized form of neuroimaging analysis for localizing statistically significant changes in spatially normalized images on a voxel-by-voxel basis.[46,47]

Normalization

All converted SPECT images were normalized into the SPM SPECT template, which approximates the standard space of Talairach and Tournoux.[48] The spatial normalization included both affine transformations and a linear combination of smooth spatial 7 × 8 × 7 basis functions that model global nonlinear differences in shape.[49] The spatially normalized structural images (now in stereotactic space) were resliced to a final voxel size of approximately 2 × 2 × 2 mm^3.

Smoothing

Normalized images were smoothed using a 12-mm FWHM isotropic Gaussian kernel. This process conditioned the residuals to conform more closely to the Gaussian random field model underlying the statistical process used for adjusting p values.[46]

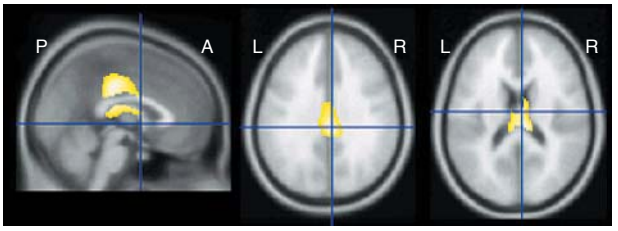
Group Comparisons

Group comparisons of rCBF were performed using SPM99, employing the general linear model. Age was covariated, as there was an age effect on rCBF in the regions. Region-specific differences between groups were assessed statistically using a 2-tailed contrast, that is, testing for an increased or decreased probability of a particular voxel. Global CBF was controlled for proportional scanning, and a gray matter threshold of 0.8 was used. In order to examine regional differences, the images were scaled to a mean global CBF of 50 mL/100 g/min. Then the adjusted rCBF images were compared to reveal the relative rCBF distributions in the 2 groups. Thresholds for statistical analysis were set at $p < .001$ uncorrected.

RESULTS

A comparison of the whole SLE patient group (N = 20) and the control group (N = 19) revealed significantly decreased rCBF in the posterior cingulate gyrus and medial dorsal nucleus of the thalamus in SLE patients as shown in Figure 1. The peak Talairach coordinates (x, y, z [mm]) and Z score were (0, –24, 32; Z score = 4.33) and (4, –18, 12; Z score = 4.24), respectively, as shown in Table 2. If the patients were further divided on the basis of their psychiatric symptoms, those with major symptoms (N = 7) also showed decreased rCBF in the posterior cingulate gyrus, thalamus, and precuneus (Figure 2) (peak Talairach coordinates [0, –28, 34; Z score = 4.58], [6, –26, 16; Z score = 4.43], and [2, –74, 26; Z score = 3.76]; Table 2) compared with the control group. The SLE patients with minor psychiatric symptoms (N = 7) showed decreased rCBF in the left superior temporal gyrus and left inferior parietal lobule (Figure 3) (peak Talairach coordinates [–44, –26, 8; Z score = 4.17] and [–44, –40, 22; Z score = 3.25]; Table 2) compared with controls. On the other hand, there was no significant rCBF decrease in the patients without psychiatric symptoms in comparison with the control group. Furthermore, there were no correlations between rCBF and corticosteroid dosage or duration.

Figure 1. Decreased rCBF in SLE Patients Compared to Controls[a,b]



[a]The colored areas show the regions where rCBF decreased significantly in SLE patients compared to controls using SPM99.
[b]Statistically significant differences can be seen on T1 images. Threshold is set at $p < .001$ uncorrected.
Abbreviations: A = anterior, L = left, P = posterior, R = right, SLE = systemic lupus erythematosus, rCBF = regional cerebral blood flow, SPM99 = statistical parametric mapping.

DISCUSSION

Many SPECT studies[12,22–30,32–38] have demonstrated decreased CBF in SLE patients. However, most of them were done on the basis of visual inspection or ROI analysis and were not well controlled in terms of brain morphological CT and MRI findings. To the best of our knowledge, this is the first SPECT study using the SPM method to investigate SLE patients. Our results showed reduced rCBF in the posterior cingulate gyrus and thalamus of SLE patients without morphological abnormalities on their MRI, and that this reduction in CBF was related to the severity of their psychiatric symptoms. Although the posterior cingulate gyrus is located in one of the important limbic systems, this region might have been missed in previous studies using ROI analysis.

It is possible that the rCBF decrease is derived from organic change, such as microvascular damage in the brain. Vasculopathy is the major pathogenesis in SLE patients, consisting of the cuffing of small blood vessels in the brain.[3,7,50] This process was formerly attributed to deposition of immune complexes in the walls of these blood vessels, but later the cause of the activation of complement was proposed.[51] Vasculopathy might alter rCBF and result in hypoperfusion of the brain, as has been demonstrated in SPECT studies.[23,25,32–35,37,52,53]

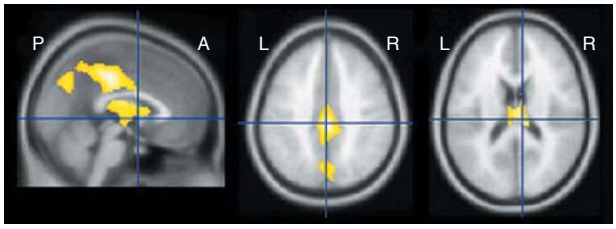
Interestingly, the region including the posterior cingulate gyrus is known to be important for memory.[54] In very

Table 2. Decreased Regional Cerebral Blood Flow in Patients With Systemic Lupus Erythematosus (SLE) (N = 20) Compared to Controls (N = 19)[a]

Variable	Peak Coordinate x	y	z	Region	Z score
SLE < controls	0	–24	32	Posterior cingulate gyrus	4.33
	4	–18	12	Thalamus medial dorsal nucleus	4.24
SLE major psychiatric symptoms < controls	0	–28	34	Posterior cingulate gyrus	4.58
	6	–26	16	Right extra-nuclear	4.43
	2	–74	26	Right precuneus	3.76
SLE minor psychiatric symptoms < controls	–44	–26	8	Left superior temporal gyrus	4.17
	–44	–40	22	Left inferior parietal lobule	3.25

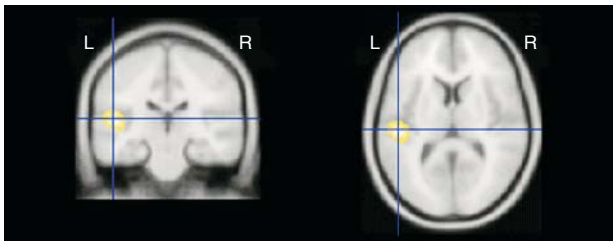
[a]Seven SLE patients had major psychiatric symptoms, and 7 had minor psychiatric symptoms.
Symbol: < = decreased regional cerebral blood flow in SLE patients compared to controls.

Figure 2. Decreased rCBF in SLE Patients With Major Neuropsychiatric Symptoms Compared to Controls[a,b]



[a]The colored areas show the regions where rCBF decreased significantly in SLE patients compared to controls using SPM99.
[b]Statistically significant differences can be seen on T1 images. Threshold is set at p < .001 uncorrected.
Abbreviations: A = anterior, L = left, P = posterior, R = right, rCBF = regional cerebral blood flow, SLE = systemic lupus erythematosus, SPM99 = statistical parametric mapping.

Figure 3. Decreased rCBF in SLE Patients With Minor Neuropsychiatric Symptoms Compared to Controls[a,b]



[a]The colored areas show the regions where rCBF decreased significantly in SLE patients compared to controls using SPM99.
[b]Statistically significant differences can be seen on T1 images. Threshold is set at p < .001 uncorrected.
Abbreviations: A = anterior, L = left, P = posterior, R = right, rCBF = regional cerebral blood flow, SLE = systemic lupus erythematosus, SPM99 = statistical parametric mapping.

early Alzheimer's disease or even in mild cognitive impairment, decreases of rCBF and glucose metabolism in the posterior cingulate gyrus (and precuneus) have been reported in SPECT and positron emission tomography studies.[55–57] Ablation studies suggest that connections between the posterior cingulate gyrus and parahippocampal cortices contribute to spatial orientation, monitoring sensory eye movement and responding to sensory stimuli.[58] On the other hand, the medial dorsal nucleus of the thalamus is suggested to regulate the affective state.[59–61] Insufficiency of this region has a relationship with psychiatric disorders, such as schizophrenia[62–65] and mood (affective) disorder.[59,66]

By comparing patient groups with healthy controls, we were able to clarify the CBF changes in SLE patients. The regions where rCBF reduction was seen in SLE patients partially overlapped with those seen in other neuropsychiatric disorders, such as schizophrenia,[62–65] mood disorder,[59,66] and Alzheimer's disease.[55–57] However, the pattern of rCBF reduction as a whole was assumed to be different from those of other neuropsychiatric diseases. So far as mood disorder was concerned, we examined rCBF using the methodology with the present study and found that depressed patients showed rCBF reduction in the frontal, temporal lobes and anterior cingulate gyrus but not in the posterior cingulate where we found rCBF reduction in SLE patients.[67] Because of the variety of psychiatric symptoms in our SLE patients, it was difficult to gather sufficient "psychiatric" controls and to compare SLE patients with them. However, before we can conclude whether CNS SLE patients can be differentiated from patients with other types of neuropsychopathology, further studies in the use of "psychiatric" controls will be required.

The present study labors under certain limitations. As the number of subjects was small, various psychiatric symptoms were assorted in the same group. Thus, we simply categorized patients into 3 groups according to their psychiatric symptoms using a modified Carbotte, Denburg, and Denburg method. Other limitations may arise from the fact that most patients were receiving various amounts of medications such as corticosteroids, antipsychotic agents, antidepressants, and so on during the study. Regarding corticosteroids, it was reported that their dosage and usage duration are not correlated with rCBF.[68] However, there have been inconsistent findings regarding the effects of antipsychotics[69] and antidepressants[70] on rCBF. Although in this study there was no correlation between rCBF and corticosteroid dosage, and the class and

dose of psychotropic drugs seemed to have no influence on rCBF, a controlled study of the effects of medications is awaited.

In conclusion, using SPECT with ^{99m}Tc ECD and SPM99, we investigated rCBF in SLE patients whose MRIs showed no brain morphological abnormalities from the view of psychiatric symptoms, and we compared the results with the data from controls. The SLE patients showed decreased rCBF in the region containing the posterior cingulate gyrus and thalamus.

Furthermore, a marked reduction in rCBF in this region was seen only in those patients with major psychiatric symptoms. These findings indicate that SLE patients with psychiatric symptoms may have dysfunction in the posterior cingulate gyrus and thalamus, suggesting the possibility of damage in the pathway including the limbic region.

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