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ORIGINAL ARTICLE

Transient global amnesia: a study with Tc-99m ECD SPECT shortly after symptom onset and after recovery

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PURPOSE
Transient global amnesia (TGA) is characterized by sudden loss of memory of recent events, transient inability to retain new information, and retrograde amnesia. We investigated the changes of regional cerebral blood flow in patients with TGA shortly after symptom onset and after recovery using Tc-99m-ethyl cysteinate dimer single-photon emission computed tomography (Tc-99m ECD SPECT) and statistical parametric mapping (SPM) analysis.

METHODS
Six right-handed patients with TGA were studied using Tc-99m ECD SPECT shortly after symptom onset and after recovery. As a control group, six healthy individuals were also studied. Images were analyzed using SPM8 using voxel-based analysis to estimate the differences between TGA patients and controls.

RESULTS
There was significant hypoperfusion in the left hippocampus, left thalamus, and bilateral cerebellum. In the follow-up SPECT scan, hypoperfusion in hippocampus and thalamus were restored, while hypoperfusion was noted in the temporoparietal region.

CONCLUSION
Our results suggest that the underlying mechanism of TGA may be temporary ischemia in the hippocampus and thalamus. There was significant restoration of perfusion in the hippocampus and thalamus after recovery from TGA.

Transient global amnesia (TGA) is characterized by a sudden onset of anterograde and retrograde amnesia that lasts up to 24 hours without other neurologic signs or symptoms (1–3). Although epilepsy, transient thromboembolic ischemia, and migraine have been suggested to play a role in its pathophysiology (4), regions of the brain that are responsible for critical memory loss during TGA attacks are yet to be elucidated.

Given the common impairment of explicit memory during the attack, damage of mesial temporal formation has been suggested in TGA. Several studies have attempted to identify structural and functional problems of mesial temporal formation in TGA. One study found increased size and incidence level of cavities in hippocampal area in TGA compared with normal volunteers (5). Recent studies using diffusion-weighted imaging (DWI) also have pointed out abnormalities in the hippocampus (6). The findings in brain perfusion studies are controversial during TGA attack. Decreased perfusion in mesial temporal regions, basal ganglia, and thalamus has been reported (7). On the other hand, some studies showed increased perfusion in various limbic regions such as hippocampus, amygdala, and thalamus (1, 8, 9). However, most publications describing findings of single-photon emission computed tomography (SPECT) in such patients are in the form of case reports or small cohorts in which the authors have depended upon visual inspection or region of interest (ROI) method. These numerical and methodologic limitations obstruct detection of subtle changes in regional cerebral blood flow (rCBF) during TGA.

Statistical parametric mapping (SPM) is a statistical technique created by Karl Friston for examining differences in brain activity recorded during functional neuroimaging experiments using neuroimaging technologies such as functional magnetic resonance imaging or positron emission tomography. This approach produces a "map" of the scanned area (using x, y, and z axis coordinates) that is represented as voxels. Each voxel typically represents

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the activity of a particular coordinate in three-dimensional space. The exact size of a voxel will vary depending on the technology used.

In this study, we aimed to use SPM analysis and Tc-99m-ethyl cysteinate dimer (ECD) SPECT scan in TGA shortly after symptom onset and after recovery to examine if the hippocampus is preferentially affected during TGA attack and whether such changes in rCBF in the hippocampus are related with the disappearance of amnesic episode.

Methods

Subjects

Six right-handed patients with TGA (mean age 55±3.2 years; five males, one female) underwent Tc-99m ECD SPECT after attack (1–7 days) and four patients completed the follow-up scan after recovery (1–60 months). Patients with cerebrovascular disorders, seizures, or recent head injury were excluded during the initial recruitment. One patient had prior history of TGA, but this did not affect the next event. The following variables were recorded for each patient during the clinical interview: age, gender, diabetes mellitus, hypertension, epilepsy, and trauma history. Clinical data are summarized in Table 1.

Seven healthy volunteers (mean age 46±2.6 years; two males, five females) with no history of neurologic problems participated as controls; their Tc-99m ECD SPECT scans were also obtained. The research was performed according to the World Medical Association Declaration of Helsinki with retrospective design.

SPECT scanning

Before tracer administration, all subjects lay in supine position in a quiet room with dimmed lights, with their eyes closed; 25 mCi of 99mTc-ECD was injected intravenously while subjects were awake. Approximately 30–60 minutes after radiotracer injection, SPECT images were acquired using a three-headed Triad XLT system equipped with low-energy high-resolution collimators (Trionix Research Laboratory). Images were acquired with each head rotating 120° in 3° steps, creating 120 raw image sets and with a 10% symmetric window centered and reconstructed with a Butterworth filter (cutoff, 0.4 cycle/cm; power, 7) and displayed in a 128×128 matrix (pixel size, 3.56×3.56 mm with a slice thickness of 3.56 mm). Transaxial images were reoriented parallel to the canthomeatal plane as identified by the fiducial markers. Attenuation correction was performed using Chang's method (attenuation coefficient, 0.11/cm) (10).

Main points

- The changes of regional cerebral blood flow (rCBF) of patients with transient global amnesia (TGA) can be visualized by Tc-99m ECD SPECT.
- The quantification of rCBF can be analyzed by statistical parametric mapping analysis.
- There is significant restoration of perfusion in the hippocampus and thalamus after recovery of TGA.

Table 1. Characteristics of patients with transient global amnesia

	PT1	PT2	PT3	PT4	PT5	PT6
Age (yrs)/Sex	51/M	60/M	55/M	55/M	53/M	57/F
Prior TGA	No	No	No	No	Yes	No
Prior trauma (yrs ago)	-	-	-	-	-	30
Diabetes mellitus	-	-	-	-	-	-
Hypertension	-	+	+	-	-	-
Length of TGA (hrs)	4	16	24	2	<24	72
Initial scan (days)*	3	1	2	3	7	4
Follow-up scan (months)**	60	21		36	1	

PT, patient; M, male; F, female; TGA, transient global amnesia.
*Days from symptom onset; **Months from symptom onset.

Image analysis

The changes of regional perfusion of TGA were tested using SPM8 (Wellcome Department of Cognitive Neurology, Institute of Neurology http://www.fil.ion.ucl.ac.uk/spm). Parametric images of 99mTc-ECD SPECT were spatially normalized into the MNI (Montreal Neurological Institute, McGill University) standard template. To minimize individual anatomical variability and raise signal-to-noise ratio, the normalized images were smoothed by convolution with an isotropic Gaussian kernel with 8 mm FWHM (full width at half maximum) prior to statistical analysis.

The count of each voxel was normalized to the average count of the whole brain before voxel-based analysis. Two-sample t-test was performed on every voxel to identify the significant differences between brain perfusion of TGA patients and those of controls ($P < 0.005$ uncorrected, k=100) after removing age factor as a covariate of no interest. In the regions defined in our *a priori* hypothesis (i.e., hippocampus), we performed a spherical small volume correction (radius 10 mm) and results were considered significant at cluster-based (family-wise error) corrected $P < 0.05$. For ROI analysis, the data were analyzed by one-way ANOVA, followed by the Tukey's HSD post hoc test and differences were considered significant when $P < 0.05$.

Results

Initial scans were acquired 1–7 days after resolution of amnesia. The follow-up scans were performed 1–60 months after TGA attack. The mean global CBF for the TGA (63.84±30.42) did not significantly differ from that of the controls (79.29±13.95) (Student's t=1.21, $P = 0.25$). In the initial scan, parametric image analysis revealed that TGA patients showed significantly lowered perfusion in the left hippocampus (Brondmann area 28), left thalamus and bilateral cerebella compared with normal controls (Fig. and Table 2). Hypoperfusion observed in the left hippocampus during the initial scan was recovered in the follow-up scan, and individual rCBFs extracted from volume-of-interest centered at the statistical peak (x= -18, y= -12, z= -22, radius=3) defined by the parametric maps confirmed these findings. There were significant differences in rCBF of left hippocampus among normal control, TGA initial, and TGA follow-up scans ($F_{2,16} = 7.69$, $P = 0.006$); subsequent post-hoc analysis revealed that TGA showed recovered perfusion in the follow-up scan, which was not different from normal control ($P = 0.82$). However, decreased rCBF could be found in this region on the initial scan compared with the follow-up scan ($P = 0.02$) or normal control scan ($P = 0.01$).

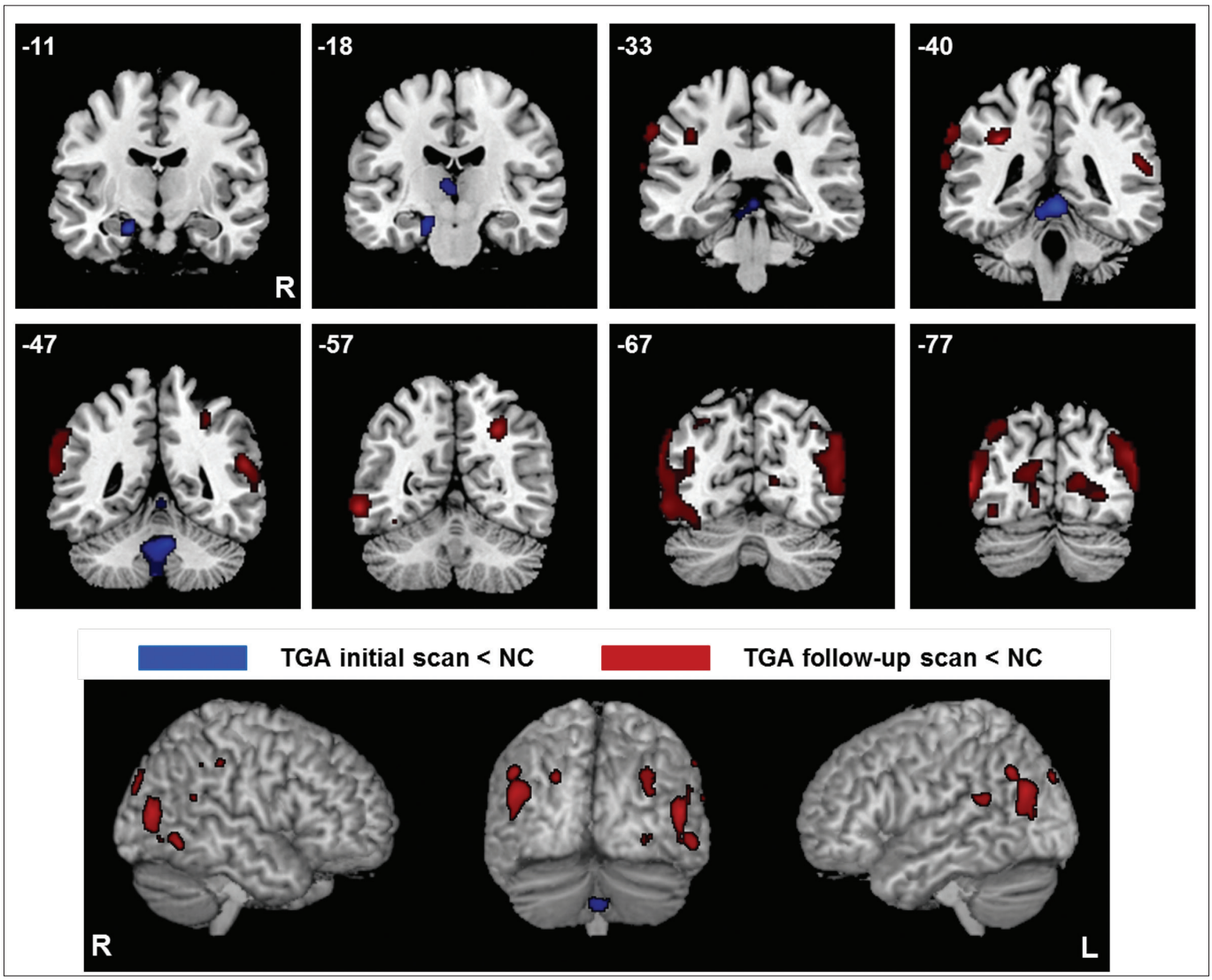

Figure. Whole brain group comparison of regional cerebral blood flow differences in transient global amnesia patients ($P < 0.005$ uncorrected, k=100). The brain areas that showed significant decrease in the initial *(blue areas)* and follow-up *(red areas)* scans are overlaid on multisliced (upper and middle rows) and rendered (lower row) images using standard brain MRI. The hypoperfused areas are defined in Table 2. TGA, transient global amnesia; NC, normal control.

In the follow-up scan, significantly lowered perfusion was observed in the bilateral middle temporal and left inferior temporal gyri, right superior and inferior parietal lobule, left postcentral gyrus, and left cerebellum. Additional hypoperfusion was observed in several visual areas including right middle occipital gyrus, left precuneus, and right cuneus (Fig. and Table 2). Significant hyperperfusion was not seen in either the initial or follow-up scans compared with the control group.

Discussion

In this study we were able to find significant hypoperfusion in the left hippocampus, left thalamus, and bilateral cerebellum on the basal scan. In the follow-up SPECT scan, restoration of perfusion in hippocampus and thalamus was found, while hypoperfusion of temporoparietal region remained.

During amnesic attack all patients had typical history of TGA, exhibited repetitive question of "Where am I?" and also reported loss of time orientation. Impairment of recent memory did not last for more than 24 hours except in one patient who lost her memory for three days. None of the patients had recent history of head trauma other than one patient who had history of trauma 30 years ago which was considered to be irrelevant.

During the initial scan, we found decreased perfusion in the left hippocampus and thalamus, which are major components of the Papez circuit that comprises the hippocampus, fornix, mammillary bodies, anterior thalamus, and cingulate cortex (11). Impairment of these regions has frequently been described in patients with permanent memory loss and hypoperfusion in the hippocampus during amnestic episodes. Takeuchi et al. (12) suggested that thalamus and angular regions are interrelated to the symptoms of TGA. Furthermore, significantly decreased rCBF in medial temporal structures including hippocampus during memory loss of TGA patients has been suggested (12, 13).

In our study, hypoperfusion was also noted in the cerebellum. This finding can be associated with transient oculomotor abnormalities during the TGA attack. Yang et al. (14) observed oculomotor abnormalities during TGA attack, which supports the occurrence of cerebellar dysfunction. Another

Table 2. Distribution of voxels and local maxima with hypoperfused lesions in patients with TGA on initial and follow-up scans

X	Y	Z	Brain area	BA	Z-value
NC>TGA initial					
2	-40	-6	Right cerebellum		3.91
-8	-40	-10	Left cerebellum		3.22
-18	-12	-22	Left hippocampus	BA28	3.80
-6	-22	6	Left thalamus		2.96
NC>TGA follow up					
-54	-74	14	Left middle temporal gyrus	BA39	4.53
50	-72	26	Right middle temporal gyrus	BA39	4.36
-60	-56	-8	Left inferior temporal gyrus	BA37	4.07
-32	-86	36	Left precuneus	BA19	3.64
52	-62	38	Right inferior parietal lobule	BA40	4.23
26	-90	34	Right cuneus	BA18/19	4.04
28	-54	44	Right superior parietal lobule	BA7	3.92
56	-46	20	Right superior temporal gyrus	BA22	3.78
-62	-28	44	Left postcentral gyrus	BA2	3.56
26	-80	6	Right middle occipital gyrus	BA19	3.12
-24	-84	-44	Left cerebellum		3.17

BA, Brondmann areas; NC, normal control; TGA, transient global amnesia.

case report showed left thalamic and cerebellar hypoperfusion on hexamethylpropyleneamine oxime brain SPECT (15). In our patients, impaired perfusion was only found in the left hemisphere during acute attack. These findings are congruous with most studies of TGA, which reported hypoperfusion or hyperperfusion in the hippocampus, amygdala, and thalamus of the left cerebral hemisphere (1, 9, 16). We also found hypoperfusion in the cerebellar vermis. This has been previously reported by Yang et al. (14) and recent reports have demonstrated the relationship between the vermis and memory function. One study showed that cerebellar vermis blockade causes amnesia in adult rats when performed immediately after recall of fear memories, which influences long-term fear memories.

Findings of previous studies on TGA were inconsistent, but mostly describe hypoperfusion in the temporal lobes (including hippocampus), thalamus, and striatum (1, 3, 8, 9, 17–19). The inconsistency of findings among studies is probably due to variable patient characteristics including timing of scan after the TGA attack, degree of ischemia during the scan, and varying cognitive deficits during and after the episodes (16, 17, 19–21).

Hypoperfused lesions detected on initial scans were all resolved on follow-up scans. This result is consistent with previous reports (19, 22, 23). Interestingly, a few articles have demonstrated marginal memory impairment after recovery from TGA attack (21). We found additional hypoperfusion in bilateral temporoparietal and occipital visual areas. Hypoperfusion in temporal cortex during TGA attack has been reported in some studies (6, 15), but none of them reported impaired rCBF after TGA recovery in this region. It is not clear how patients developed hypoperfusion in temporoparietal regions. One study reported predominant left temporal parietal hypometabolism in patients with a history of TGA who developed primary progressive aphasia (24). In addition, many reports described hypoperfusion in temporoparietal area in Alzheimer disease. In this regard, hypoperfusion in follow-up scans may possibly be associated with the development of Alzheimer disease after TGA (25–28).

There are a few limitations in our study. Since the study was performed in a retrospective manner, some subjects underwent initial SPECT scan after the symptoms had been relieved. Furthermore, not all patients underwent a follow-up study. Lastly, the small number of subjects may be responsible for low statistical significance. Future follow-up studies with large numbers of subjects are required to ascertain the mechanism of TGA.

In conclusion, this study suggests that the underlying mechanism of TGA may be temporary ischemia in the hippocampus and thalamus. Additionally, we were able to find restoration of these structures to a certain degree after recovery of TGA.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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