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Early and delayed Tc-99m ECD brain SPECT in SLE patients with CNS involvement

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We compared early and delayed Tc-99m ECD SPECT scans in 32 SLE patients (Group 1, definite neuropsychiatric disorders; Group 2, minor neurologic symptoms or normal) with those of normal controls by visual inspection and semi-quantitative evaluation. With visual interpretation, 13 out of 14 patients in Group 1 (93%) and 7 out of 18 patients in Group 2 (39%) had diffuse uneven decrease in early scans. Seven patients in Group 2 (39%) who had normal early scans demonstrated focal decrease in the medial frontal lobe in delayed scans. With cerebral region to cerebellar ratios, in early scans, the medial frontal lobe in Group 1 and Group 2 was significantly lower than in normal controls, and lateral frontal lobe and occipital lobes in Group 1 were significantly lower than in normal controls. Nevertheless, in delayed scans, every cortical region except for the parietal lobe in Groups 1 and 2 was significantly lower than in normal controls. The retention rates in all regions in SLE patients were significantly lower than in normal controls. No case showed SPECT improvement on follow-up studies in either group in spite of clinical improvement. Delayed Tc-99m ECD brain SPECT of high sensitivity might be useful in detecting CNS involvement. Although the SPECT findings did not correlate with the neuropsychiatric symptoms, early and delayed Tc-99m ECD SPECT seems to provide useful objective diagnostic information in SLE patients.

Key words: technetium-99m ECD, systemic lupus erythematosus (SLE), single photon emission computed tomography (SPECT), central nervous system (CNS), neuropsychiatric lupus erythematosus

INTRODUCTION

CENTRAL NERVOUS SYSTEM (CNS) involvement occurs in 10–75% of patients with systemic lupus erythematosus (SLE),[1,2] but management of CNS lupus patients remains unsatisfactory.[1] Symptoms of CNS lupus include organic brain syndrome (disorientation, forgetfulness, disturbances of attention), seizures, chorea, stroke and psychotic and depressive illnesses.[1,2] The exact pathogenic mechanism of CNS lupus is yet unknown, but various etiologies have been proposed, including immune complex vasculitis, neuron reactive autoantibodies, thrombosis associated with antiphospholipid antibodies, and cytokine enhanced autoimmunity.[1] Accurate diagnosis of neuropsychiatric SLE is difficult because of the lack of sensitive diagnostic methods. Recently various cerebrospinal fluid (CSF) indices, such as immunoglobulins (IgM, IgA, and IgG), interleukin-6 (IL-6) and interferon-γ (IFNγ), have been proposed as useful markers of CNS disease activity in SLE.[3–5]

The usefulness of nuclear medicine imaging techniques in the evaluation of CNS lupus has been examined in the last few years and compared with X-ray computed tomography (X-ray CT) and magnetic resonance imaging

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(MRI). These techniques include measuring cerebral blood flow (CBF) with single photon emission computed tomography (SPECT),[6-9] and detecting F-18 fluorodeoxyglucose (FDG) with positron emission computed tomography (PET).[10,11] Most reports have demonstrated a higher sensitivity for SPECT and PET in this field compared to CT and MRI. On the other hand, several investigators have demonstrated the benefits of identifying white matter lesions with MRI,[12-14] which cannot be detected with SPECT or PET. The majority of previous brain SPECT studies on SLE were analyzed by Tc-99m HM-PAO[6-10] except for a few brief reports that used Tc-99m ECD.[15,16]

In this study we evaluated the diagnostic utility of early and delayed Tc-99m ECD SPECT in SLE patients with suspected CNS involvement and a subgroup of these patients were re-assessed by follow-up SPECT studies to examine sequential changes in CNS lupus.

MATERIALS AND METHODS

Subjects

Thirty-two SLE patients with CNS involvement suspected by a rheumatologist and a psychiatrist clinically were enrolled in this study (4 males, 28 females, mean age: 32.5 ± 11.0 years). The patients were subdivided into two groups: Group 1 (n = 14) were patients with definite neuropsychiatric symptoms (e.g., convulsions, depression and anxiety) and included 3 males and 11 females with a mean age of 29.2 ± 11.0 years. Group 2 consisted of 18 patients with non-specific neurologic symptoms (e.g., headache and numbness in the extremities), or without any neuropsychiatric symptoms, and included 1 male and 17 females with a mean age of 35.1 ± 10.6 years. Follow-up SPECT studies were performed in three patients in Group 1 and three patients in Group 2. Patients with cerebrovascular accidents (CVA), anti-phospholipid syndrome (APS) and apparent steroid-induced psychosis were excluded from the study. Ten patients in Group 1 and 14 patients in Group 2 were also examined by X-ray CT and/or MRI scans. These imaging techniques were used to evaluate the involvement of basal ganglia and detect abnormal cortical findings but excluding cortical atrophy.

We also examined ten normal volunteers (7 males and 3 females, mean age: 27.0 ± 3.3 years) as the control group. None had any prior or present history of cerebrovascular disorder, psychiatric illness or head trauma which could affect CBF and all had normal SPECT findings with visual interpretation. Written informed consent was obtained from each normal volunteer on forms and the project was approved by the Human Ethics Review Committee of Fujita Health University, School of Medicine.

SPECT Imaging

A ring-type SPECT system (HEADTOME SET-031, Shimadzu Corp., Japan) was used, which consisted of three detector rings with 64 NaI crystals per ring. Three SPECT images of 20, 55 and 90 mm slices were obtained above the orbitomeatal (OM) line. Data acquisition was performed every 12 sec with a 64 × 64 matrix, and tomographic images were reconstructed by the filtered back projection method. Full width at half-maximum (FWHM) was 12.0–12.4 mm with a high-resolution (HR) collimator.[17] Attenuation correction was automatically performed by calibrating the counts in each detector with those calculated from the geometric distribution of activity by means of a 20 cm diameter cylindrical phantom filled with an aqueous Tc-99m solution.[18] The energy window level was adjusted to 119–161 (± 15%) for the photopeak of Tc-99m (140 keV). Each subject received an injection of 600 MBq of Tc-99m ECD. SPECT scans were carried out for 17 min starting at 10 min (early scan) and 3 hr (delayed scan) post-injection.

Data Analysis

1) Visual Interpretation. Two observers visually compared early and delayed scans of each patient with those of normal controls. The definition of SPECT abnormalities was derived from criteria formulated by Lin et al.[8] as follows. A single lesion or multiple small lesions confined to less than two lobes was considered to be a focal pattern, whereas the presence of lesions involving three or more lobes was regarded as a diffuse pattern. Each SPECT image was displayed on the color monitor over 10% of the maximum count in the image according to the color scale.

2) Semi-quantitative measurements. First, one irregular shaped region of interest (ROI) in each of the following cortical regions on the early scan was manually placed with a pixel size over twice as large as FWHM: cerebellum, medial frontal (superior frontal gyrus), lateral frontal (frontal lobe except for the superior frontal gyrus), occipital lobe, temporal lobe and parietal lobe in each hemisphere on slices 20, 55 and 90 mm above the OM line. All ROIs were placed by the same investigator with visual identification based on the stereotactic atlas.[19] Each ROI was then transferred to the delayed scan, and was superimposed on the same cortical region. To evaluate the regional Tc-99m ECD distribution in early and delayed scans, the ratio of each right and left average cerebral cortical region to right and left average cerebellum ratio was calculated. Mean values for average ratios in each cerebral region were compared among groups and normal volunteers. All values are shown as mean values ± S.D. Scheffe's F test for multiple comparisons was applied to detect the statistically significant difference as defined by ANOVA. A value of $p < 0.05$ was considered statistically significant. And to identity the time change in uptake from early to delayed scans, retention rates were calculated by $[B/A(100)]$ based on the method proposed by Flores II et al.[20] A is the count for the early scan, presumed to be

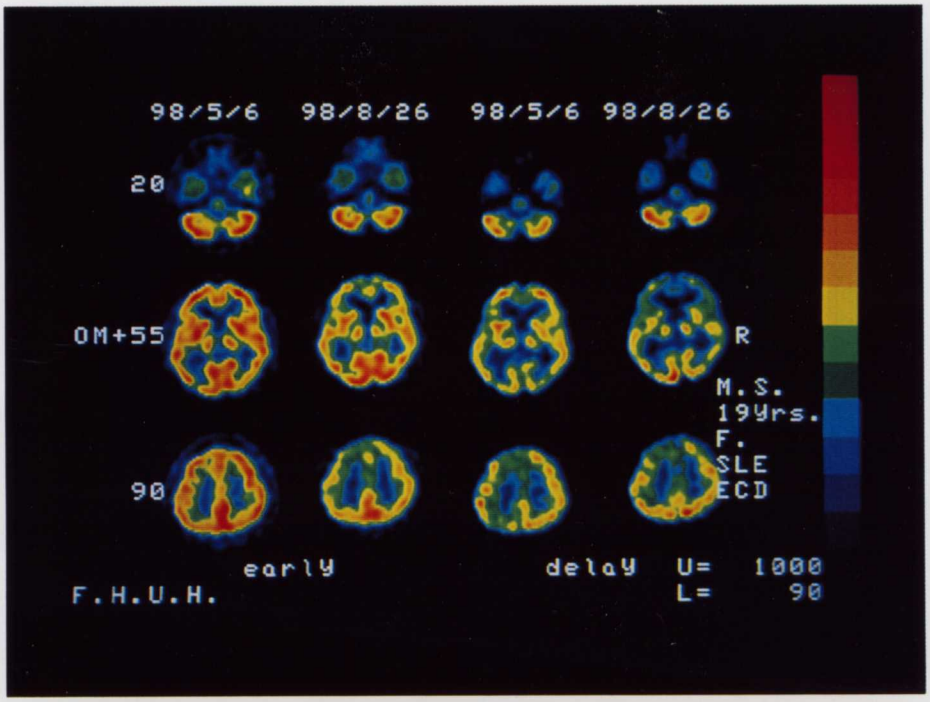

Fig. 1 A 19 year-old-woman with abnormal behavior in Group 1. The first (May 6, 1998) early scan (early, left side) and delayed scan (delay, left side) show diffuse uneven decreased activities in both cerebral hemispheres. The clinical symptoms disappeared after steroid pulse therapy. However, the second (August 26, 1998) early scan (early, right side) and delayed scan (delay, right side) show more uneven reduced activities in both cerebral cortices. X-ray CT and MRI were normal before and after therapy.

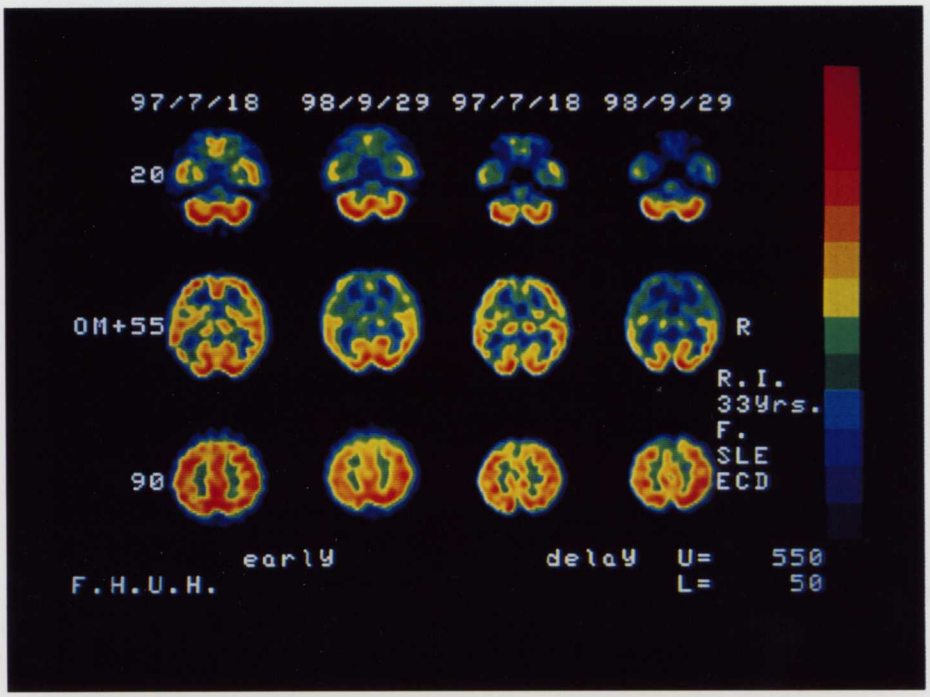

Fig. 2 A 33 year-old-woman without neuropsychiatric symptoms in Group 2. The first (July 18, 1997) early scan (early, left side) is normal, and delayed scan (delay, left side) shows focal decreased activity in both medial frontal lobes (delay, left side). After one year, psychotic symptoms (depressive mood) appeared. The second (September 29, 1998) early scan (early, right side) and delayed scan (delay, right side) show diffuse uneven decrease mainly in the fronto-temporal lobes. X-ray CT and MRI were normal before and after therapy.

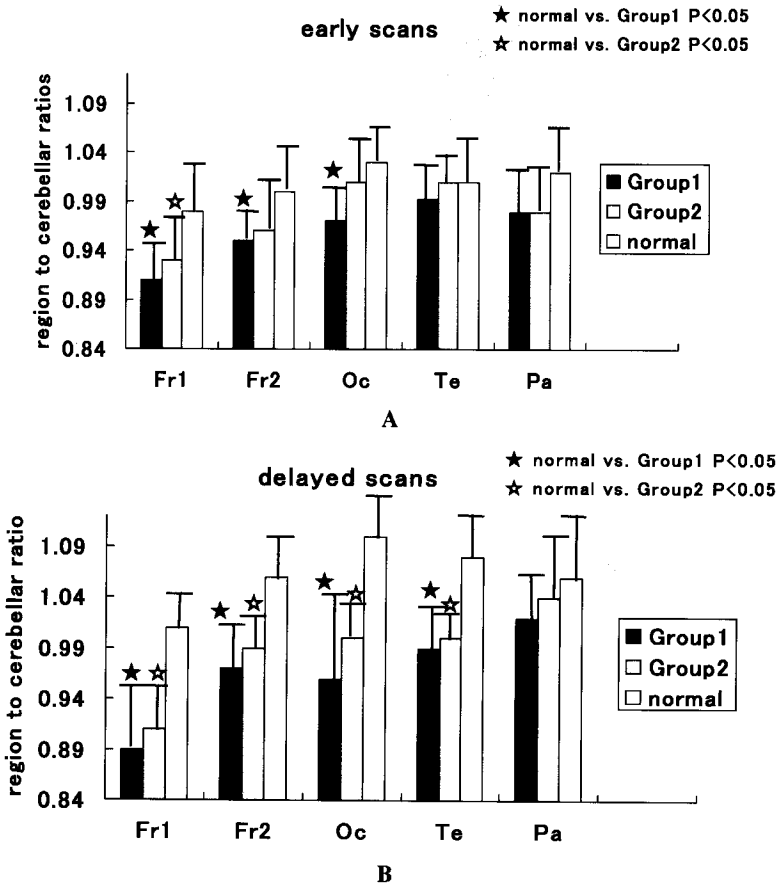

Fig. 3 Comparisons of each mean cerebral region to cerebellar ratio of Tc-99m ECD in early scans (A) and delayed scans (B) in Group 1, Group 2 and normal controls (Fr1: medial frontal lobe, Fr2: lateral frontal lobe, Oc: occipital lobe, Te: temporal lobe, Pa: parietal lobe). Values are expressed as mean ± S.D. ratios.

100%, and B is the decay-corrected count from the delayed scan. The retention rates for normal volunteers and SLE patients (Group 1 + 2) in each region were compared with the unpaired t-test. A p value less than 0.05 was considered significant.

RESULTS

Visual interpretation

Thirteen out of 14 patients in Group 1 (93%) and 7 out of 18 patients in Group 2 (39%) had diffuse uneven decreases in early and delayed scans. In addition, 7 patients in Group 2 (39%) who had normal early scans had focal decreases in the medial frontal lobe in delayed scans (overall positive rate in Group 2; 78%).

All three patients in Group 1 who had repeat SPECT studies clinically improved after treatment, but in follow-up SPECT studies, one patient from this group who had a normal initial SPECT scan had an uneven diffuse decrease in early and delayed scans 8 months later. Furthermore, the other two patients in the same group had much worse uneven diffuse decreases in early and delayed scans after 3 and 4 months (Fig. 1). One patient in Group 2 who had a normal pattern (early scan) and focal decrease in both medial frontal lobes (delayed scan) on the initial SPECT had an uneven diffuse decrease mainly in the fronto-temporal lobes (early and delayed scans) on the second SPECT after the appearance of depressive mood (Fig. 2). Two patients in Group 2 with an uneven diffuse decrease in early and delayed scans on the first SPECT had a much worse uneven diffuse decrease in follow-up SPECT studies (one patient became symptomatic with abnormal behavior, but the one remained asymptomatic). These follow-up studies demonstrated a lack of improvement in SPECT in all tested patients from Groups 1 and 2.

Semi-quantitative measurements

In early scans (Fig. 3A), the mean cerebral region ratio was statistically of lower significance on the medial frontal lobe in Groups 1 and 2 than in normal controls, and Group 1 had statistically much lower mean cerebral region ratios in the lateral frontal lobe and occipital lobe than in normal controls. There was no statistically significant difference between Groups 1 and 2.

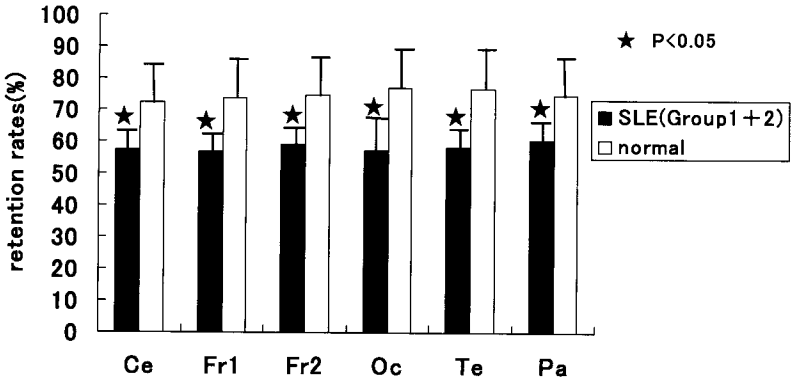

Fig. 4 Comparisons of between retention rates of Tc-99m ECD between SLE patients (Group 1 + 2) and normal controls (Ce: cerebellum, Fr1: medial frontal lobe, Fr2: lateral frontal lobe, Oc: occipital lobe, Te: temporal lobe, Pa: parietal lobe). Values are expressed as mean ± S.D. (%).

In delayed scans (Fig. 3B), mean cerebral region ratios were statistically of lower significance on the medial frontal lobe, lateral frontal lobe, occipital lobe and temporal lobe in Groups 1 and 2 than in normal controls. There was no statistically significant difference between Groups 1 and 2.

The retention rates in all cortical regions and the cerebellum in SLE patients (Groups 1 and 2) were significantly lower than in normal controls (Fig. 4).

X-ray CT and MRI findings

In Group 1 abnormal CT and MRI findings were detected in 5 of 10 patients. These abnormalities included lacunar infarctions in bilateral basal ganglia in one patient, small white matter lesions in two patients, and small cortical infarctions in two cases. In Group 2, small white matter lesions were detected in four patients (4 of 14 patients; 29%). None of these patients had stroke episodes.

DISCUSSION

Previous SPECT studies of CNS lupus erythematosus evaluated the Tc-99m HM-PAO scan by visual interpretation.[6–10] In these studies, 88–100%[6–8] of SLE patients with definite neuropsychiatric symptoms and 51%[6] and 48%[8] of patients with minor neurologic symptoms or without any neuropsychiatric symptoms, which were in agreement with our results (93% and 39%), had abnormal SPECT findings. Furthermore, 20 to 38% of patients with only mild symptoms or none[6,8] had positive X-ray CT and MRI findings, which were also consistent with our results (29%). In definite neuropsychiatric SLE patients, 39%[6] and 30%[8] of patients had a diffuse pattern, whereas 60%[6,7] of patients had a focal pattern. But in early scans in our study, all patients with abnormal SPECT findings in Groups 1 and 2 had an uneven diffuse decrease. Lass et al.[21] pointed out that although visual interpretation may sometimes be superior to semiquantitative analysis, some subtle changes may be overlooked. Visual interpretation without comparison with normal controls and including cerebral infarctions and hemorrhages with morphological abnormalities, might explain the low incidence of a diffuse pattern in previous studies.[6,7] In this regard, most CNS lupus cases in our study had neuropsychiatric symptoms without definite focal signs. On the other hand, semiquantitative analysis relative to cerebellar uptake showed less than two lobes of significantly reduced regions in early scans in Groups 1 and 2. Quantification of absolute regional cerebral blood flow (CBF)[22] and pixel by pixel comparisons in a standard normalized brain[23] should be analyzed for exact measurements in the future.

In terms of regional distributions of CBF and glucose metabolism, previous studies have shown that the parietal lobe was the most common abnormal area.[6–8] Otte et al.[11] reported significantly reduced glucose metabolism in the parieto-occipital region on positron emission tomography (PET) scans of all 13 SLE patients tested in their study. They speculated that since the parieto-occipital region is located at the boundary of the blood supply carried by all three major cerebral arteries, it could be the most vulnerable zone in the cerebrum and may be affected at an early stage of CNS involvement. On the other hand, Colamussi et al.[9] found that 75% of CNS lupus patients who had low cerebral perfusion in the frontal lobes had cognitive dysfunction. Grünwald et al.[10] reported a case of SLE without CNS involvement showing normal glucose metabolism on a PET scan but with marked global reduction in the cortical perfusion reserve particularly in both frontal lobes on acetazolamide-enhanced SPECT scan. They pointed out that this "hypofrontality" might be related to the preclinical psychotic aspects of CNS lupus. Because of the age of this patient (70 years), cerebrovascular disorder was also taken into account. In our study, 39% of patients without definite neuropsychiatric symptoms who had normal early scans demonstrated reduced uptake on medial frontal lobes in delayed scans. And the medial frontal lobe in CNS and non-CNS patients had significantly reduced uptake ratios in early and delayed

scans. Nevertheless, the presence of cerebrovascular disorder could be excluded in our study for the following reasons: (1) patients with symptomatic CVA and APS were excluded from our study, (2) the mean age of our patients was only 32.5 years, and (3) regions of reduced uptake in frontal lobes did not correspond with vascular territories. One patient without definite symptoms who had a normal early scan, and focal reduced activity in the medial frontal lobes in delayed scans, had an uneven diffuse decrease mainly in the fronto-temporal lobes on the second SPECT scan after the appearance of depressive mood. These abnormal regional distributions were similar to the selective dysfunction of paralimbic brain regions in unipolar depression.[24] Whether the "delayed washout in medial frontal lobes" is related to the preclinical psychotic aspects of CNS lupus should be analyzed by follow-up studies of several asymptomatic cases.

What are the underlying mechanisms involved in the higher incidence of significantly reduced cerebral regions in delayed scans relative to early scans and "delayed washout in medial frontal lobes"? First, regional differences in Tc-99m ECD clearance in the brain should be considered. Ichise et al.[25] evaluated the sequential *in vivo* stability of Tc-99m ECD in healthy subjects. They reported a slow Tc-99m ECD wash out from the normal brain with a significant regional variation. They speculated that such a variation might be related to regional differences in esterase activity and/or blood-brain-barrier permeability. Flores II and coworkers[20] reported a tendency for the retention rate to increase in up to 3 hours of imaging followed by a decrease in most regions of the brain in normal subjects. The kinetic behavior of Tc-99m ECD in the human brain was investigated by Friberg et al.[26] and Ishizu et al.[27] with a three-compartment model. They reported that the k5 value could not be ignored in the kinetic model because a slow loss of hydrophilic tracer or metabolites not subject to detectable re-uptake in tissue was seen. The tracer loss from 1 to 24 hr was found to be 3.5%/h.[26] Tamgac et al.[28] reported a patient with subacute ischemic stroke who had non-matched images with I-123 IMP and Tc-99m ECD. I-123 IMP images showed a significant increased activity whereas Tc-99m ECD displayed hypoactivity in the same area and its asymmetry index increased with time at 3 hours post-injection. They speculated that this finding may be due to the higher flow and faster turnover of Tc-99m ECD and/or a leaky blood-brain-barrier allowing leakage of Tc-99m ECD metabolites. We have also identified a case of Sturge Weber syndrome studied with Tc-99m ECD. A focal hyperperfusion area was detected in an early scan at 10 minutes and a focal hypoperfusion area in delayed scans at 3 hours (Matsumura et al., unpublished observation). The same case showed a high intensity area on T2 weighted MRI and mild enhancement on enhanced X-ray CT. Discordance between Tc-99m ECD early SPECT scan and other cerebral blood flow SPECT and PET scans (Xe-133, I-123 IMP, Tc-99m HM-PAO, O-15 labeled gas) were reported in patients with subacute cerebral infarction,[29–31] Alzheimer's disease,[32] and herpes encephalitis.[33] Basic experiments demonstrated that the cellular uptake and hydrophilic conversion of Tc-99m ECD is mediated by esterase.[34,35] Low uptake of Tc-99m ECD in early scans would therefore reflect not only reduced cerebral blood flow but also a loss of the lypophilic compounds for decreased enzyme reaction in certain areas of the damaged brain.[29–32] Nevertheless, in view of the rapid metabolic conversion of lypophilic Tc-99m ECD to hydrophilic tracer in the kinetic model,[26,27] the delayed Tc-99m ECD washout in our SLE patients might reflect a greater loss of converted hydrophilic tracer or metabolites through a leaky blood-brain-barrier than in normal subjects. Actually, in our study, all regions showed significantly greater decreased retention ratios in SLE patients than in normal controls.

There were no CNS lupus patients in the present study who showed improvement on follow-up SPECT scans even though the repeat studies were performed after clinical improvement, but Szer et al.[36] reported that all children with CNS lupus improved clinically, and visually interpreted perfusion SPECT abnormalities were also improved. In our study one patient with steroid-induced psychosis showed signs of recovery of the cerebral to cerebellar region ratio after steroid withdrawal (data not shown). The discrepancies in these results should be analyzed with repeated quantitative SPECT studies. It is possible that the use of steroids in the treatment of SLE plays a role.[8] Specifically, the effect of a given dose and duration of steroid therapy relative to SPECT findings should be discussed in future.

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