EXTENDED REPORT

Abnormal regional cerebral blood flow on ^{99m}Tc ECD brain SPECT in patients with primary Sjögren's syndrome and normal findings on brain magnetic resonance imaging

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Ann Rheum Dis 2002;**61**:774–778

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Accepted 20 March 2002

Objective: Technetium-99m ethyl cysteinate dimer (^{99m}Tc ECD) single photon emission computed tomography (SPECT) of the brain was used to detect abnormal regional cerebral blood flow (rCBF) in patients with primary Sjögren's syndrome (pSS) and normal findings on brain magnetic resonance imaging (MRI).

Methods: ^{99m}Tc ECD brain SPECT was performed to detect brain lesions showing hypoperfusion in 32 female patients with pSS and definite neuropsychiatric symptoms or signs. Seventeen female patients with pSS without neuropsychiatric symptoms and signs were included as a control group for comparison. All of the 49 patients with pSS had normal findings on brain MRI.

Results: ^{99m}Tc ECD brain SPECT showed brain regions with hypoperfusion in 18 (56.3%) of the 32 patients, and parietal lobes were the most common areas with such lesions. By contrast, ^{99m}Tc ECD brain SPECT showed brain regions with hypoperfusion in only three (17.6%) of the 17 patients with pSS without neuropsychiatric symptoms or signs.

Conclusion: This study suggests that ^{99m}Tc ECD SPECT is a sensitive tool for detecting regions of hypoperfusion in the brains of patients with pSS and neuropsychiatric symptoms or signs and normal findings on brain MRI. However, a review of the literature showed that the ^{99m}Tc ECD SPECT findings in patients with pSS were non-specific.

Sjögren's syndrome (SS) is a common autoimmune connective tissue disease affecting a conservatively estimated 2% of the adult population.[1 2] It occurs most often in middle aged women and is mainly characterised by dryness of the eyes (keratoconjunctivitis) and mouth (xerostomia).[3] The neurological manifestations of SS were first described by Henrik Sjögren in 1933 and include stroke, seizure, cognition impairment, depression, mental retardation, drowsiness, syncope, vertigo, unstable gait, headaches, dizziness, insomnia, and memory impairment.[4] The overall occurrence of neuropsychiatric disturbances in SS has been estimated to be 28%.[5]

Because of the lack of effective imaging techniques, diagnosis of brain involvement in patients with SS is difficult. Magnetic resonance imaging (MRI) has been considered to be highly sensitive, and it has been used to identify structural lesions in patients with SS with definite neuropsychiatric manifestations.[6–8] However, neuropsychiatric manifestations may be silent and mild. Positron emission tomography (PET) can identify fluctuations in regional cerebral blood flow (rCBF), even when no structural brain lesions in MRI are present. However, PET is not suitable for routine clinical use owing to its expense and lack of availability compared with SPECT. Therefore, single photon emission tomography (SPECT) of the brain with technetium-99m hexamethylpropylene amine oxime (^{99m}Tc HMPAO) was used to assess regional cerebral blood flow (rCBF) in patients with primary SS (pSS) with or without neuropsychiatric manifestations and normal MRI findings.[9] However, ^{99m}Tc HMPAO is limited in that its rapid decomposition in vitro necessitates its use within 30 minutes of preparation and interpretable imaging must be delayed for at least 40 minutes after injection.[10 11] Technetium-99m ethyl cysteinate dimer (^{99m}Tc ECD) is presently under clinical evaluation as a new marker of rCBF because it is without the problems of radiochemical instability and delayed imaging.[11 12] To date, no complete reports have been published on the clinical application of ^{99m}Tc ECD SPECT to evaluate rCBF in the brains of patients with pSS.

Therefore, in this preliminary report, we used ^{99m}Tc ECD SPECT to detect abnormal rCBF in the brains of patients with pSS with neuropsychiatric manifestations and normal brain MRI findings.

PATIENTS AND METHODS

Patients

From January 1995 to December 2000 in Changhua county, Taipei city/county, Taichung city/county, and Tainan city/county, 32 female patients with pSS (aged 28 to 50) with definite neuropsychiatric symptoms or signs were enrolled in this study (table 1). Seventeen female patients with pSS (aged 28 to 50 years) with no neuropsychiatric symptoms or signs were included as the control group for comparison (table 2). Required criteria for enrolment comprised (*a*) ocular symptoms, (*b*) oral symptoms, (*c*) ocular signs (Schirmer-I test, ≤5 mm in five minutes), (*d*) histopathological features, (*e*) salivary gland involvement (salivary scintigraphy or unstimulated salivary flow, ≤1.5 ml in 15 minutes), and (*f*) autoantibodies, but excluding pre-existing lymphoma, acquired immunodeficiency syndrome, sarcoidosis, graft versus host

Abbreviations: MRI, magnetic resonance imaging; PET, positron emission tomography; pSS, primary Sjögren's syndrome; rCBF, regional cerebral blood flow; SLE, systemic lupus erythematosus; SPECT, single photon emission computed tomography; ^{99m}Tc ECD, technetium-99m ethyl cysteinate dimer; ^{99m}Tc HMPAO, technetium-99m hexamethylpropylene amine oxime

Table 1 Detailed data of the patients with primary Sjögren's syndrome with neuropsychiatric symptoms or signs

Patient No	Age (years)	Hypoperfusion regions on ^{99m}Tc ECD brain SPECT	Neuropsychiatric symptoms or signs	Serology		
				Anti-Ro (SS-A) antibody	Antiphospholipid antibodies	Antineuronal antibodies
1	28	Negative	Cognition impairment	–	–	–
2	28	Bil P-T-O	Unstable gait	+	+	–
3	29	L F-P-B	Cognition impairment	–	+	+
4	29	Negative	Memory impairment	–	+	+
5	30	Bil P-O	Memory impairment	–	+	+
6	31	Bil P-T-O	Dizziness, headache	+	+	–
7	33	Bil F-P-T	Conscious disturbance	+	–	–
8	33	L F-P-T	Vertigo	–	–	–
9	34	Negative	Frequent syncope	–	+	+
10	34	Bil P-T	Memory impairment	+	+	–
11	35	Negative	Seizure, headache	–	+	–
12	35	Negative	Memory impairment	–	+	–
13	35	Bil P-T	Memory and cognition impairment	–	–	–
14	36	Negative	Memory impairment	–	–	+
15	36	R P-T	Cognition and memory impairment	–	+	+
16	37	R F-P-T	Memory and cognition impairment	–	+	–
17	38	R P-O	Drowsiness, depression	–	–	–
18	39	Negative	Cognition impairment	–	–	+
19	40	Negative	Seizure, syncope	–		–
20	40	L F-P-T	Memory impairment	–	+	+
21	41	R F-P-T	Cognition impairment	+	–	+
22	42	Negative	Seizure, memory, and cognition impairment	–	–	+
23	43	L P-T-B	Depression		+	–
24	43	Negative	Memory impairment	–	–	–
25	43	Lt P-T-B	Drowsiness, depression	–	+	+
26	44	R F-P	Insomnia, depression	–	–	–
27	45	Bil F-P-T-B	Mental retardation, memory impairment	+	+	+
28	45	Negative	Cognition impairment	–	–	+
29	46	Negative	Cognition impairment	–	–	
30	48	Negative	Conscious disturbance	–	+	+
31	49	R F-P-B	Insomnia, dizziness	+	+	
32	50	Negative	Memory impairment	–	–	

L, left; R, right; Bil, bilateral; F, frontal lobe; P, parietal lobe; T, temporal lobe; O, occipital lobe; B, basal ganglion.

Table 2 Detailed data of the patients with primary Sjögren's syndrome without neuropsychiatric symptoms/signs

Patient No	Age (years)	Hypoperfusion regions on ^{99m}Tc ECD brain SPECT	Neuropsychiatric symptoms or signs	Serology		
				Anti-Ro (SS-A) antibody	Antiphospholipid antibodies	Antineuronal antibodies
1	28	Negative	Negative	–	–	–
2	30	Negative	Negative	–	–	–
3	34	Negative	Negative	–	–	–
4	34	Negative	Negative	–	–	–
5	35	Negative	Negative	–	–	–
6	36	Negative	Negative	–	–	–
7	37	R P-T	Negative	+	+	–
8	39	Negative	Negative	–	–	–
9	40	Negative	Negative	–	–	–
10	41	L F-P-T	Negative	–	–	+
11	42	Negative	Negative	–	–	–
12	43	Negative	Negative	–	–	–
13	44	R F-P	Negative	–	+	–
14	45	Negative	Negative	–	–	–
15	46	Negative	Negative	–	–	–
16	48	Negative	Negative	–	–	–
17	50	Negative	Negative	–	–	–

disease, and other allergic, immunological, and rheumatological diseases.[13] All of the 49 patients with pSS had normal findings on brain MRI. Three autoantibodies (anti-Ro (SS-A) antibody, antiphospholipid antibodies, and antineuronal antibodies) related to immunopathogesis of pSS with brain involvement were measured in the two groups of patients for comparison. None of the 49 patients had evidence of vasculitis.

A neurology consultant evaluated all of the 32 patients with pSS with definite neuropsychiatric symptoms or signs due to SS which were defined as those which could not be attributed to any other cause (such as uraemia, hypertension, or infection), and included stroke, seizure, cognition impairment, depression, mental retardation, drowsiness, syncope, vertigo, unstable gait, headaches, dizziness, insomnia, and memory impairment.

^{99m}Tc ECD SPECT of the brain

^{99m}Tc ECD was prepared according to the instructions on a commercial vial (Neurolite, Dupont Company, USA). The

Figure 1 A 40 year old healthy female control. Normal ^{99m}Tc ECD SPECT findings consisted of homogeneous rCBF in the grey matter of the cerebral cortex, basal ganglia, and cerebellum without focal hypoperfusion or visible asymmetry.

radiochemical purity of the final ^{99m}Tc ECD complex was measured by thin layer chromatography on Whatman MKC 18 plates developed with acetone and 0.5 M ammonium acetate (60:40). The radiochemical purity was calculated by comparing the peak for the ^{99m}Tc ECD complex with the sum of all other peaks on the plate.[12] The radiochemical purities of batches of ^{99m}Tc ECD were higher than 97%. Brain SPECT with ^{99m}Tc ECD was performed with the patients in a dark and quiet room. The position of the patient's head was fixed and maintained during SPECT imaging using a hemicylindrical plastic headholder with a radiolucent plastic neck contoured head rest. Fifteen to 45 minutes after intravenous ^{99m}Tc ECD injection (740 MBq), SPECT data were obtained using a dual headed gamma camera (ADAC, Vertex plus) equipped with fanbeam collimators. Data were collected from 64 projections in the 140 keV photopeak over 360° (180° for each head) in 128×128 matrices, with an acquisition time of 30 s/view. A zoom factor of 1.46 was used. After data acquisition, the data

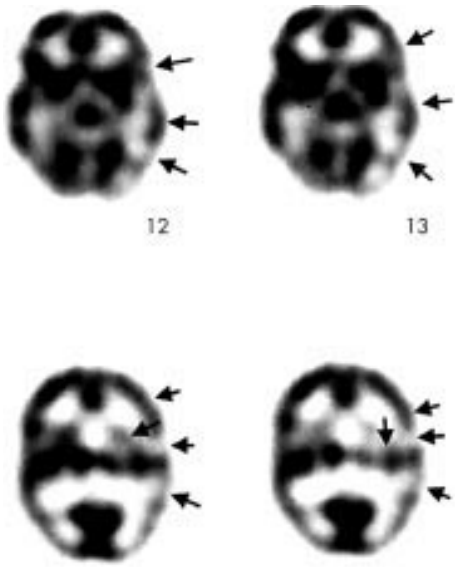

Figure 2 A 43 year old woman with primary Sjögren's syndrome and definite neuropsychiatric symptoms or signs (patient No 25 in table 1). ^{99m}Tc ECD SPECT showed regions of hypoperfusion in the left parietal-temporal lobes and basal ganglion (arrows).

were normalised for the correction of the rotating camera head speed in different directions (upward and downward) and decay of ^{99m}Tc from the first to last frame, so that the number of counts within each frame of SPECT was the same. Transaxial, coronal, and sagittal slices were reconstructed. Reconstruction of images was performed with attenuation correction using a Butterworth filter at the optimum cut off and order levels were determined by acquisition counts. For SPECT images, the transaxial sections were reoriented parallel to the base of the brain This enabled us to obtain coronal and sagittal reconstructions for the determination of the correct anatomical regions of the brains. After image reconstruction, all slices of the SPECT images were normalised to produce the final SPECT images, the contrast of which was set within the same range of 0–255 grey scales based on the computer screen. To identify areas of abnormal perfusion, visual interpretation of the SPECT images from each patient was carried out twice in random order with agreement of at least two of three independent experienced observers blind to the clinical information. Normal ^{99m}Tc ECD SPECT findings consisted of homogeneous rCBF in the grey matter of the cortex and basal ganglion without regions of hypoperfusion or visible asymmetry (fig 1). Abnormal findings included heterogeneous rCBF with regions of hypoperfusion or visible asymmetry on at least two consecutive slices noted twice by at least two of three observers (fig 2). This meant that at least four of a total of six individual interpretations had to be the same for an agreement.

RESULTS

Tables 1 and 2 show detailed data for the patients. ^{99m}Tc ECD brain SPECT showed regions of hypoperfusion in 18 (56.3%) of the 32 patients with pSS and definite neuropsychiatric symptoms or signs. By contrast, ^{99m}Tc ECD brain SPECT showed regions of hypoperfusion in only three (17.6%) of the 17 patients with pSS without neuropsychiatric symptoms or signs. Table 3 gives the detailed findings of ^{99m}Tc ECD SPECT of the brain in patients with pSS with definite neuropsychiatric symptoms or signs: (*a*) ^{99m}Tc ECD SPECT showed regions of hypoperfusion in the basal ganglion and cortex in five (15.6%) and 18 (56.3%) of the 32 patients with pSS; (*b*) parietal lobes were the most common hypoperfusion areas (56.3%, 18/32); (*c*) the cerebellum was the least common hypoperfusion area (0%, 0/32). In addition, there were significantly higher positive rates of anti-Ro (SS-A) antibody, antiphospholipid antibodies, and antineuronal antibodies in the 32 patients with definite neuropsychiatric symptoms or signs (21.9%, 53.1%, and 43.8%) than in the 17 patients without neuropsychiatric symptoms or signs (5.9%, 11.8%, and 5.9%), respectively (Fisher's test, $p<0.05$).

DISCUSSION

Exact sensitivity and specificity data of diagnostic modalities for the detection of brain anomalies in patients with pSS are unavailable. In a review of the literature, there has been only one report on the use of ^{99m}Tc HMPAO brain scans for the diagnosis of pSS with or without neurological manifestation and negative brain MRI findings.[1] ^{99m}Tc ECD is claimed to have at least two advantages over ^{99m}Tc HMPAO: it has better in vitro stability and has more rapid clearance from extracerebral tissue. These result in more favourable dosimetry and a better brain to background ratio than ^{99m}Tc HMPAO, therefore leading to better image quality. Previous reports comparing SPECT investigations with ^{99m}Tc ECD and ^{99m}Tc HMPAO in healthy volunteers and patients showed a superior image quality for ^{99m}Tc ECD.[14–17] This enabled an easier interpretation of which brain structures were affected. Therefore, in this preliminary study we used ^{99m}Tc ECD SPECT to detect abnormal brain regions in patients with pSS. In addition, our research is the first study to use ^{99m}Tc ECD SPECT for diagnosing brain

Table 3 Detailed findings of ^{99m}Tc ECD brain SPECT in the patients with primary Sjögren's syndrome and neuropsychiatric symptoms or signs

	Hypoperfusion lesions on ^{99m}Tc ECD brain SPECT						
	Frontal lobe	Parietal lobe	Temporal lobe	Occipital lobe	Basal ganglion	Cerebellum	Total
Patient No	9	18	12	4	5	0	18
%	28.1	56.3	37.5	12.5	15.6	0.0	56.3

involvement in pSS. In our study, ^{99m}Tc ECD SPECT showed regions of hypoperfusion in the brains of 56.3% and 17.6% of patients with pSS with and without definite neuropsychiatric symptoms or signs respectively. Our findings were very similar to the results of a previous study using ^{99m}Tc HMPAO brain SPECT.[9] Some semiquantitative methods (such as calculations of regional indices) for the interpretation of the ^{99m}Tc ECD SPECT findings have been reported.[18] However, we did not think that the method was valuable for our study as brain involvement in patients with pSS is always multifocal and can symmetrically affect the brain structure.

Brain regions with hypoperfusion as shown by ^{99m}Tc ECD SPECT are relatively non-specific. These abnormal features may be secondary to subclinical brain involvement. Also according to our results, most hypoperfused areas were found in the parietal lobes—the territory of the middle cerebral artery (MCA)— and the territory of the MCA is at higher risk for cerebral vascular abnormalities resembling embolism than other territories.[19] However, a comparison of the the brain SPECT findings for rCBF previously reported in patients with systemic lupus erythematosus (SLE)[20–22] showed that ^{99m}Tc ECD SPECT findings in patients with pSS were non-specific and similar brain regions showing hypoperfusion have been found in various other acute neurological disorders, including infarction and dementia.[23 24] Nishimura *et al* suggested that neuropsychiatric dysfunctions associated with SS were at least in part attributable to small vessel vasculopathies such as focal inflammation or oedema.[25] Gerraty *et al* suggested that cerebral vasculitis is the pathogenetic mechanism of the brain manifestations of SS.[26] Berman *et al* described angiographic evidence of cerebral vasculitis and multiple infarcts present on neuroimaging in a patient with SS and brain involvement.[27] de-la-Monte *et al* examined brain abnormalities in 11 patients with SS and found cerebral vasculopathy, including necrotising vasculitis.[28] Alexander *et al* studied 16 patients with SS and brain disorders and suggested that an immune vasculopathy may play a part in the pathogenesis of disease of the central nervous system in SS.[29] Because vasculopathy is the major pathogenesis in SS with neuropsychiatric symptoms or signs, as suggested by previous studies,detection of changes in rCBF may be easier than detection of structural changes.[25–29] However, no patient had a brain biopsy; therefore we cannot provide any pathological evidence of vasculitis of cerebral arteries in the patients in our study.

On the ^{99m}Tc ECD SPECT, relatively higher uptake was found in the frontal lobe, parietal lobe, occipital lobe, left superior temporal temporal lobe, and superior region of the cerebellum. On the ^{99m}Tc HMPAO SPECT, relatively higher uptake was seen in the medial lobes, thalami, periventricular white matter, and brain stem.[30] In all brain regions, ^{99m}Tc ECD SPECT showed a higher lesion contrast than ^{99m}Tc HMPAO SPECT; therefore, the sensitivity in lesion detection of ^{99m}Tc ECD was superior to that of ^{99m}Tc HMPAO.[31 32] In addition, ^{99m}Tc HMPAO is limited in that its rapid decomposition in vitro necessitates its use within 30 minutes of preparation and interpretable imaging must be delayed until at least 40 minutes after injection. By contrast, ^{99m}Tc ECD does not have problems of radiochemical instability and delayed imaging. Therefore, in this study, we selected ^{99m}Tc ECD to evaluate rCBF in patients with pSS.

We conclude that ^{99m}Tc ECD brain SPECT is a more sensitive tool than brain MR I for detecting regions of hypoperfusion in patients with pSS and neuropsychiatric symptoms or signs. Therefore, we recommend that ^{99m}Tc ECD brain SPECT should be a standard implement for evaluaing regions of hypoperfusion in the brain of patients with pSS and neuropsychiatric symptoms or signs. Also, ^{99m}Tc ECD brain SPECT is a potential tool for early and objective identification of brain involvement in patients with pSS. This allows for early treatment and monitoring of the response to avoid severe complications.

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