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# Evaluation of SPECT Analysis in Patients with Transient Global Amnesia

Bo-Young Choe*, Euy-Neyng Kim[1], Yong-An Chung[1], Hyung-Sun Sohn[1], Sung-Hoon Kim[1], Soo-Kyo Chung[1], Hyoung-Koo Lee, Tae-Suk Suh

Departments of Biomedical Engineering, [1]Nuclear Medicine, Kang-Nam St. Mary's Hospital, College of Medicine, The Catholic University of Korea, #505 Banpo-Dong, Seocho-Gu, Seoul 137-040, Korea

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***Abstract :*** Objectives: This study investigated alterations in regional cerebral blood flow (rCBF) in patients with transient global amnesia (TGA) using statistical parametric mapping 99 (SPM99).
Methods: Noninvasive rCBF measurements using 99mTc-ethyl cysteinate dimer (ECD) SPECT were performed on 8 patients with TGA who have ongoing symptoms and 17 age matched controls. The relative rCBF maps in patients with TGA and controls were compared.
Results: In patients with TGA, significant decreased rCBF was found along the L superior temporal extending to L parietal region of the brain and L thalamus. There were areas of increased rCBF in the R temporal, R frontal region and R thalamus.
Conclusion: We could demonstrate decreased perfusion in left cerebral hemisphere and increased perfusion in right cerebral hemisphere in patients with TGA using SPM99. The imbalanced change of rCBF between bilateral cerebral hemisphere in patients with TGA might suggest that imbalanced neuronal activity between the bilateral hemispheres may have strong relationship to the pathogenesis of the TGA. For quantitative SPECT analysis in TGA patients, we recommend SPM99 rather than the ROI method because of its definitive advantages.
Key Words: brain, rCBF, transient global amnesia, and statistical parametric mapping

## INTRODUCTION

Transient global amnesia (TGA) is a clinical syndrome characterized by sudden loss of memory of recent events, transient inability to retain new information, and retrograde amnesia in the absence of other neurological signs and symptoms, resolving within 24 hours Its etiology remains unknown although transient ischemic attacks, epilepsy, or migraine

* To whom : bychoe@catholic.ac.kr

have been proposed as possible causes [1-3]. It has been several reports about the various findings of single photon emission computed tomography (SPECT) in patients with TGA [4-10]. The findings include unilateral reduction of regional cerebral blood flow (rCBF) in the left medial temporal lobe [4], uni- or bilaterally decreased rCBF in the posteromedial part of B temporal lobes or thalamus [5-7], unilateral increased rCBF in right temporal region [8-9], and unilateral increased rCBF in left temporal region [10].

Formerly, the region of interest (ROI) method has been used to conventional analysis of positron emission tomography (PET) or SPECT imaging to detect intra-individual CBF changes in patients with certain organic illnesses such as TGA. However, it has long been known that ROI definition, particularly on functional images, is time-consuming, subjective and prone to operator bias. Large ROIs, encompassing an entire brain structure, may dilute small regional differences, with a subsequent loss of sensitivity. ROI analysis lacks the power to accurately distinguish regional variations between a set of images. The solution to this problem has been the development of pixel-based statistical analyses, where the regions are effectively reduced to single pixels. Statistical parametric mapping 99 (SPM99) is a system for making pixel-by-pixel statistical comparisons between sets of images [11]. Originally developed for the analysis of PET and functional magnetic resonance imaging activation studies, SPM99 is now being applied to the pixel-based analysis of patient and control groups [12, 13], and may be useful in measuring regional neurodegeneration in disorders like Parkinson's disease [14, 15].

Recently, we encountered eight cases of TGA diagnosed according to the criteria of Hogdes and Warlow [2]. These patients underwent a brain SPECT study a 1-3 days after the disappearance of amnesic episode. To evaluate rCBF difference in patients with TGA, we carried out quantitative CBF analysis using the SPM99 method in 8 cases of TGA patients and control groups.

## MATERIAL AND METHOD

### *Subjects*

Noninvasive rCBF measurements using $^{99m}$Tc-ethyl cysteinate dimer (ECD) SPECT were performed on 8 patients with TGA (M:F = 4:4, Ages: 57-69 years, mean 63 years) and 17 age-matched healthy controls (M:F = 7:10, Ages: 56-69 years, mean 62 years). We used the raw data to compare these two groups with SPM99. The diagnosis of TGA was established according to diagnostic criteria [2], administered by a trained clinician. None of the patients had a history of epilepsy, migraine or cerebral ischemic events. During TGA, neurological examination disclosed no physical abnormalities or cognitive deficits other than amnesia. The beginning of the resolution of amnesia was assessed by repeatedly probing patients' orientation and memory for the course of the examination. At the time of the SPECT study, amnesia was fully resolved.

Healthy control had no self-reported personal or familial psychiatric history. All

subjects gave written informed consent to participate in the study. The Human Subjects Committee at the Catholic Medical Center approved the study.

***SPECT***

SPECT imaging was initiated 20 minutes after intravenous injection of approximately 740-925 MBq of $^{99m}$Tc ECD using a multi-detector scanner (ECAM plus; Siemens, Erlangen, Germany) equipped with a low-energy, fan-beam collimator. The head unit consists of two rings of 59 probe-type detectors. Inside the right of crystals, there is a rotating collimator with septa varying from 0 degree to 35.2 degree. Both the detector ring and the collimator rotate. Data were acquired on 128 x 128 matrix with a 20 % symmetric window at 140 keV. Continuous transaxial tomograms of the brain were reconstructed after filtered backprojection with a Butterworth (cutoff frequency 0.4 cycles/pixel, order 5) to reduce statistical noise. $^{99m}$Tc ECD images were corrected for tissue attenuation using a standard commercial correction routine, which assumes uniform attenuation with the circular shape of the head.

***Image Formatting***

All subsequent image manipulation and data analysis were performed on a personal computer using a WIN 98 operating system (Microsoft, Redmond, Wash, USA). The software for image manipulation included Matlab, version 5.3 (Mathworks, Inc., Natick, MA) and statistical parametric mapping 99 (SPM99: Institute of Neurology, University College of London, UK) software [16].

The reconstructed SPECT data with attenuation and scatter correction were reformatted into Analyze (Mayo Foundation, Baltimore, Md., USA) header format. The header format of the SPET data includes 348 bytes of header, 3.9 mm of $x$ and $y$ pixel size, and 3.9 mm of slice thickness. The SPECT images of the control group and TGA patients were separately co-registered to remove variations due to different size and shape of individual brains. The parameters for co-registration were: intra-modality, linear algorithm, 12 affine parameter model for controlling the number of degrees of freedom used in registration, and tri-linear interpolation. All slices of a brain image were then sampled and averaged to arrive at mean pixel intensity for that image. The intensity threshold was set at 80% of the whole-brain mean. This level eliminated low-intensity background noise inherent in the images and effectively removed brain-edge halo caused by partial-volume error, without losing any image data specific to the brain. The global cerebral blood flow rate was normalized to an arbitrary mean of 50 ml/100 ml per minute by a group-wise analysis of covariance (ANCOVA). The data were then normalized to a better resolution

SPECT template (MNI template: Montreal Neurological Institution Template)[17] and smoothed with 8 mm FWHM prior to SPM99 statistical analysis. The final image format was 16-bit, with a size of 79 x 95 x 68 and a voxel size of 2 x 2 x 2 mm. For the graphic resentation of the results, sections were displayed as transverse, sagittal and coronal slices with a hot color map.

***Image analysis***

The normalized SPECT data of investigation was compared to a normal database constituted from 17 subjects without morphological or neurological pathology for detection of hypo- or hyperperfusion areas. After specifying the appropriate design matrix, changes in rCBF produced by the different subject groups were estimated according to the general linear model at each voxel. An ANCOVA model was fitted, and a t-statistic image (SPM [t]) for the contrast condition effect was constructed. The resulting set of voxel t-values constitutes the statistical parametric mapping SPM [t] with a threshold value of 3.30 (or P = 0.001, uncorrected) and a minimal cluster size of 50 voxels. For visualization of the *t*-score statistics, the *t*-score voxel clusters were projected onto the standard high-resolution MRI data set, using the projection protocol, which additionally displays the Talairach coordinates, thus allowing anatomic identification.

## RESULTS

As compared with control group, SPECT of TGA patients showed decreased uptake of radiotracer within the left temporal gyrus, postcentral gyrus and supramarginal gyrus of left parietal lobe, left posterior cingulate, left thalamus, and left precentral gyrus (Table 1).

Table 1. Areas of decreased rCBF in patients with TGA

| Regions | Number of Voxels in Cluster | Voxel T | x,y,z {mm} |
|---|---|---|---|
| L Superior Temporal Gyrus | | 8.68 | -56, -4, -2 |
| L Parietal Lobe, Postcentral Gyrus | 6785 | 8.03 | -52, -20, 32 |
| L Parietal Lobe, Supramarginal Gyrus | | 7.99 | -56, -48, 30 |
| L Posterior Cingulate | 436 | 7.03 | -22, -60, 12 |
| L Thalamus | 363 | 5.90 | -8, -24, 16 |
| L Precentral Gyrus | 179 | 5.01 | -28, -22, 52 |
| L Parietal Lobe | 157 | 4.58 | 20, -42, 38 |

L: left, R: right

In patients with TGA, there were areas of increased uptake of radiotracer in the right temporal lobe, right inferior frontal gyrus, anterior cingulate gyrus, right cerebellum, and right thalamic pulvinar (Table 2). Fig. 1 is fused images of SPM99 results and template T1 weighed high-resolution brain MRI, allowing anatomical identification. Fig. 2 is maximum intensity projection images of differences of rCBF between two groups.

Table 2. Areas of increased rCBF in patients with TGA

| Regions | Number of Voxels in Cluster | Voxel T | x,y,z {mm} |
|---|---|---|---|
| R Temporal Lobe (Middle Temporal Gyrus) | 1508 | 9.98 | 66, -42, 10 |
| R Inferior Frontal Gyrus | 130 | 4.99 | 60, 26, 2 |
| Anterior Cingulate Gyrus | 74 | 4.70 | 18, 38, 10 |
| R Cerebellum | 196 | 4.68 | 48, -72, -44 |
| R Inferior Frontal Gyrus ( Brodmann area 47) | 56 | 4.41 | 50, 40, -12 |
| Thalamus, Pulvinar | 93 | 4.21 | 16, -28, 6 |

L: left, R: right

## DISCUSSIONS

Because TGA episodes are short-lived by nature, most patients are not seen during the acute phase and it is difficult to obtain brain SPECT during acute episode. However, because the changes in CBF causing TGA appear to last longer than the clinical manifestation, there are several reported cases in which positive SPECT findings were obtained within 4 days of onset [18-19]. As in many clinical situations, if SPECT is performed a few days after the onset of TGA, the changes in CBF may be too subtle to be detected by qualitative methods such as ROI studies. In this study, however, with the aid of the SPM99 method, we were able to find abnormal regional CBF in SPECT 2-3 days after resolution of the TGA attack with regard to comprehensiveness, objectivity, and reliability superior to conventional methods including the ROI.

There are variable discrepancies between the results of the functional imaging studies in patients with TGA. It might be due to different timing of the SPECT examinations in respect to the chronology of each individual attack. Jung HH et al.[8] described a case of TGA with serial brain SPECT. In this report, first brain SPECT study during the TGA attack disclosed a focus of increased activity uptake in the posterior caudal region of the right medial temporal lobe. Second SPECT study three weeks after TGA disclosed slightly decreased activity uptake in the region of the previously demonstrated increased uptake in right temporal region and, in addition, decreased activity uptake in the region of the left

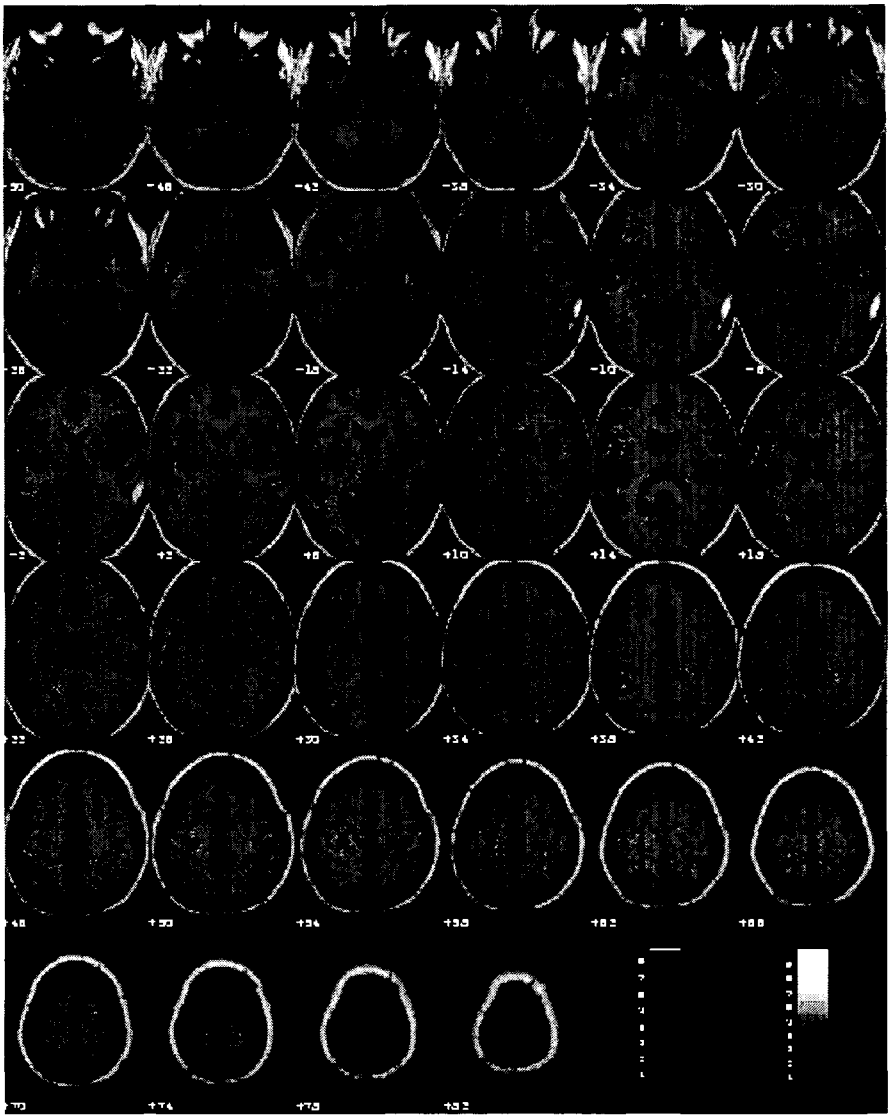

Fig. 1. Fusion of SPM99 results to transverse template T1 weighted high-resolution brain MRI. Areas of increased (red) and decreased (blue) rCBF are noted in patients with TGA (n=8) compared with normal control (n=17).

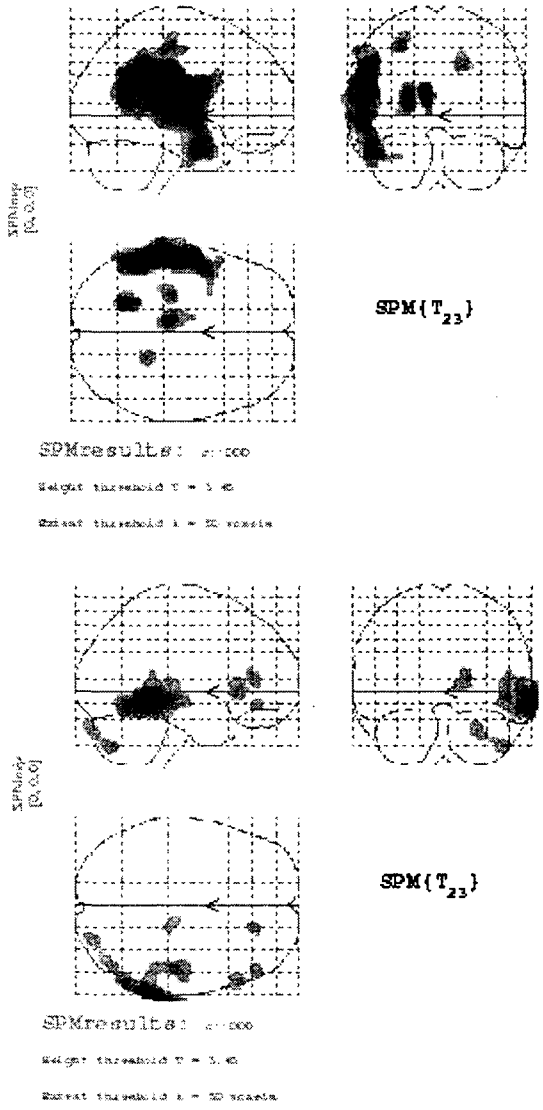


Fig. 2. Maximum intensity projection images of decreased rCBF (top) and decreased rCBF (bottom) in patients with TGA (n=8) compared with normal control (n=17).

temporal lobe pole. Third SPECT study three months after transient global amnesia, showed symmetric activity uptake. In this reports, they suggested that the hyperperfusion seen during this TGA attack might be due to dynamic phenomena similar to those seen in migraine attacks. The result of second SPECT was similar to that of this study, so it is

supposed that the discrepant result of this study might be due to chronological etiology.

The pathogenesis of the functional changes leading to TGA remains controversial. Most SPECT studies performed during or soon after it have shown changes of perfusion in memory relevant brain structures, suggesting a primary change of rCBF due to functional vascular changes or a secondary diminution due to decreased neuronal activity [4-7]. Warren JD et. al [20] suggested that because the right hemisphere and left temporal lobe may reflect episodic memory retrieval and memory encoding respectively, involvement of the right hemisphere or both cerebral hemispheres consistently predicts severe retrograde amnesia, in addition to the typical loss of anterograde memory observed during TGA. Regarding the proposed concept of 'acute arterial dyscontrol' in TGA, Asada T et al. [9] suggested that impaired CBF, either decreased or increased transient self-limited alternation of vascular tone in the posterior circulation might cause TGA.

It is still unknown whether there is some compensatory reaction between the left temporal region and right temporal region related to memory function in TGA or not, it is postulated that the imbalanced change of rCBF or neuronal activity between bilateral cerebral hemisphere is strongly related to TGA as seen in results of this study.

In summary, we could demonstrate decreased perfusion in left cerebral hemisphere and increased perfusion in right cerebral hemisphere in patients with TGA using SPM99. The imbalanced change of rCBF between bilateral cerebral hemisphere in patients with TGA might suggest that imbalanced neuronal activity between the bilateral hemispheres may have strong relationship to the pathogenesis of the TGA. The quantitative SPECT analysis appears to be valuable for the evaluation of TGA as shown hear. For this purpose, we recommend SPM99 rather than the ROI method because of its definitive advantages.

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