Technetium-99m-HMPAO Brain SPECT in Systemic Lupus Erythematosus with CNS Involvement

Wan-Yu Lin, Shyh-Jen Wang, Tzu-Chen Yen and Joung-Liang Lan
Departments of Nuclear Medicine and Internal Medicine, Taichung Veterans General Hospital, Taichung; and National Yang-Ming University, Shih-Pai, Taipei, Taiwan

Functional brain SPECT is playing an increasingly important role in evaluating CNS conditions in patients with systemic lupus erythematosus (SLE). However, SPECT findings varied in different studies because of their small population. Furthermore, earlier researchers, being restricted by the resolution of the camera, might not have been able to evaluate deep-seated nuclei such as the basal ganglia and thalamus. In this study, we describe the different patterns of SPECT findings in SLE patients with CNS involvement. **Methods:** Seventy-two SLE patients (aged 14–67 yr; mean 33.2 yr) were divided into three groups: Group 1 with definite neuro-psychiatric disorder (including stroke, seizures and psychosis); Group 2 with minor neuropsychiatric disorders (headache, dizziness and recent memory impairment); and Group 3 without any neuropsychiatric symptoms or signs. Ninety minutes after injection of 1110 MBq ^{99m}Tc-HMPAO, brain SPECT was performed using a dual-head camera and fan-beam collimator. In addition, MRI and an electroencephalography (EEG) were also performed. **Results:** SPECT findings were normal in 87% of the Group 3 patients and abnormal in all Group 1 patients; 84.6% of the Group 2 patients had abnormal SPECT findings. The parietal, frontal and temporal lobes were the most common areas of CNS involvement. Parietal lobes were involved in 95.6% of Group 1 patients and 80.7% in Group 2 patients. Frontal lobes were involved in 56.5% of Group 1 patients and 65.3% of Group 2 patients. Temporal lobes were involved in 56.5% of Group 1 patients and 46.1% of Group 2 patients. The basal ganglion was involved in about 30% of Group 1 patients and 11.5% of Group 2 patients, while the thalamus and cerebellum were less involved in neuropsychiatric SLE. MR images showed less sensitivity in the detection of CNS involvement than the SPECT and were normal in 27.3% of patients with definite neuropsychiatric disorders. The EEG and anticardiolipin antibody did not correlate well to the clinical diagnosis. **Conclusion:** HMPAO brain SPECT had the best correlation with the clinical diagnosis and may provide additional and objective information on SLE patients with potential CNS involvement.

Key Words: systemic lupus erythematosus; central nervous system; technetium-99m-HMPAO; SPECT

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Involvement of the central nervous system (CNS) is one of the most important complications of systemic lupus erythematosus (SLE) (*1*). About 30%–70% of patients with SLE will develop CNS involvement manifested as cerebrovascular disease, seizures, cognitive disorders, headaches, psychosis and myelopathy (*1–3*). CNS complications are a cause of death in 10%–20% of SLE patients (*1*). The diagnosis and management of neuropsychiatric SLE is difficult because of the lack of useful diagnostic methods. None of the laboratory markers is found to be reliable and well-correlated with disease severity and activity (*4*). Lumbar puncture and cerebral angiography are often insensitive (*5*). An electroencephalogram (EEG) rarely shows any correlation with the clinical manifestations (*6*). Computerized tomography (CT) and magnetic resonance imaging (MRI), which can detect structural abnormalities, have also shown low sensitivity in evaluating neuropsychiatric SLE (*7,8*). In contrast, PET with ^{18}F-FDG shows cerebral involvement in patients with neuropsychiatric SLE who have no morphological changes detectable by CT and MRI (*9,10*). PET is considered to be a sensitive and reliable method for evaluating SLE patients with CNS involvement. However, PET is not suitable for routine clinical use because it is expensive and not available in many hospitals.

Brain SPECT with ^{99m}Tc-labeled HMPAO has been used to assess regional cerebral blood flow (rCBF), which always has a strong correlation with changes in glucose metabolism. Brain SPECT has been proven accurate in detecting many neurological and psychiatric diseases (*11–15*). However, there has been little research concerning the application of HMPAO-SPECT in patients with neuropsychiatric SLE, and the SPECT findings varied in different studies because of their small population (*16–19*). Furthermore, earlier researchers, being restricted by camera resolution, may not have been able to evaluate small disturbances of rCBF and deep-seated nuclei such as the basal ganglia and the thalamus.

In this study, a high-resolution, dual-head gamma camera with a fan-beam collimator was used to evaluate CNS conditions in SLE patients. We compared the scintigraphic findings with clinical manifestations and other diagnostic modalities, including serum marker [anticardiolipin antibodies, (ACA)], MRI and EEG.

MATERIALS AND METHODS

Patients

Seventy-two patients (6 men, 66 women; age range 14–67 yr; mean age 33.2 yr) who fulfilled the criteria for SLE, were enrolled in this study. Patients' were evaluated by a neurologic consultant. Neuropsychiatric symptoms due to SLE were defined as those that could not be attributed to any other cause (such as uremia, hypertension or infection). The patients were divided into three groups based on the type of neurological involvement found: Group 1 = 23 patients with definite neuropsychiatric disorders (including strokes, seizures and psychosis). Group 2 = 26 patients with minor neuropsychiatric disorders (headaches, dizziness and recent memory impairment). Group 3 = 23 patients without any neuropsychiatric symptoms or signs. Technetium-99m-HMPAO brain SPECT, EEG and a serum marker (ACA) were performed on all patients. In addition, MRI was performed on 44 patients (21 from Group 1, 15 from Group 2 and 8 from Group 3).

Technetium-99m-HMPAO Brain SPECT Imaging

Technetium-99m-HMPAO was prepared from a freeze-dried kit by adding about 1250 MBq of freshly eluted [^{99m}Tc]pertechnetate to 5 ml of saline solution. The solution was injected no more than 30 min after preparation. Patients were placed in a supine position in a quiet room with dimmed lights and were allowed to relax with

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For correspondence or reprints contact: Wan-Yu Lin, MD, Department of Nuclear Medicine, Taichung Veterans General Hospital, No. 160, Sec. 3, Taichung Harbor Rd., Taichung 407, Taiwan.

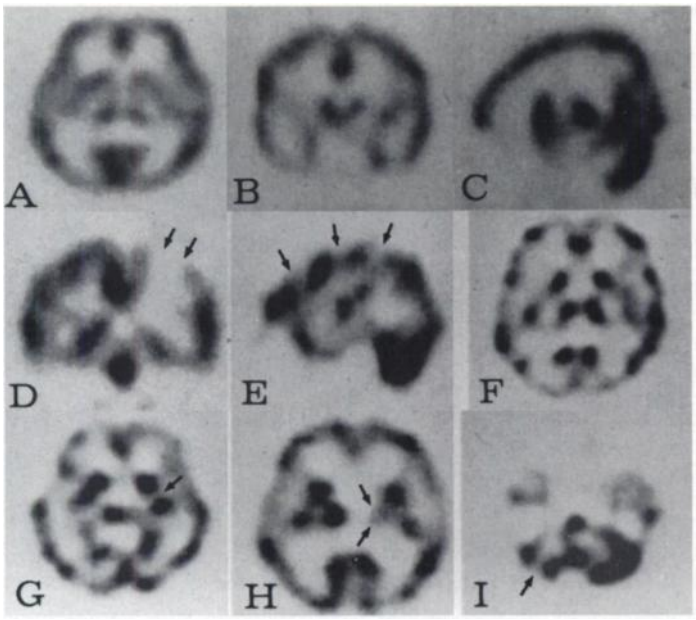

FIGURE 1. Different types of ^{99m}Tc-HMPAO SPECT findings in SLE patients. (A) Normal SPECT in transverse section. (B) Normal SPECT in coronal section. (C) Normal SPECT in sagittal section. (D) An area of perfusion defect in the left parieto-occipital area (arrows) (focal pattern). (E) Uneven distribution of radioactivity in the frontal and pareital areas (arrows) (focal pattern). (F) Diffusely uneven distribution of radioactivity in the cerebral cortices (diffuse pattern). (G) Small areas of decreased perfusion in the left basal ganglion (arrow). (H) Decreased perfusion in the left thalamus (arrows). (I) Areas of decreased perfusion in the right cerebellum (arrow).

their eyes closed for 15 min prior to intravenous administration of 1110 MBq (30 mCi) ^{99m}Tc-HMPAO. After injection of ^{99m}Tc-HMPAO, the patients were asked not to move or talk for at least 10 min. Imaging performed 90–120 min after injection.

Patients were positioned supine on the imaging table with forehead and chin restrained. The scanning equipment consisted of a rotating, large field of view, dual-headed gamma camera fitted with a fan-beam collimator. Data were acquired in a 64 × 64 matrix with a 1.3 zoom through 360° (180° for each head) rotation at 3° intervals, for 25 sec per arc interval. Approximately 7.5 million counts were acquired. Image reconstruction was performed with attenuation correction using Hanning filters to produce transaxial sections. The spatial resolution of this camera was 6.3-mm FWHM. Transaxial sections were reoriented parallel to the base of the brain to obtain sagittal and coronal reconstructions.

To identify areas of abnormal perfusion, visual interpretation of the SPECT images was carried out by two observers blinded to the clinical information. Normal findings consisted of homogenous brain perfusion without focal uptake defects or visible asymmetry (Fig. 1A–C). A single lesion or multiple small lesions confined to less than two lobes was considered to be a focal pattern (Fig. 1D,E). Lesions involving three or more lobes were defined as a diffuse pattern (Fig. 1F).

RESULTS

The diagnostic sensitivities of different modalities are shown in Table 1. Table 2 shows the detailed results of the SPECT findings. Our data suggest that SPECT findings were normal in 87% of the Group 3 patients and abnormal in all Group 1 patients. Interestingly, 84.6% of the Group 2 patients had abnormal SPECT findings. The parietal, frontal and temporal lobes were the most common areas of CNS involvement. The basal ganglion was involved in about 30% of Group 1 patients and 11.5% of Group 2 patients (Fig. 1G), while the thalamus and the cerebellum were less involved in neuropsychiatric SLE

TABLE 1
Results of HMPAO SPECT and MRI in SLE Patients

Group	No. of patients	HMPAO		MRI	
		Pos.	Neg.	Pos.	Neg.
1	23	100%	0%	71.4%	28.6%
2	26	84.6%	15.4%	46.7%	53.3%
3	23	13.0%	87.0%	0%	100%

Pos. = positive result; Neg. = negative result.

(Fig. 1 H,I). MR images showed less sensitivity in the detection of CNS involvement than the SPECT and were normal in 27.3% of patients with definite neuropsychiatric disorders. The EEG and ACA did not correlate well to the clinical diagnosis.

DISCUSSION

As with most other diseases of this nature, the pathogenesis of cerebral lupus is likely to be multifactorial. However, the most common neuropathological change in the brain in patients dying from SLE is microinfarction, the cause of which is probably related to a vasculopathy with thickening of the intima and fibrinoid degeneration, mainly of the small blood vessels (*20*). In a recent evaluation of brain pathology in 10 patients with SLE Hanly et al. (*21*) reported that multifocal cerebral cortical microinfarcts, associated with microvascular injury, were documented in four of seven patients with CNS lupus and constituted the predominant histopathologic abnormality. Multifocal cerebral microinfarcts represent the predominant histopathologic finding attributable to SLE (*2,21,22*). In our study, only a few patients with symptoms of stroke had a single lesion. Most of the lesions were multifocal; they may be diffused or confined to one or two lobes. The parietal, temporal and frontal lobes were most commonly involved. These results were consistent with the findings of Colamussi et al. (*23*). The fact that most of the hypoperfused areas were found in the frontal, temporal and parietal lobes (the territory of the middle cerebral artery), is difficult to explain. However, since cerebral vascular abnormalities resembling embolic disease have been reported in approximately 40% of autopsied SLE patients (*22*), and since the territory of the middle cerebral artery is at a higher risk for cerebral embolism than others, a relation between these two observations may exist.

The quick development of high-resolution instrumentation and sophisticated computers has improved SPECT image quality and has made the detection of deficits in central cerebral structures more accurate. In our study, the involvement of the basal ganglion, also a territory of the middle cerebral artery, was not unusual in the neuropsychiatric SLE patients. In Group 1, the incidence was over 30%. In contrast, the incidence of the thalamus involved in neuropsychiatric SLE patients was much lower.

Although the exact sensitivity and specificity data for all the diagnostic modalities were not available because there is no "gold standard" in the diagnosis of cerebral lupus, our study, consistent with previous reports, shows that SPECT images were more sensitive than MRI, EEG and ACA (*9,17,19,24*). In Group 1, all patients had abnormal SPECT findings, while MRI had a positive rate of only 71.4%. We suppose that detection of the functional disturbances, such as a change in regional blood flow, may be important in the disease. The most common MRI findings in our study were multiple small areas of increased intensity, especially in the cerebral white matter or periventricular area, and microinfarctions. These were also reported by

TABLE 2
HMPAO-SPECT Findings in Neuropsychiatric SLE Patients

Group	Type	No. of patients	Pari.	Fron.	Temp.	Occi.	Basa.	Thal.	Cereb.
1 (n = 23)	F	14 (60.9%)	56.5%	21.7%	17.4%	0%	13.0%	4.3%	0%
	D	9 (39.1%)	39.1%	34.8%	39.1%	30.4%	17.4%	0%	4.3%
	Total	23 (100%)	95.6%	56.5%	56.5%	30.4%	30.4%	4.3%	4.3%
2 (n = 26)	F	12 (46.2%)	42.3%	26.9%	11.5%	0%	3.8%	3.8%	0%
	D	10 (38.4%)	38.4%	38.4%	34.6%	26.9%	7.7%	3.8%	7.7%
	N	4 (15.4%)	0%	0%	0%	0%	0%	0%	0%
	Total	26 (100%)	80.7%	65.3%	46.1%	26.9%	11.5%	7.7%	7.7%
3 (n = 23)	F	1 (4.3%)	4.3%	4.3%	0%	0%	0%	0%	0%
	D	2 (8.7%)	8.7%	8.7%	8.7%	8.7%	0%	0%	0%
	N	20 (87.0%)	0%	0%	0%	0%	0%	0%	0%
	Total	23 (100%)	17.4%	17.4%	8.7%	8.7%	9.6%	0%	0%

F = focal uptake defects; D = diffuse uptake defects; Pari. = parietal area; Fron. = frontal area; Temp. = temporal area; Occi. = occipital area; Basa. = basal ganglion; Thal. = thalamus; Cereb = cerebellum.

Vermess et al. (*8*), Aisen et al. (*25*) and McCune et al. (*26*). These focal white matter lesions were similar to those found in patients with cerebral ischemic disease and multiple sclerosis (*26,27*). Therefore, specificity for SLE-induced CNS changes remains of limited value. According to the previous literature, the correlation between serum ACA positivity and neurological involvement was poor (*17,19*) and the EEG also rarely showed any correlation with the clinical manifestations (*6*). Our data shows the positive rates of ACA and the EEG were all below 50% in Group 1 patients. As for the CT scan, not evaluated in our study, it is considered by most authors to be with low diagnostic value in neuropsychiatric SLE patients although it is useful for detecting cerebral infarct (*28–30*).

Interestingly, approximately 13% of group three patients had positive SPECT images. This finding was consistent with those of Rubbert et al. (*17*) who found a 10% incidence of cortical perfusion abnormalities in the SLE patients without neuropsychiatric symptoms. Similar to these SPECT findings, abnormalities of PET scanning have been documented in patients with SLE without neuropsychiatric abnormalities (*31*). These abnormal features may be secondary to either false-positive results or subclinical CNS involvement. The usage of steroids in treatment of SLE may play a role, since it has been reported that corticosteroids may result in the cerebral atrophy (*29*), and cerebral atrophy is a frequent finding in SLE patients examined with CT (*32*). In addition, age may be another considerable factor affecting interpretation of the SPECT images. An uneven distribution of radiotracer in an old man may represent no clinical significance while the same picture in a young man may be abnormal. McCune et al. (*26*) and Rubbert et al. (*17*) found most of patients with normal SPECT findings were younger than 40. To solve this problem, brain SPECT images from normal control subjects according to different ages should be established.

PET scanning seems promising for detecting abnormal metabolic sites in patients with cerebral lupus. Stoppe et al. (*9*) reported that of 10 patients with cerebral lupus, all had disturbances in glucose metabolism as shown by a PET scan, and that 18 FDG-PET scans in three patients without CNS involvement were normal (*9*). Recently, however, a case reported by Grunwald et al. (*33*) had decreased cortical perfusion in SPECT images, particularly after acetazolamide enhancement, but the PET scan showed no major abnormalities. Since vasculopathy is the major pathogenesis in neuropsychiatric SLE, detection of changes in regional brain blood flow may be easier than detecting changes in glucose in metabolism. Further study will needed to compare these two diagnostic modalities in the same group of patients.

A quantification of the degree of the disease severity will be more objective and may reduce the inter-subject or even the intra-subject variation. However, an absolute quantification of regional cerebral blood flow is not acceptable for routine clinical use because it requires arterial blood sampling, careful correction for attenuation, complex modeling of enzyme kinetics and in vitro measurements of blood samples. Some semiquantitative methods for the interpretation of the SPECT results have been reported (*7,17*). However, we did not think the semiquantitative method is valuable in neuropsychiatric SLE patients since CNS involvement in SLE is always multifocal and can symmetrically involve the brain structure. In the experience of Colamussi et al. (*23*) the visual analysis of SPECT images (performed by independent observers trained with a normal base data obtained in their laboratory) has more potential to identify lesions. Therefore, in this study, we selected visual interpretation instead of a quantitative method.

A longitudinal brain SPECT study may provide objective information on SLE patients with CNS involvement. Furthermore, it may also be useful in monitoring the effect of treatment. One patient had diffuse perfusion abnormalities in the cerebral cortex, basal ganglion and the cerebellum. After pulse therapy with methylprednesolone, the brain SPECT images showed much improvement of the perfusion in the brain, especially in the cerebellum (Fig. 2). We believe, therefore, that the SPECT accurately reflects CNS abnormalities with SLE and correlates with subsequent improvement.

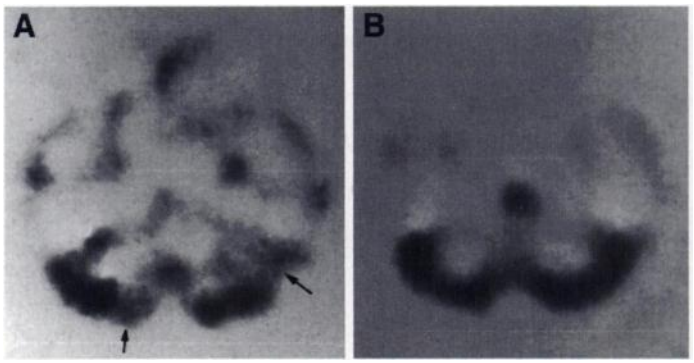

FIGURE 2. A 21-yr-old woman with SLE who suffers from vertigo, dizziness and emotional change. (A) SPECT image shows perfusion abnormalities in the cerebellum (arrows) (B) SPECT scan after pulse therapy shows improved perfusion in the cerebellum.

CONCLUSION

SPECT imaging of brain perfusion is more sensitive than EEG and MRI in the evaluation of central nervous system involvement in SLE. In the SPECT findings, cerebral cortices, especially the parietal, temporal and frontal lobes, are the most common sites to be involved in neuropsychiatric SLE patients. Furthermore, with the improvement of SPECT resolution, detection of the deep-seated structure in the brain has become possible. We found that involvement of basal ganglion is also not uncommon while the thalamus and the cerebellum are less involved in neuropsychiatric SLE. In the future, we believe the functional brain SPECT will play an increasingly important role in evaluating CNS conditions in patients with SLE.

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Normal Brain Perfusion Pattern of Technetium-99m-Ethylcysteinate Dimer in Children

Christiaan Schiepers, Alfons Verbruggen, Paul Casaer and Michel De Roo

Department of Nuclear Medicine, Division of Neuro-Pediatrics, University Hospital Gasthuisberg, Leuven, Belgium

The purpose of this study was to assess the normal perfusion pattern of the pediatric brain with ^{99m}Tc-ethylcysteinate dimer (^{99m}Tc-ECD). **Methods:** Tomographic imaging was performed with a dedicated system with high sensitivity and resolution. Sixteen children, referred for brain imaging in the workup of seizure disorder, were included since they turned out negative after a 1-yr follow-up. A standardized brain presentation was obtained after reslicing and reorienting of the three-dimensional volumetric dataset. **Results:** Quantitative analysis did not reveal significant left-right uptake differences per patient. Three age clusters were investigated that showed differences in regional uptake, mainly a relatively increased uptake in basal ganglia, visual and motor cortex. An uptake ratio or perfusion index was calculated after normalization. Normal limits were established for the children in the three groups. **Conclusion:** Technetium-99m-ECD is a safe agent for children and should be the radiopharmaceutical of choice for brain perfusion studies because of favorable radiation dosimetry and stability. The age dependence of perfusion necessitates a database comparison before concluding that the observed perfusion pattern is normal.

Key Words: brain imaging; neuropediatrics; technetium-99m-ethylcysteinate dimer; cerebral blood flow

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For correspondence or reprints contact: Christiaan Schiepers, MD, PhD, Department of Radiological Sciences, Olive View-UCLA Medical Center, 14445 Olive View Dr., Sylmar, CA 91342.

Cerebral blood flow (CBF) or perfusion imaging with ^{99m}Tc-labeled radiopharmaceuticals is a routine procedure in nuclear