A Higher Prevalence of Abnormal Regional Cerebral Blood Flow in Patients With Syndrome X and Abnormal Myocardial Perfusion

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SUMMARY

To test the hypothesis that syndrome X is a systemic vascular disorder, technetium-99m ethyl cysteinate dimer (Tc-99m ECD) brain single photon emission computed tomography (SPECT) was used to detect abnormal regional cerebral blood flow (rCBF) in 30 patients with syndrome X.

These patients were separated into group 1, 20 patients with definite myocardial perfusion defects diagnosed by thallium-201 (Tl-201) myocardial perfusion SPECT; and group 2, 10 patients without any myocardial perfusion defects.

Tc-99m ECD brain SPECT demonstrated hypoperfusion brain lesions in 95% (19/20) and 20% (2/10) of patients in groups 1 and 2, respectively. This difference in the incidence between the two groups was significant. In group 1 and 2 patients, parietal lobes were the most common hypoperfusion areas, while the cerebellum was the least common hypoperfusion area of the brain.

Syndrome X is a systemic vascular disorder with a high incidence of hypoperfusion lesions of the brain based on the findings of Tc-99m ECD brain SPECT, and is usually coincident with myocardial defects based on the Tl-201 myocardial perfusion SPECT findings. (Jpn Heart J 2003; 44: 145-152)

Key words: Regional cerebral blood flow, Tc-99m ECD brain SPECT, Syndrome X

SOME 20%-30% of all patients undergoing coronary angiography have normal or near-normal coronary arteries.¹⁾ In 1973, Kemp²⁾ introduced the term syndrome X to describe patients with chest pain and a normal coronary angiogram. Investigations over the past two decades have not found a specific cause for syndrome X. It is now acknowledged that syndrome X most likely encompasses several pathophysiological diseases. In the presence of normal coronary arteries, many explanations have been put forth to explain myocardial ischemia, including small

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vessel abnormalities, coronary artery spasm, cardiomyopathy, metabolic abnormalities, misinterpretation of the coronary angiograms, impaired coronary flow reserve, oxyhemoglobin dissociation defects, psychosomatic factors, altered pain perception, increased sympathetic drive, and endothelial dysfunction.^{3,4)}

Although most studies have focused on functional changes of the heart,^{5,6)} neuroregulatory abnormalities, extracardiac symptoms like migraine, pathologic pain perception and a reduced vasodilator reserve in peripheral vessels have been demonstrated in patients with syndrome X, pointing to a more generalized disease.^{7,8)} From a review of the literature, there has been only two previous studies published concerning the application of technetium-99m hexamethylpropylene amine oxime (Tc-99m HMPAO) brain single photon emission computed tomography (SPECT) in patients with syndrome X.^{9,10)} However, Tc-99m HMPAO is limited in that its rapid decomposition *in vitro* necessitates its usage within 30 minutes of preparation and interpretable imaging delayed at least 40 minutes after injection is necessary.^{11,12)} Technetium-99m ethyl cysteinate dimer (Tc-99m ECD),^{12,13)} which is without the problems of radiochemical instability and delayed imaging, is presently under clinical evaluation as a new marker of rCBF. To date, no complete reports have been published concerning the clinical application of Tc-99m ECD brain SPECT to evaluate rCBF in patients with syndrome X.

Therefore, to test the hypothesis that syndrome X is a systemic vascular disorder, we used Tc-99m ECD brain SPECT to detect abnormal rCBF in two homogenous groups of patients with syndrome X.

PATIENTS AND METHODS

Patients: Thirty patients (12 females and 18 males, ages, 37 to 50 years) with syndrome X defined as typical anginal chest pain, a positive stress ECG test finding, and normal coronary arteries on angiography were enrolled in this study. All 30 patients had normal values for left ventricular ejection fraction, body mass indexes, total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides. The patient characteristics are shown in Table I. Patients with neuropsychiatric symptoms/signs or with a history of cerebral ischemia, hypertension, diabetes, smoking, or other known cerebral disorders and systemic vascular diseases were excluded. Dipyridamole-stress and resting thallium-201 (Tl-201) myocardial perfusion SPECT studies were performed in all 30 patients. Each thallium-201 myocardial perfusion SPECT result was interpreted by the agreement of at least two of three observers without knowledge of the patient prior histories, results of stress ECG, or coronary angiogram findings. Based on the Tl-201 myocardial perfusion SPECT results, the 30 patients were separated into group 1: 20 patients (8 females, 12 males, ages, 38 to 50 years) who had positive

Table I. Patient Characteristics

	Normal Reference	Group 1	Group 2	<i>P</i> value
F/M		8/12	4/6	
Age (years)		38–50	37–49	
LVEF	> 50	56.1±3.5	55.3±3.2	< 0.05
BMI (kg/m ²)	18.5–27	24.2±2.7	23.9±3.5	< 0.05
T-Chol (mg/dL)	125–240	213.2±11.2	210±12.9	< 0.05
HDL-C (mg/dL)	> 35	52.1±4.0	51.2±4.8	< 0.05
LDL-C (mg/dL)	< 160	145.3±7.2	143.1±8.9	< 0.05
TG (md/dL)	20–200	156.3±10.1	158.4±10.2	< 0.05

F = female, M = male; LVEF = left ventricular ejection fraction; BMI = body mass index; T-Chol = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride.

Tl-201 myocardial perfusion SPECT findings, including 12 patients with reversible defects, 5 patients with persistent defects, and 3 patients with reverse redistribution; as well as group 2: 10 patients (4 females, 6 males, ages, 37 to 49 years) who had negative Tl-201 myocardial perfusion SPECT findings.

Tl-201 myocardial perfusion SPECT: The patients were instructed to avoid coffee, tea, and drinks containing caffeine for 24 hours before Tl-201 myocardial perfusion SPECT. They were also instructed to fast for at least 2 hours before the stress studies. An intravenous line of normal saline solution, with a 20 gauge cannula, was positioned in an antecubital vein. The dose of the dipyridamole infusion was 0.28 mg/kg over a 4-minute interval (0.07 mg/kg/min). Two mCi of Tl-201 was injected 3 minutes after the dipyridamole infusion. Tl-201 myocardial perfusion SPECT was performed on a rotating dual-head gamma camera with a low energy, medium sensitivity, medium resolution collimator. A symmetric 10% window was centered at 71 keV, and images were acquired into a 64×64 computer matrix through a 180° rotation at an angular interval of 30° for RAO 45° to LPO 45°. Reconstruction was performed by a standard back projection using a Hanning filter for a 64×64 matrix image. After a four-hour rest, the redistribution Tl-201 myocardial SPECT was obtained. Acquisition parameters were identical for both the stress and redistribution studies.

Tc-99m ECD brain SPECT: Tc-99m ECD was prepared according to the manufacturer's instructions (Neurolite, Dupont Company, USA). The radiochemical purity of the final Tc-99m 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 Tc-99m ECD complex to the sum of all other peaks on the plate.¹³⁾ The radiochemical purities of Tc-99m ECD were higher than 97%. Tc-99m ECD

brain SPECT was performed with 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 Tc-99m 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 sec/view. A zoom factor of 1.46 was used. After data acquisition, the data were normalized for the correction of the rotating camera head speed in different directions (upward and downward) and decay of Tc-99m from the first to last frame. The number of counts within each frame of SPECT was the same. Transaxial, coronal, and sagittal slices were reconstructed. Image reconstruction was performed with attenuation correction using a Butterworth filter at the optimum cut-off and order levels determined by the acquisition counts. For SPECT images, the transaxial sections were reoriented parallel to the base of the brain to obtain coronal and sagittal reconstructions in order to determine the proper anatomical regions of the brain. After image reconstruction, all slices of the SPECT images were normalized to produce the final SPECT images whose contrast was set within the same range of 0-255 gray 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 by the agreement of at least two of three independent experienced observers blind to the clinical information. Normal Tc-99m ECD brain SPECT findings consisted of homogenous rCBF in the gray matter of brain cortex and basal ganglion without hypoperfusion lesions or visible asymmetry (Figure 1). Abnormal findings included heterogeneous rCBF with hypoperfusion

Figure 1. Healthy female control. Normal Tc-99m ECD brain SPECT findings consisted of homogenous regional cerebral blood flow in the gray matter of the cerebral cortex, basal ganglia, and cerebellum without focal hypoperfusion or visible asymmetry.

Figure 2. Forty-two year-old female patient. Tc-99m ECD brain SPECT revealed multiple small hypoperfusion lesions in the bilateral cerebral cortex and basal ganglia.

lesions or visible asymmetry on at least two consecutive slices noted twice by at least two observers (Figure 2).

RESULTS

The results showed that 95% (8 females and 11 males) of 20 group 1 patients and 20% (1 female and 1 male) of 10 group 2 patients, respectively, had hypoperfusion lesions on Tc-99m ECD brain SPECT. The statistical difference in the incidence of positive Tc-99m ECD brain SPECT findings between groups 1 and 2 was significant (P value < 0.001 , Fisher's exact test). In addition, parietal lobes were involved in all of the patients in both groups 1 (95%, 18/20) and 2 (20%, 2/10). Cerebellum was the least involved area in both group 1 (10%, 2/20) and 2 (0%, 0/10) patients (Table II).

Table II. Detailed Results of Tc-99m ECD Brain SPECT Findings

Hypoperfusion Lesions on Tc-99m ECD Brain SPECT							
	Total	Frontal Lobe	Parietal Lobe	Temporal Lobe	Occipital Lobe	Cerebellum	Basal Ganglia
Group 1 ($n=20$)	19 95%	10 50%	19 95%	15 75%	8 40%	2 20%	10 50%
Group 2 ($n=10$)	2 20%	1 10%	2 20%	1 10%	0 0%	0 0%	1 10%

DISCUSSION

Tc-99m ECD is claimed to have at least two advantages in comparison to Tc-99m HMPAO: better *in vitro* stability and rapid clearance from extracerebral tissue. These result in a more favorable dosimetry and a better brain-to-background ratio than Tc-99m HMPAO, therefore leading to better image quality. Previous reports, which compared SPECT investigations with Tc-99m ECD and Tc-99m HMPAO in healthy volunteers or patients, demonstrated a superior image quality for Tc-99m ECD¹⁴⁻¹⁷⁾ making it easier to interpret affected and unaffected brain structures. On the Tc-99m ECD brain SPECT, relatively higher uptake was observed in the frontal lobe, parietal lobe, occipital lobe, left superior temporal lobe, and superior region of the cerebellum. On the Tc-99m HMPAO brain SPECT, relatively higher uptake was observed in the medial lobes, thalami, periventricular white matter, and brain stem.¹⁸⁾ Therefore, in the preliminary report, we used Tc-99m ECD brain SPECT to detect brain lesions in patients with syndrome X. In addition, our research is the first study to use Tc-99m ECD brain SPECT for diagnosing brain involvement in patients with syndrome X.

Our results showed that Tc-99m ECD brain SPECT is a sensitive method for detecting hypoperfusion brain lesions in 70% (21/30) of patients with syndrome X. These findings are similar to previous study results (72/95, 76%) using Tc-99m HMAO brain SPECT.¹⁰⁾ However, these abnormal features may be secondary to subclinically functional brain involvement, because patients with neurologic symptoms or with a history of cerebral ischemia and other known cerebral disorders were excluded from this study.

In addition, group 1 patients (19/20, 95%) with positive Tl-201 myocardial perfusion SPECT findings demonstrated a higher incidence of positive Tc-99m ECD brain SPECT findings than that of group 2 patients (2/10, 20%) with negative Tl-201 myocardial perfusion SPECT findings. These findings are in agreement with those of a previous study using Tc-99m HMAO brain SPECT.⁹⁾ The parietal lobes were predominantly affected and more than one brain region was involved in most of the patients (Table II). These findings are similar to those of previous reports.^{9,10)} According to our results, most hypoperfused brain lesions (parietal lobes) are in the territory of the middle cerebral artery (MCA), most likely because the territory of the MCA is at a higher risk for cerebral vascular abnormalities resembling embolism than other territories. However, the hypoperfusion lesions demonstrated on Tc-99m ECD brain SPECT in this study are relatively nonspecific. Similar hypoperfusion anomalies in the brain can be found in a variety of psychoneurologic disorders.¹⁹⁻²¹⁾ Therefore, we were not able to detect a consistent pattern of brain involvement "typical" for syndrome X.

In conclusion, there was a high prevalence of abnormal brain hypoperfusion

(positive Tc-99m ECD brain SPECT findings) in group 1 syndrome X patients with microvascular cardiac disorders (positive thallium-201 myocardial SPECT results). The relationship between syndrome X patients with positive Tc-99m ECD brain SPECT findings and with positive Tl-201 myocardial perfusion SPECT findings is suggestive of perfusion abnormalities not only in the brain but also in the myocardium. Our observations support the hypothesis of a generalized disturbance of vascular function in syndrome X as postulated by Sax, *et al*²²⁾ and our previous study.⁹⁾ They found an impaired vasodilator reserve in the peripheral vascular bed of syndrome X. However, a more intensive evaluation of extracardiac vessels will be necessary to better understand the pathophysiology of syndrome X. In addition, further longitudinal studies to follow up and compare the outcomes of these patients are necessary to confirm that syndrome X with abnormal brain SPECT is more likely to develop symptomatic neuropsychiatric sequelae.

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