# The role of FDG-PET, HMPAO-SPET and MRI in the detection of brain involvement in patients with systemic lupus erythematosus

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**Abstract.** Involvement of the brain is one of the most important complications of systemic lupus erythematosus (SLE); however, its diagnosis is difficult due to the lack of effective imaging methods. We combined three brain imaging modalities – positron emission tomography with fluorine-18 2-fluoro-2-deoxy-D-glucose (FDG-PET), single-photon emission computed tomography with technetium-99m hexamethylpropylene amine oxime (HMPAO-SPET) and magnetic resonance imaging (MRI) – in order to detect brain involvement in SLE. Thirty-seven SLE patients, aged 22–45 years, were divided into three groups. Group 1 (G1) consisted of ten patients with major neuropsychiatric manifestations; group 2 (G2) consisted of 15 patients with minor manifestations; and group 3 (G3) consisted of 12 patients without manifestations. FDG-PET findings were abnormal in 51% of patients: 90% of G1, 67% of G2 and 0% of G3 patients respectively. HMPAO-SPET findings were abnormal in 62% of patients: 100% of G1, 73% of G2 and 17% of G3 patients respectively. MRI findings were abnormal in 35% of patients: 70% of G1, 40% of G2 and 0% of G3 patients respectively. Grey matter was more commonly involved than white matter; 62% of patients presented with lesions in the cerebral cortex, 27% with lesions in the basal ganglion, 5% with lesions in the cerebellum, and 19% with lesions in white matter. No white matter lesions were found on FDG-PET or HMPAO-SPET. However, in 19% of patients, MRI demonstrated abnormally high signal lesions in white matter. Forty-three percent of cases had positive serum anticardiolipin antibodies (ACA). However, ACA was not related to FDG-PET, HMPAO-SPET or MRI findings. It may be concluding that HMPAO-SPET is a more sensitive tool for detecting brain involvement in SLE patients when compared with FDG-PET or MRI. However, MRI is necessary for detecting lesions in white matter.

*Key words:* Fluorine-18 2-fluoro-2-deoxy-D-glucose – Positron emission tomography – Technetium-99m hexamethylpropylene amine oxime – Single-photon emission tomography – Magnetic resonance imaging - Systemic lupus erythematosus

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## Introduction

Involvement of the brain is one of the most important and fatal complications of systemic lupus erythematosus (SLE) [1–3]. Thus, diagnosis of neuropsychiatric SLE (NP-SLE) is critical. However, due to the lack of effective imaging, diagnosis of brain involvement in SLE patients is difficult.

Magnetic resonance imaging (MRI) has been considered highly sensitive, and is often used to identify focal lesions in NP-SLE patients with clinical evidence of recent stroke but with no observed abnormalities on contrast-enhanced CT scans [4]. However, brain imaging based on metabolic function may prove to be even more sensitive than MRI in locating and diagnosing the extent of brain involvement in NP-SLE patients. Positron emission tomography of glucose metabolism with fluorine-18 2-fluoro-2-deoxy-D-glucose (FDG-PET) can identify fluctuations in regional cerebral metabolism in NP-SLE patients, even when no structural lesions are evident on MRI [5]. However, PET is not suitable for routine clinical use due to its expense and lack of availability. Single-photon emission tomography with technetium-99m hexamethylpropylene amine oxime (HMPAO-SPET) is

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an alternative modality, used to assess regional cerebral blood flow (rCBF). HMPAO-SPET has been proven to be more sensitive than MRI in detecting brain involvement in autoimmune connective tissue disease [6–8].

To date, there have been few reports concerning the combined application of FDG-PET, HMPAO-SPET, and MRI of the brain in SLE patients. In this study, we compared the accuracy of the three brain imaging techniques for locating brain involvement in SLE patients.

## Materials and methods

*Patients.* Thirty-seven female patients, aged 22–45 years, who fulfilled the American Rheumatism Association criteria for SLE [9] were enrolled in this study. Neuropsychiatric manifestations due to SLE were defined [10,11] as those that could not be attributed to any other cause. Neuropsychiatric manifestations were classified as major and minor manifestations according to the previous publications [10, 12–14]. Based on neuropsychiatric evaluation, the patients were divided into three groups. Group 1 (G1) consisted of ten patients with major manifestations (such as stroke, seizure, psychosis) present for at least 1 year before inclusion in the study. Group 2 (G2) consisted of 15 patients with minor manifestations (such as headache, dizziness and memory impairment). Group 3 (G3) consisted of 12 patients without any neuropsychiatric manifestations. FDG-PET, HMPAO-SPET and MRI of the brain were performed on all 37 patients within 1 week to detect brain lesions. HMPAO-SPET and MRI are routine examinations for SLE patients with neuropsychiatric manifestations in our hospitals. For FDG-PET, this study was approved by the Review Board of the Research Committee of Taichung Veterans General Hospital (Project No. TCVGH-876705C). All 37 patients gave informed consent prior to entry into the study. In order to avoid the effects of age on interpretation of brain images, HMPAO-SPET and FDG-PET images from ten normal female controls with the same age distribution as the patients served as the diagnostic standards in this study. Meanwhile, serum levels of anticardiolipin antibodies (ACA) were measured by enzyme linked immunoassay kits (Quanta Lite ACA IgG/IgM and IgA, INOVA Diagnostics, Inc., San Diego, Calif., USA).

*Brain FDG-PET.* Patients fasted overnight before the brain FDG-PET study. No patient in this study was found to have a glucose level higher than 120 g/dl. The imaging device was an 18-ring, 35-slice GE advance PET scanner (General Electric Medical Systems, Milwaukee, Wis., USA) with an axial resolution of 4.5 mm at the centre of the field of view. The position of the head was fixed in a hemicylindrical plastic headholder with a radiolucent plastic neck-contoured head rest, and maintained during PET imaging using a laser beam. Then, 370 MBq (10 mCi) of FDG was intravenously injected. The effective dose equivalent was estimated to be 8.9 mSv/370 MBq FDG [15]. Static scanning of the brain began 30 minutes after injection of FDG. Attenuation correction was performed, and images were reconstructed by the filtered backprojection method using a Hanning filter with a filter cut-off frequency of 4 cycles/pixel. For PET images, the transaxial sections were reoriented parallel to the base of the brain to obtain sagittal and coronal reconstructions. Each tomogram slice from each patient was visually inspected twice in random order by three independent experienced observers blind to the clinical information of the patients. Normal FDG-PET brain imaging findings consisted of homogeneous glucose metabolism in the grey matter of cerebral cortex and basal ganglia/thalamus without focal hypometabolism or visible asymmetry. Positive findings included heterogeneous glucose metabolism with focal hypometabolism or visible asymmetry noted in at least two consecutive slices by at least two observers [16].

*Brain HMPAO-SPET.* $^{99m}$Tc-HMPAO was prepared from a commercial kit (Ceretec, Amersham International plc, U.K.) by adding 1110 MBq (30 mCi) of freshly eluted $^{99m}$Tc pertechnetate to 5 ml of saline solution. The solution was administered to the patient no more than 30 min after preparation. The effective dose equivalent was estimated to be 12.2 mSv/1110 MBq $^{99m}$Tc-HMPAO [17]. SPET was performed at least 1 h after intravenous injection of $^{99m}$Tc HMPAO. As in the brain FDG-PET study, the position of the head was fixed in a hemicylindrical plastic headholder with a radiolucent plastic neck-contoured head rest and maintained during SPET imaging using a laser beam. The scanning equipment consisted of a rotating, large-field-of-view, dual-head gamma camera (Helix HR, Elscint Ltd., Haifa, Israel) fitted with a fan-beam collimator. Data were acquired in a 64×64 matrix with 1.3 zooming, through a 360° (180° for each head) rotation at 3° intervals, for 25 s per arc interval. Reconstruction of the image was performed using attenuation correction, with Hanning filters, to produce transaxial sections. The system spatial resolution of the camera with fan-beam collimator was 6.3 mm full-width at half-maximum (FWHM) (provided by Elscint Ltd., Haifa, Israel). For SPET images, the 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 SPET images from each patient was carried out twice in random order by three independent experienced observers blind to the clinical information of the patients. Normal $^{99m}$Tc-HMPAO brain imaging findings consisted of homogeneous rCBF in the grey matter of cerebral cortex and basal ganglia/thalamus without focal hypoperfusion or visible asymmetry. Abnormal findings included heterogeneous rCBF with focal hypoperfusion or visible asymmetry noted in at least two consecutive slices by at least two observers [16, 18–20].

*Brain MRI.* Post Gd-DTPA brain MR scans were performed, via a Picker Vista MR2055 HP (1.0 T) scanner (Picker Ltd., Cleveland, Ohio, USA), with a spin-echo T1-weighted sequence of 500–750/20/1–2 (repetition time/echo time/excitations), a proton density image of 2000–3000/20/1–2 and a T2-weighted sequence of 2000–3000/80–100/1–2. The section thickness was 5–7 mm with an intersection gap of 1 mm. To identify areas with abnormal signals, visual interpretation of the MR images from each patient was carried out twice in random order by three independent experienced observers blind to the clinical information of the patients. Abnormal findings of brain MRI consisted of foci of high signal intensity on T2-weighted images within the white matter of the brain stem, basal ganglia, cerebral hemispheres or cerebellum. Otherwise, the findings were considered to be normal [18].

*Interpretation of correlative images.* Depending on the prominent brain structures ("landmarks" included the caudate, putamen, thalamus, corpus callosum, ventricles, cingulate gyrus and the cortical surface outline, particularly at the anterior point of the frontal lobe and the vertex of the occipital lobe) presented on FDG-PET, HMPAO-SPET and MRI, corresponding slices of FDG-PET, HMPAO-SPET and MRI scans were displayed and evaluated.

**Table 1.** Incidences of abnormal FDG-PET, HMPAO-SPET and MRI findings in the brains of SLE patients

| | No. of Patients | Brain Imaging | Grey matter | | | | White matter |
|---|---|---|---|---|---|---|---|
| | | | Cortex | Basal ganglia | Cerebellum | Subtotal | |
| Group 1 | 10 | FDG-PET | 9 | 6 | 1 | 9 (90%) | 0 (0%) |
| | | HMPAO-SPET | 10 | 7 | 1 | 10 (100%) | 0 (0%) |
| | | MRI | 6 | 3 | 0 | 6 (60%) | 5 (50%) |
| Group 2 | 15 | FDG-PET | 10 | 2 | 0 | 10 (67%) | 0 (0%) |
| | | HMPAO-SPET | 11 | 2 | 1 | 11 (73%) | 0 (0%) |
| | | MRI | 4 | 1 | 0 | 4 (40%) | 2 (13%) |
| Group 3 | 12 | FDG-PET | 0 | 0 | 0 | 0 (0%) | 0 (0%) |
| | | HMPAO-SPET | 2 | 1 | 0 | 2 (17%) | 0 (0%) |
| | | MRI | 0 | 0 | 0 | 0 (0%) | 0 (0%) |
| Total | 37 | | 23 (62%) | 10 (27%) | 2 (5%) | 23 (62%) | 7 (19%) |

**Table 2.** Serum ACA in relation to FDG-PET, HMPAO-SPET and MRI findings

| ACA | No. of patients | FDG-PET | | HMPAO-SPET | | MRI | |
|---|---|---|---|---|---|---|---|
| | | Positive | Negative | Positive | Negative | Positive | Negative |
| Positive | 16 (43%) | 8 | 8 | 10 | 6 | 5 | 11 |
| Negative | 21 (57%) | 11 | 10 | 13 | 8 | 8 | 13 |

## Results

Our results showed:

1. FDG-PET findings were abnormal in nine (90%) G1 patients, ten (67%) G2 patients and no (0%) G3 patients. HMPAO-SPET findings were abnormal in ten (100%) G1 patients, 11 (73%) G2 patients and two (17%) G3 patients. MRI findings were abnormal in seven (70%) G1 patients, six (40%) G2 patients and no (0%) G3 patients.

2. Grey matter (23, 62%) was more commonly involved than white matter: 23 (62%) patients demonstrated lesions in the cerebral cortex, ten (27%) demonstrated lesions in the basal ganglia, two (5%) demonstrated lesions in the cerebellum, and seven (19%) demonstrated lesions in white matter (Table 1).

3. No white matter lesions were found on FDG-PET or HMPAO-SPET. However, in 19% (7/37) of the patients, MRI revealed abnormally high signal lesions in white matter (Table 1).

Sixteen of 37 (43%) patients had positive serum ACA. However, ACA was not related to FDG-PET, HMPAO-SPET or MRI findings (by chi-square tests, all $P$ values >0.5) (Table 2).

## Discussion

Exact sensitivity and specificity data for all of the diagnostic modalities have been unavailable due to the lack of standards for the diagnosis of SLE with brain involvement. However, in a review of the literature, HMPAO-SPET and FDG-PET demonstrate abnormalities more frequently than MRI, but are also extremely non-specific for NP-SLE [11, 20–22]. Abnormalities on HMPAO-SPET or FDG-PET are frequently found in patients without obvious NP-SLE [5, 11, 20–24]. Our findings were consistent with the results of previous reports. In our study, abnormal HMPAO-SPET and FDG-PET findings were found in 6/37 (16%) and 10/37 (27%) SLE patients with normal MRI findings (Fig. 1). From these results, we suppose that metabolic or functional changes in the brain, such as fluctuations in glucose metabolism or rCBF, are more easily detected than changes in the anatomical structure of the brain in SLE patients. However, MRI seems to be more sensitive than FDG-PET and HMPAO-SPET for detecting white matter lesions, as in 19% (7/37) of our SLE patients (Fig. 2). This finding is compatible with previous reports [25, 26] that MRI is more sensitive in detecting small white matter infarctions and deep white matter lesions.

Microinfarction is the most common neuropathological finding in patients with NP-SLE. The cause of this finding is probably a wall thickening of cerebral blood vessels which is associated with recurrent vasculitis [2, 27–29]. In addition, Cespany et al. found a decreased ce-

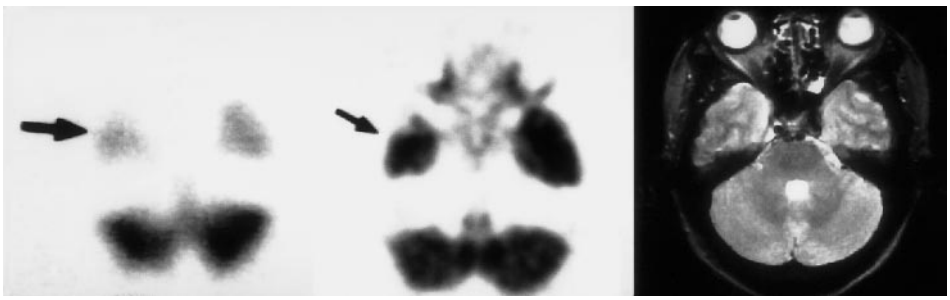

**Fig. 1.** Thirty-year-old female. Brain HMPAO-SPET (*left*) and FDG-PET (*middle*) revealed areas of hypoperfusion and hypometabolism in the right temporal lobe (*arrows*). However, brain MRI (*right*) revealed no significant abnormality

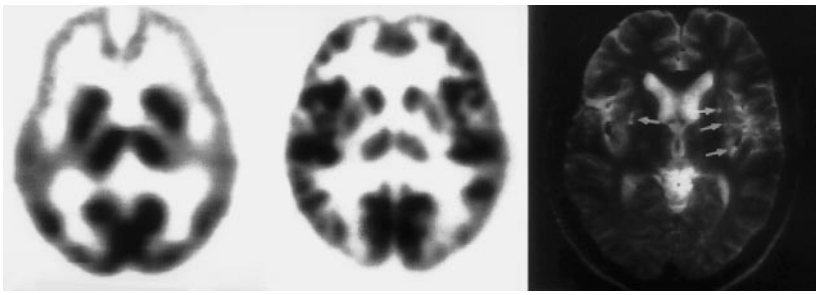

**Fig. 2.** Twenty-nine-year-old female. Brain HMPAO-SPET (*left*) and FDG-PET (*middle*) revealed normal perfusion and metabolism in the brain. However, while brain MRI (*right*) showed normal grey matter, there was a high signal area in the bilateral white matter between the insular gyri and lentiform nuclei (*arrows*)

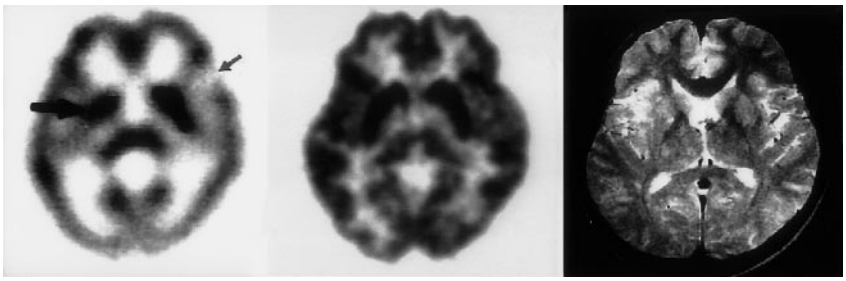

**Fig. 3.** Thirty-nine-year-old female. Brain HMPAO-SPET (*left*) revealed areas of hypoperfusion in the left parietal and temporal lobes (*small arrow*) and right basal ganglion (*large arrow*). However, brain FDG-PET (*middle*) and MRI (*right*) revealed normal metabolism and signal intensity in these areas

rebrovascular reserve capacity in SLE patients with and without neuropsychiatric manifestations [30]. These studies prove that NP-SLE is primarily a cerebrovascular disorder rather than a neuronal tissue disorder. Thus, in NP-SLE, decreased rCBF due to loss of cerebral perfusion reserve may occur earlier than decreased glucose metabolism due to death of neuronal tissues. This phenomenon could explain the finding of reduced rCBF on HMPAO-SPET but preserved glucose metabolism on FDG-PET in NP-SLE patients in our study. Discrepancy between rCBF and glucose metabolism was found in 1/10 (10%) G1 patients, 1/15 (7%) G2 patients and 2/12 (17%) G3 patients (Fig. 3). Grunwald et al. [31] recently compared acetazolamine HMPAO-SPET and FDG-PET for the detection of brain involvement in SLE patients. They also found hypoperfusion on HMPAO-SPET, but no glucose hypometabolism on FDG-PET. However, to avoid the possible severe adverse side-effects which might cause myocardial ischaemia [32, 33], acetazolamine HMPAO-SPET is not recommended for routine and regular examination in our hospital.

Interestingly, 17% (2/12) of G3 patients (without neuropsychiatric manifestations) had abnormal HMPAO-SPET studies. This finding was similar to the results of Lin et al. and Rubbert et al., who found 10% and 13% incidences, respectively, of hypoperfusion abnormalities in SLE patients without neuropsychiatric symptoms [20, 23]. We suppose that these abnormal features are secondary to either corticosteroid usage [34] or subclinical brain involvement.

The prevalence of ACA in SLE varies from 20% to 50% [35]. Emmi et al. [11] found no correlation between serum ACA and brain involvement. Maeshima et al. [36] found no correlation between SPET abnormalities and ACA. Lin et al. found that serum ACA did not correlate well with the clinical diagnosis of SLE with brain involvement [20]. These previous reports are similar to our findings that ACA (16/37, 43%) was not related to FDG-PET, HMPAO-SPET or MRI findings.

Absolutely quantitative or semiquantitative measurements of glucose metabolism and rCBF are very time-consuming for routine clinical use and invasive for the study patients. The visual analysis of FDG-PET and HMPAO-SPET images performed by independent and experienced observers and dependent on normal databases obtained in our own laboratory [16–20] and from

previous studies [37–41] was sufficient to identify lesions. In addition, according to previous studies [42–46], readers' reproducibilities for visual interpretation of FDG-PET and HMPAO-SPET are good. Therefore, in this study, we selected visual interpretation instead of a quantitative method.

We conclude that in SLE patients, the change in rCBF evaluated by HMPAO-SPET is more sensitive to detection than the change in glucose metabolism evaluated by FDG-PET and the change in anatomical structure evaluated by MRI. However, none of the white matter lesions could be detected by FDG-PET or HMPAO-SPET whereas MRI did show abnormally high signal lesions in white matter. Therefore, MRI is necessary for detecting brain lesions in white matter of SLE patients.

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