Regional Cerebral Blood Flow and Glucose Metabolism in Sjögren's Syndrome

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Involvement of the brain is one of the most important complications of Sjögren's syndrome (SS). However, diagnosis of brain involvement in SS patients is difficult due to the lack of effective imaging methods. In this study, we compared two updated brain imaging modalities, ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) PET and ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO) SPECT, in SS patients with neuropsychiatric manifestations, to detect glucose metabolism of the brain and regional cerebral blood flow. **Methods:** Sixteen primary female SS patients with normal brain MRI findings were enrolled in this study. **Results:** Technetium-99m-HMPAO SPECT findings were abnormal in 13 (81%) patients. Parietal and temporal lobes were the most common areas of brain involvement. Fluorine-18-FDG PET findings were abnormal in 3 (19%) patients. Temporal lobes were the most common areas of brain involvement. **Conclusion:** We conclude that brain HMPAO SPECT has better correlation with clinical manifestations than brain FDG PET or CT/MRI.

Key Words: Sjögren's syndrome; fluorine-18-2-fluoro-2-deoxy-D-glucose; PET; technetium-99m-hexamethyl propyleneamine oxime; SPECT

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Sjögren's syndrome (SS) is a common autoimmune connective tissue disease affecting a conservatively estimated 2% of the adult population (*1*). It occurs most frequently in middle-aged women and is mainly characterized by dryness of the eyes (keratoconjunctivitis) and mouth (xerostomia) (*2,3*). The neurological manifestations of SS were first described in 1935 by Henrik Sjögren and include bilateral facial nerve palsy and transient sensory changes associated with sicca syndrome (*4*). Nervous system involvement in SS has been reported in an increasing number of articles (*1,5–9*). The overall occurrence of neuropsychiatric disturbances has been estimated to be 28% (*6*). Involvement of the brain can be focal or diffuse. Acute onset of stroke is distinctly unusual. Seizure disorders (accompanied by abnormal electroencephalogram) usually are petit mal (absence) or temporal lobe (psychomotor); grand mal seizures, focal motor seizures, status epilepticus and epilepsy partialis continua have been observed less commonly (*1*). Recently, psychiatric abnormalities in SS have also been reported (*5–7*). Despite increased knowledge, the overall clinical picture of SS with its neurological complications has remained somewhat unclear. Diagnosis and management of neuropsychiatric SS (NP-SS) are critical. However, due to the lack of effective imaging techniques, diagnosis of brain involvement in SS patients is difficult.

MRI has been considered to be highly sensitive, as it has been used to identify structural lesions in NP-SS patients (*9*). PET studies of glucose metabolism with ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) have proven to be even more sensitive than MRI for documenting the location and extent of brain involvement in rheumatologic patients, even when no structural lesions have been evident on MRI (*10,11*). However, PET is not suitable for routine clinical use due to its expense and lack of availability. Another imaging modality for studying brain involvement is SPECT with ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO). This technique has been used for the assessment of regional cerebral blood flow (rCBF), which has a strong correlation with changes in glucose metabolism. Technetium-99m-HMPAO SPECT of the brain has proven accurate in detecting many neurological and psychiatric diseases (*12–15*).

In this study, we compare the sensitivities of brain HMPAO SPECT and brain FDG PET for diagnosing brain involvement in NP-SS patients with normal brain MRI findings.

MATERIALS AND METHODS

Patients

Sixteen female primary SS patients (age range 30–61 yr) who fulfilled the criteria for SS, i.e., questionnaires regarding both ocular and oral involvement by typical symptoms/signs, histopathologic features, positive diagnostic test results and existence of autoantibodies, but excluding pre-existing lymphoma, acquired immunodeficiency syndrome, sarcoidosis or graft-versus-host disease (*8*), were enrolled in this study. All of the patients had normal brain MRI (Picker Vista MR2055 HP scanner; Picker International, Cleveland, OH) findings. A neurologic consultant evaluated patients with neurologic symptoms/signs. Neuropsychiatric symptoms/signs due to SS were defined as those that could not be attributed to any other cause (such as uremia, hypertension or infection). Brain ^{99m}Tc-HMPAO SPECT and brain FDG PET were performed on all 16 patients.

Brain Technetium-99m-HMPAO SPECT

Technetium-99m-HMPAO was prepared from a commercial kit (Ceretec; Amersham International, Aylesbury, United Kingdom) by adding 1110 MBq (30 mCi) freshly eluted ^{99m}Tc-pertechnetate to 5 ml saline solution. The solution was administered to the patient no more than 30 min after preparation. SPECT was performed at least 1 hr after intravenous injection of ^{99m}Tc-HMPAO. 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-head gamma camera (Helix HR; Elscint, Haifa, Israel) fitted with a fanbeam collimator. Data were acquired in a 64 × 64 matrix with 1.3 zooming, at 3° intervals through a 360° (180° for each head) rotation, for 25 sec/arc interval. Reconstruction of the image was performed using attenuation correction with Hanning filters to produce transaxial sections. The spatial resolution of the camera with fanbeam collimator was 6.3 mm FWHM. The transaxial sections were reoriented parallel to the base of the brain to obtain sagittal and coronal reconstructions. To identify areas of hypoperfusion in the brain, visual interpretation of SPECT images was performed by three observers who were blinded to the

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TABLE 1
Detailed Patient Data

Patient	Age (yr)	Hypoperfusion areas on HMPAO SPECT	Hypometabolism areas on FDG PET	Neurologic symptoms/signs
1	41	Bil P-O, Rt T	Rt T	Seizure
2	44	Bil F-P, Rt T, Lt BG	Rt T	Seizure, memory impairment
3	37	Rt T	Rt T	Seizure
4	43	Bil F-P-T	Negative	Cognition impairment
5	35	Bil-F-P-T-O, Bil BG	Negative	Memory and cognition impairment
6	33	Bil P, Bil BG	Negative	Drowsiness, depression
7	61	Bil P, Rt BG	Negative	Memory impairment
8	30	Bil P, Lt T, Lt BG	Negative	Seizure, memory and cognition impairment
9	40	Bil P-T-O	Negative	Cognition impairment, headache
10	23	Rt F-P-T	Negative	Vertigo, unstable gait
11	43	Lt T	Negative	Memory impairment
12	43	Bil P	Negative	Syncope
13	31	Bil F-P-T	Negative	Memory and cognition impairment
14	44	Negative	Negative	Memory impairment, depression
15	49	Negative	Negative	Insomnia, dizziness, depression
16	40	Negatve	Negative	Memory and cognition impairment

Bil = bilateral; Rt = right; Lt = left; F = frontal lobe; P = parietal lobe; T = temporal lobe; O = occipital lobe; BG, = basal ganglia.

clinical information. Normal findings of ^{99m}Tc-HMPAO brain imaging consisted of homogeneous rCBF in the gray matter of the cerebral cortex and basal ganglia/thalamus without focal hypoperfusion or visible asymmetry. Otherwise, the findings of ^{99m}Tc-HMPAO brain imaging were considered to be abnormal (*16*).

Brain FDG PET

Patients fasted overnight before the brain FDG PET study. No patient in this study had a glucose level higher than 120 g/dl. The imaging device was an 18-ring, 35-slice General Electric Advance PET scanner (GE Medical Systems, Milwaukee, WI) with an axial resolution of 4.5 mm at the center of the field of view. Laser beams and physical examination were used to ensure accurate patient positioning. Then, 370 MBq (10 mCi) FDG were injected intravenously. Static scanning of the brain began 30 min after injection of FDG. Attenuation correction was performed, and images were reconstructed by the filtered backprojection method using a Hanning filter with a filter cutoff frequency of four cycles per pixel. To detect areas of hypometabolism, each slice was inspected visually by three experienced nuclear medicine specialists who were blinded to the clinical information. Normal findings of FDG PET brain imaging consisted of homogeneous glucose metabolism in the gray matter of the cerebral cortex and basal ganglia/thalamus without focal hypometabolism or visible asymmetry. Otherwise, the findings of FDG PET brain imaging were considered abnormal.

RESULTS

The detailed data are listed in Table 1. Technetium-99m-HMPAO SPECT findings were abnormal in 13 (81%) patients. Parietal (n = 11; 69%) and temporal lobes (n = 9; 56%) were the most common areas of involvement. Basal ganglia (n = 5; 31%), frontal lobe (n = 4; 25%) and occipital lobe (n = 3; 19%) were less common areas of brain involvement. FDG PET findings were abnormal in 3 (19%) patients. Temporal lobes (n = 3; 19%) were the most common areas of brain involvement (Fig. 1).

DISCUSSION

The exact sensitivity and specificity data for all of the diagnostic modalities have been unavailable due to the lack of standards for the diagnosis of NP-SS. FDG PET seems to have a higher sensitivity than MRI for detecting abnormal metabolic sites in the brains of patients with autoimmune diseases such as systemic lupus erythematosus (*10,11*). The results of previous reports are compatible with our results; 3 of 16 cases with normal brain MRI findings revealed hypometabolism of the brain on FDG PET. In addition, our results showed that HMPAO SPECT is more sensitive than MRI for detecting brain involvement in SS patients; 13 of 16 cases with normal brain MRI findings showed hypoperfusion of the brain on ^{99m}Tc-HMPAO SPECT. These findings are consistent with those of a previous study (*1*). In that study, ^{99m}Tc-HMPAO brain scans, which measure rCBF, demonstrated multiple areas of cortical hypoperfusion in SS patients with cognitive or neuropsychiatric dysfunction and normal brain MRI findings (*1*). In both that previous study and this study, it was suggested that there are cortical and subcortical (basal ganglia) abnormalities in SS patients with brain involvement, which could contribute to cognitive impairment and neuropsychiatric disturbances. In addition, alterations in rCBF may be an early marker of brain involvement in SS patients. From these results, we suppose that metabolic or functional changes in the brain, such as fluctuations in glucose metabolism or rCBF, may be more easily detected than changes in brain anatomic structure in NP-SS patients.

We found decreased rCBF on ^{99m}Tc-HMPAO SPECT im-

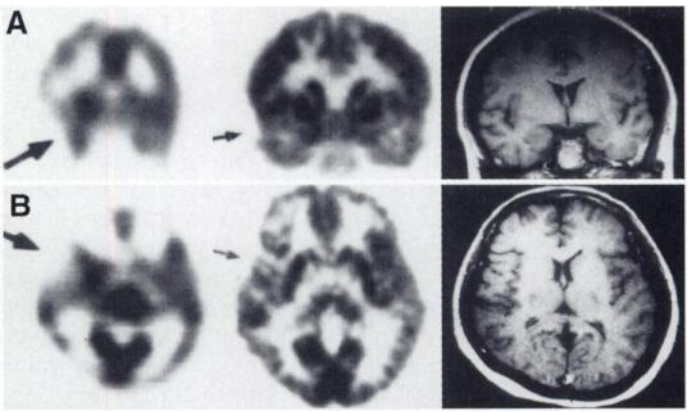

FIGURE 1. Coronal sections (A) and transaxial sections (B) of 37-yr-old female patient (Patient 3). Brain ^{99m}Tc-HMPAO SPECT (left) and brain FDG PET (middle) reveal area of both hypoperfusion and hypometabolism in right temporal lobe (arrow). However, brain MR image (right) shows no significant abnormality.

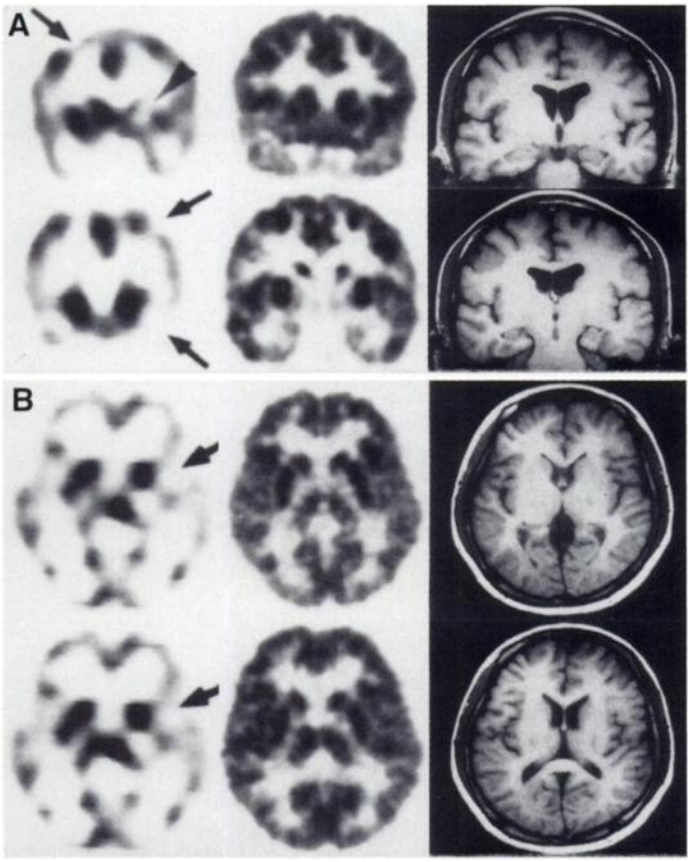

FIGURE 2. Coronal sections (A) and transaxial sections (B) of 30-yr-old female patient (Patient 8). Brain ^{99m}Tc-HMPAO SPECT (left) reveals hypoperfusion areas in bilateral parietal lobes (arrows, upper and lower), left temporal lobe (arrow, upper) and left basal ganglion (arrowhead, lower). However, brain FDG PET (middle) and MR images (right) reveal normal metabolism and signal intensity in these areas found in ^{99m}Tc-HMPAO SPECT.

ages, but no abnormalities in glucose metabolism on brain FDG PET images, in 10 of 16 (63%) NP-SS patients (Fig. 2). Nishimura et al. (*17*) suggested that neuropsychiatric dysfunctions associated with SS are at least in part attributable to small-vessel vasculopathy such as focal inflammation or edema. Gerraty et al. (*18*) suggested that cerebral vasculitis is the pathogenetic mechanism of the brain manifestations of SS. Berman et al. (*19*) described angiographic evidence of cerebral vasculitis and multiple infarcts present on neuroimaging in an SS patient with brain involvement. In de-la-Monte et al. (*20*), the authors examined brain abnormalities in 11 SS patients and found cerebral vasculopathy including necrotizing vasculitis. Alexander et al. (*21*) studied 16 patients with SS and brain disorders and suggested that an immune vasculopathy may play a role in the pathogenesis of central nervous system disease in SS. Because vasculopathy is the major pathogenesis in NP-SS, as suggested by previous studies (*17–21*), detection of changes in rCBF may be easier than detection of changes in glucose metabolism. Similar results were found in systemic lupus erythematosus patients with brain involvement (*22*). The discrepancy between glucose metabolism and rCBF of the brain in NP-SS can be explained as a reduction in perfusion with preservation of glucose metabolism. This phenomenon within the brain is similar to ischemic but viable myocardium (*23*).

CONCLUSION

There is a high incidence of abnormal rCBF in NP-SS, and ^{99m}Tc-HMPAO SPECT is more sensitive than either FDG PET or MRI for diagnosing NP-SS. In our patients, no changes in the anatomic structure of the brain were detected (normal brain MRI findings). We conclude that changes in rCBF are more sensitive to detection than metabolic changes in the brain, such as fluctuations in glucose metabolism, in SS patients with brain involvement.

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