

# Clinical manifestation and imaging characteristics of transient global amnesia: patent foramen ovale as an underlying factor

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Transient global amnesia is not rare, but its etiology remains unknown. Cerebral ischemia is a suspected cause because high signal intensity is observed on diffusion-weighted brain magnetic resonance imaging; however, previous studies have not established it as a cause. Of the 128 patients (114 females) enrolled in this study, 82 (64.6%) experienced extreme stress before transient global amnesia. The number of female patients with patent foramen ovale was more than that of males. The patent foramen ovale-positive group had fewer vascular risk factors and fewer old ischemic lesions on fluid-attenuated inversion recovery magnetic resonance imaging than the patent foramen ovale-negative group. Brain magnetic resonance imaging confirmed that high signal intensity was more likely to be detected on the initial diffusion-weighted imaging when there was an old lesion detected by fluid-attenuated inversion recovery. Furthermore, a longer period from symptom onset to brain magnetic resonance imaging was associated with a positive initial diffusion-weighted imaging result. It is difficult to attribute one underlying mechanism to all the transient global amnesia cases. This study confirmed that transient global amnesia patients with patent foramen ovale had lesser vascular risk factors and showed fewer old lesions on fluid-attenuated inversion recovery magnetic resonance imaging than those without. These results suggest that transient global amnesia may be caused by a paradoxical embolus rather than ischemia due to traditional vascular risk factors in patients with patent foramen ovale.

## Keywords

Cerebral ischemia; Patent foramen ovale; Transient global amnesia

## 1. Introduction

Transient global amnesia (TGA) is a clinical syndrome characterized by the sudden onset of anterograde amnesia lasting up to 24 h. TGA is characterized by a symptom of repeatedly asking questions and it disappears on its own. One of the clinical distinctions is that cognitive functions except for memory are relatively well maintained. It is known that the prognosis is relatively good without causing any permanent disability. The causes of TGA are known to be related to various factors such as physical activity including a Val-

salva action such as sexual activity, emotional stress, and rapid temperature change. Various pathomechanisms have been suggested, but they are still not fully understood. Cerebral ischemia is a one of possible pathomechanism, but its association with traditional cerebrovascular risk factors is not clear [1, 2]. TGA is episodic; therefore, studies on the abnormal findings on electroencephalography (EEG) have been conducted with the possibility that it is an epilepsy-related syndrome [3]. However, there have been no consistent conclusions [3].

Several studies have also evaluated the relationship between TGA and patent foramen ovale (PFO), but different studies reported different results. Previous study reported that the right to left shunt was found in TGA patients at a higher rate than the general population [4]. However, other studies published later did not confirm this relationship. Yet, these studies were relatively small-scale studies, and the results of these studies also suggested that the right to left shunt could have an etiologic relationship with the TGA in a subgroup of TGA. The presence of the right to left shunt, the venous thrombus can act as the paradoxical embolus in the unknown cause of stroke, and since cerebral ischemia is suggested as one of the causes of TGA, the paradoxical embolus through this right to left shunt can be possible cause of TGA.

Diverse pathomechanisms of TGA have been suggested, and various neuroimaging findings have also been reported. Usually, single or multiple lesions between 1 and 5 mm in size appear in the hippocampus on diffusion-weighted brain magnetic resonance imaging (MRI). Although the lesion has not been found in all patients, it has been reported that it was observed in up to 85% of TGA patients [5]. In addition, the lesion may look different depending on the time of imaging [6]. Some studies reported that the lesion shows reversibility after several weeks. The technique and timing of imaging greatly influence the detection of hippocampus lesions because the diffusion-weighted imaging (DWI) lesions are small size and the timing of diffusion change occurrence is different from that of arterial infarction.

For this reason, it was decided to proceed with this study. This study included patients with TGA from a single hospital. The objectives of this study were to confirm the imaging characteristics of TGA using better imaging technique, try to reveal the relationship between these imaging characteristics and PFO, and identify the possibility that the paradoxical embolus could cause TGA through PFO.

## 2. Materials and methods

### 2.1 Patients and data collection

This study included patients who were treated in the neurology department at St. Vincent's Hospital for TGA from March 2015 to December 2020. We retrospectively reviewed the medical records of these patients, including the vascular risk factors such as diabetes, hypertension, and smoking. For each patient, EEG and brain MRI with DWI were conducted during their first visit. In addition, follow-up DWI was performed after at least 24 h in patients who did not show HSI during the initial DWI. Transcranial doppler ultrasound (TCD) was performed to confirm the presence of a right-to-left shunt. Patients with a right-to-left shunt detected during the PFO study using TCD underwent transesophageal echocardiography to confirm the visible PFO.

This study was conducted with the approval of the Institutional Review Board of St. Vincent's Hospital (VC21RASI0056). All procedures were performed according to the ethical standards of the institutional and national research committees and the principles of the Declaration of Helsinki. The requirement for informed consent was waived owing to the retrospective nature of the study.

### 2.2 Imaging protocol

All enrolled patients underwent brain MRI with DWI. MRI was performed using a 3.0-T MRI scanner (Ingenia, Philips Healthcare, Netherlands). The hippocampal thin-section protocol on diffusion MRI was performed with the following parameters: field of view,  $240 \times 240 \text{ mm}^2$ ; b-value,  $1000 \text{ s/mm}^2$ ; flip angle,  $90^\circ$ ; acquisition matrix,  $132 \times 133$ ; slice thickness, 2 mm; and gap, 0.2 mm.

Axial fluid-attenuated inversion recovery (FLAIR) images and susceptibility-weighted images were also used to evaluate other structural lesions, including any old ischemic lesion or hemorrhage.

### 2.3 Imaging analysis

The presence of HSI was checked on the DWI. When there was a lesion, the size, number, and location were classified as a left, right, or bilateral lesion. The size of the largest lesion was measured when a patient had more than one lesion. Old infarction lesion and small vessel changes were evaluated using FLAIR images. Small vessel changes were graded as 0, 1, 2, or 3 (scale) based on the Fazekas scale [7]. Brain CT angiography or brain MR angiography was used to examine the vessels status and detect any intracranial or extracranial stenosis.

### 2.4 Statistical analysis

First, we compared the demographics and clinical characteristics of patients with and without PFO (PFO-positive group and PFO-negative group, respectively). Second, we compared the demographics and clinical data of the patients with lesions detected in the initial DWI (initial DWI-positive group) and in the follow-up DWI (late DWI-positive group, no lesions detected in the initial DWI). We used Pearson's chi-square or Fisher's exact test to analyze the categorical variables and Student's *t*-test to analyze the continuous variables. Third, we performed a multivariate analysis to determine the independent factors associated with late DWI-positivity in patients with TGA. To prevent variable selection caused by spurious correlations, we included only those variables in the multivariate logistic regression model that showed potential association ( $p < 0.1$ ) in the univariate analysis. Statistical significance was set at  $p < 0.05$ . All statistical analyses were performed using Statistical Product and Service Solutions, version 21.0 (SPSS, IBM Corporation, Armonk, NY, USA).

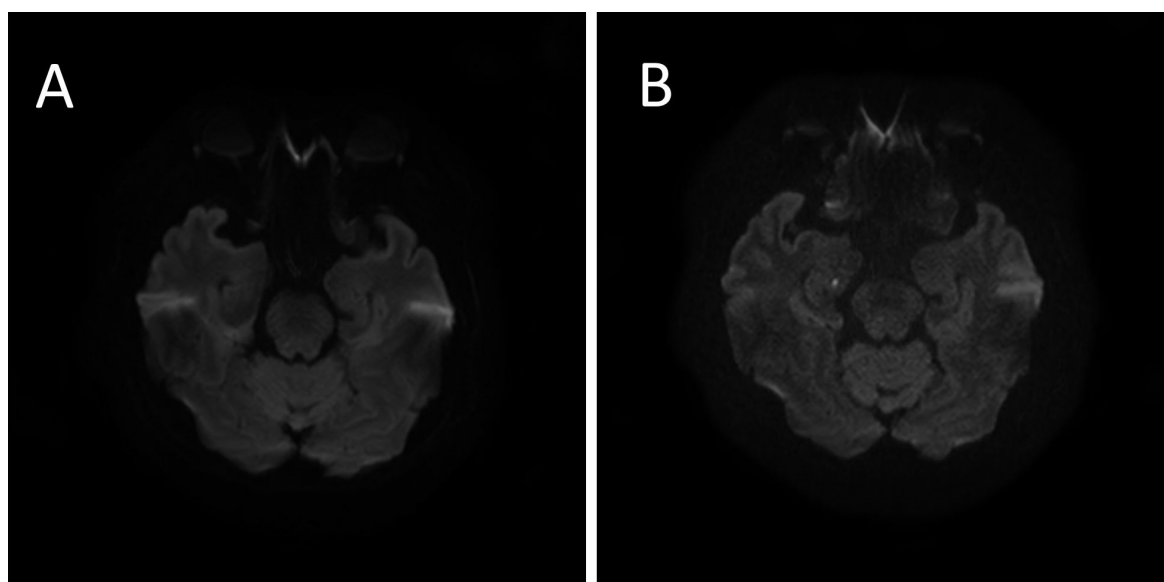
## 3. Results

This study enrolled 128 TGA patients. The baseline characteristics of the patients are presented in Table 1. In the study sample, the number of female patients (114 patients, 89.1%) was significantly higher than that of male patients (14 patients, 10.9%). The mean age was 53 years, and 82 patients (64.6%) suffered extreme stress before the onset of TGA. Extreme stress was defined as a matter accompanied by extreme agitation or crying that is not routinely experienced in life such as the death of a family member or business failure. No small vessel changes were observed in more than 70% of the patients. Headache history was confirmed in 59.1% of the study patients. When the results of EEG did not show a normal EEG pattern such as intermittent slow activity and epileptiform discharge, it was defined as abnormal findings. Abnormal findings were confirmed in 8 patients.

In this study, 33 patients (25.8%) showed HSI on initial DWI. The mean ( $\pm$ standard deviation) duration between the initial symptom onset and the initial MRI was  $19.25 (\pm 17.98)$  h. When follow-up MRI was conducted because no lesion was detected on the initial DWI, the mean duration between symptom onset and the follow-up MRI was  $35.16 (\pm 8.46)$  h. A typical DWI positive image is shown in Fig. 1.

The mean ( $\pm$ standard deviation) follow-up duration after TGA was  $4.2 (\pm 1.49)$  years. During the follow-up, the TGA symptoms recurred in 7 patients (5.5%); however, no patient experienced a vascular event, including a transient ischemic attack, in that period.

The results of comparing patients with and without right-to-left shunt during the PFO evaluation with TCD are presented in Table 2. The proportion of females was significantly higher (75.6% vs. 96.6%,  $p = 0.002$ ) than that of males in the PFO-positive group. Multiple lesions with HSI on DWI were observed more frequently in the PFO-positive



**Fig. 1. Typical diffusion weighted image lesion in transient global amnesia patient.** (A) No high signal intensity was identified in regular diffusion weighted image. (B) In hippocampus thin section MRI, high signal intensity which was not observed in regular diffusion weighted image was confirmed in the right hippocampus.

group than in the PFO-negative group (8.3% vs. 25.9%,  $p = 0.036$ ). PFO positive group have more old ischemic lesion on FLAIR images than in the PFO-negative group (19.5% vs. 3.4%,  $p = 0.015$ ). The FLAIR images showed fewer old ischemic lesions in the PFO-positive group than in the PFO-negative group (19.5% vs. 3.4%,  $p = 0.015$ ). Basal ganglia lesions were observed in the PFO-negative group but not in the PFO-positive group ( $p = 0.002$ ). Small vessel diseases were classified based on the Fazekas scale, and they were significantly more prevalent in the PFO-negative group than in the PFO-positive group ( $p = 0.046$ ). Coexistent hypertension was more common in the PFO-negative group than in the PFO-positive group, and diabetes was observed only in the former. The history of preceding unusual stress was significantly more frequent in the PFO-positive group than in the PFO-negative group (40.0% vs. 82.8%,  $p < 0.001$ ). The PFO-positive group had significantly more cases with underlying migraine headaches as compared to the PFO-negative group (35.0% vs. 81.0%,  $p < 0.001$ ). TGA recurrence was noted in 7 (12.1%) patients in the PFO-positive group ( $p = 0.039$ ) but not in the PFO-negative group. Among TCD-PFO positive patients, 55 patients are underwent transesophageal echocardiography (TEE) because of 3 patients are refuse and 49 patients are confirmed PFO.

We compared the characteristics and findings of the patients of the initial DWI-positive and late DWI-positive group (Table 3). The initial DWI-positive patients showed more old ischemic lesions on FLAIR than the late DWI-positive patients (21.2% vs. 3.1%,  $p = 0.007$ ). The initial MRI was performed relatively later after symptom onset in the initial DWI-positive group than in the late DWI-positive group ( $p < 0.001$ ). The results of multivariate analysis showed that the detection of old lesions on FLAIR and the duration be-

tween symptom onset and the initial DWI were associated with initial DWI positivity (Table 4). The patients with old lesions detected on FLAIR were significantly older ( $p < 0.001$ ) and had significantly more vascular risk factors, such as hypertension, diabetes, alcohol, smoking, and dyslipidemia, than those without (Supplementary Table 1).

#### 4. Discussion

TGA is a syndrome in which various causes are known to play a role. Cerebral ischemia is a possible mechanism, but the imaging characteristics are not the same as those of typical arterial infarction. Moreover, the relationship between TGA and vascular risk factors is unclear. According to previous studies, the size of the HSI observed during diffusion MRI of patients with TGA is between 3 and 6 mm [2]. It is smaller than that of a conventional lacuna infarction [8]. Moreover, HSI is generally observed on DWI less than an hour from the symptom onset for most arterial infarctions, but the HSI for TGA is often negative within 24 h from the onset, and it is commonly confirmed in a delayed image [6].

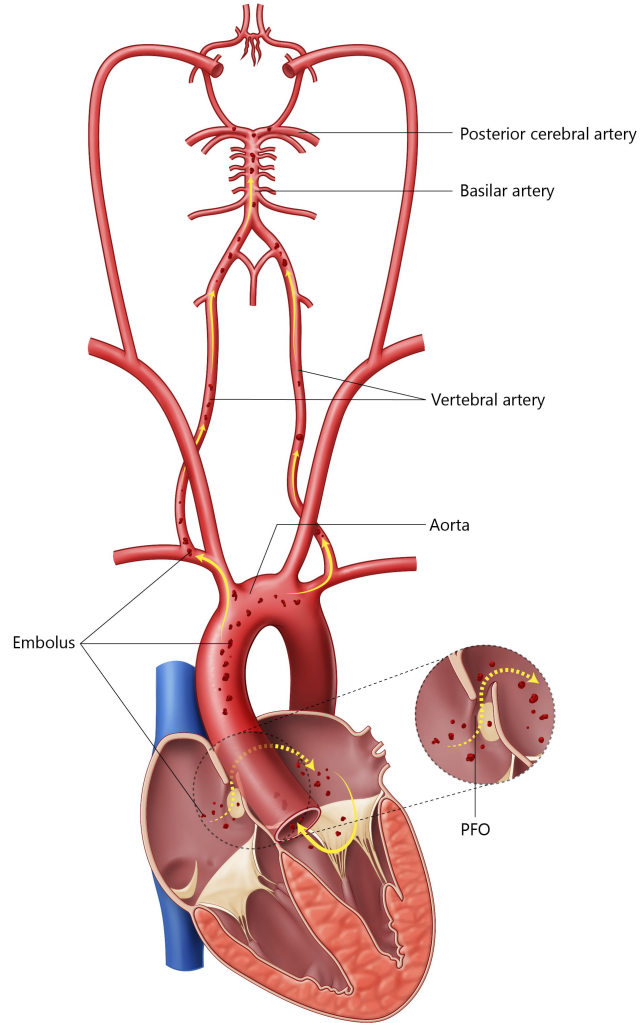
In this study, 58.6% of the TGA patients had right-to-left shunt as detected by assessing the PFO using TCD; this prevalence was higher than that of the general population (25%) [9]. Not all cases of TGA occurrence can be attributed to cerebral ischemia. However, vascular events cannot be ruled out entirely in patients with HIS on DWI. Venous thrombus is more likely to cause a paradoxical thromboembolic event in patients with a right-to-left shunt. Hayashida *et al.* [10] confirmed that shunt flow was more pronounced in the posterior circulation of the brain. This shunt flow is increased during the Valsalva situation, which increases the pressure of the right atrium, and shunting from the right to the left occurs through the PFO. This study showed that patients with PFO

**Table 1. Clinical and imaging characteristics of transient global amnesia patients.**

	Total (n = 128)
Females	114 (89.1)
Age (years)	53.57 ± 8.74
Lesion size (mm)	2.91 ± 0.98
Lesion number	
0	31 (24.2)
1	78 (60.9)
2	17 (13.3)
3	1 (0.8)
4	1 (0.8)
Multiple lesions (>2)	19 (14.8)
Lesion side	
Left	45 (46.4)
Right	45 (46.4)
Bilateral	7 (7.2)
FLAIR old lesion	11 (8.6)
BG old lesion	7 (5.5)
SVD grade	
0	91 (71.1)
1	35 (27.3)
2	2 (1.6)
Smoking	30 (23.4)
Alcohol	47 (36.7)
Hypertension	17 (13.3)
Diabetes	6 (4.7)
HbA1c level	5.64 ± 0.37
Dyslipidemia	57 (44.5)
EEG abnormality	8 (6.4)
Stress	82 (64.6)
Headache	75 (59.1)
ICAS	7 (5.5)
ECAS	19 (14.8)
Initial DWI (+)	33 (25.8)
Onset to initial DWI (h)	19.25 ± 17.98
Follow-up DWI (+)	64 (50.0)
Onset to follow-up DWI (h)	35.16 ± 8.46
Follow-up duration (years)	4.20 ± 1.49
TGA recurrence	7 (5.5)

Data are presented as numbers (%) or means ± standard deviations. DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; BG, basal ganglia; SVD, small vessel disease; HbA1c, glycated hemoglobin; EEG, electroencephalography; ICAS, intracranial atherosclerosis; ECAS, extracranial atherosclerosis; TGA, transient global amnesia.

had fewer or no underlying vascular risk factors (e.g., hypertension and diabetes) as compared to those without PFO. They also had fewer cases of typical chronic ischemia on brain MRI than those without PFO. These results suggest an ischemic event caused by a different mechanism rather than a typical vascular risk factor. The embolus formed in the venous system can travel through the shunt flow via the PFO, causing infarction mainly in the posterior circulation. The probabilities of these mechanisms are shown in Fig. 2.



**Fig. 2. Expected course of the movement of the embolus through the patent foramen ovale.** Right-to-left shunt flow occurs through the PFO, and the embolus of the venous system can move to the arterial system. PFO, patent foramen ovale, Fig. 2 is illustrated by H.G.K.

The effect of preceding extreme stress on TGA is not fully known. Among the patients with PFO and HSI on DWI, 82.8% reported experiencing extreme stress before the occurrence of TGA. This was mainly accompanied by excessive crying or anger. We believe that when patients with PFO experience extreme stress, excessive crying or anger increases the abdominal pressure, which increases the right-to-left shunting that is likely to trigger TGA. Even in the absence of PFO, extreme temperature changes, severe pain, or severe stress can over-excite the sympathetic nervous system, which causes the over-secretion of catecholamine. The resulting arterial constriction can damage the hippocampus. Damage caused by stress induced catecholamine secretion is well known in myocardial injury [11, 12]. Therefore, the effect of PFO and extreme stress on TGA should be confirmed by future large-scale prospective studies.

The reports of previous studies regarding the cause of TGA have not been consistent, and this could be because the differences in patient characteristics were not considered.



**Table 2. Comparison between the patent foramen ovale-positive and patent foramen ovale-negative groups.**

	PFO-negative (n = 41)	PFO-positive (n = 58)	p-value
Females	31 (75.6)	56 (96.6)	0.002
Age (years)	55.93 ± 9.20	52.16 ± 7.65	0.029
Lesion size (mm)	2.87 ± 0.98	2.86 ± 0.93	0.953
Lesion number			
0	5 (12.2)	0 (0)	
1	33 (80.5)	43 (74.1)	
2	2 (4.9)	14 (24.1)	0.005
3	0 (0)	1 (1.7)	
4	1 (2.4)	0 (0)	
Multiple lesions (>2)	3 (8.3)	15 (25.9)	0.036
Lesion side			
Left	20 (55.6)	23 (39.7)	
Right	14 (38.9)	30 (51.7)	0.318
Bilateral	2 (5.6)	5 (8.6)	
FLAIR old lesion	8 (19.5)	2 (3.4)	0.015
BG old lesion	7 (17.1)	0 (0)	0.002
SVD grade			
0	22 (53.7)	43 (74.1)	
1	17 (41.5)	15 (25.9)	0.046
2	2 (4.9)	0 (0)	
Smoking	18 (43.9)	7 (12.1)	<0.001
Alcohol	22 (53.7)	17 (29.3)	0.015
Hypertension	9 (22.0)	5 (8.6)	0.061
Diabetes	4 (9.8)	0 (0)	0.027
HbA1c level	5.72 ± 0.47	5.65 ± 0.32	0.383
Dyslipidemia	20 (48.8)	30 (51.7)	0.773
EEG abnormality	5 (12.5)	1 (1.8)	0.079
Stress	16 (40.0)	48 (82.8)	<0.001
Headache	14 (35.0)	47 (81.0)	<0.001
ICAS	5 (12.2)	2 (3.4)	0.122
ECAS	12 (29.3)	6 (10.3)	0.016
Initial DWI (+)	13 (31.7)	18 (31.0)	0.943
Onset to initial DWI (h)	19.07 ± 18.23	18.78 ± 17.74	0.935
Follow-up DWI (+)	24 (92.3)	40 (100)	0.152
Onset to follow-up DWI (h)	35.67 ± 7.86	34.98 ± 8.85	0.744
Follow-up duration (years)	4.24 ± 1.30	4.91 ± 0.86	0.005
TGA recurrence	0 (0)	7 (12.1)	0.039

Data are presented as numbers (%) or means ± standard deviations.

DWI, diffusion-weighted image; PFO, patent foramen ovale; FLAIR, fluid-attenuated inversion recovery; BG, basal ganglia; SVD, small vessel disease; HbA1c, glycated hemoglobin; EEG, electroencephalography; ICAS, intracranial atherosclerosis; ECAS, extracranial atherosclerosis; TGA, transient global amnesia.

The results of this study do not suggest that all cases of TGA are associated with PFO. However, there is the possibility of a paradoxical thromboembolic event due to shunting through the PFO, regardless of the known vascular risk factors. This study showed that 5% (n = 7) of the patients had recurrent TGA during the follow-up period (lasting for at least 4 years), and they all had PFO. None of the patients experienced any other vascular events during the follow-up period, regardless of the presence of PFO. Although attention should be given to statistical interpretation since the follow up duration of the PFO positive group was longer, this finding supports the argument above. Unlike previous studies, almost all the

patients in this study were female, which is a novel finding.

This study had several limitations. First, this study was a retrospective study and did not have a patient control group. Therefore, this study did not match age-sex with TGA and control groups. Second, the first MRI and follow-up MRI were not performed at the same time in all patients. Therefore, it is not possible to conclude when the most appropriate time to perform MRI in TGA patients. However, the results of this study clearly presented that MRI lesions could be found in more patients by conducting follow up imaging after 24 hours, even though the first MRI image of the TGA patient done within at least 24 hours was negative. Third,

**Table 3. Univariate and multivariate analyses of the parameters associated with late diffusion-weighted imaging-positive lesions in patients with transient global amnesia.**

	Initial DWI-positive group (n = 33)	Late DWI-positive group (n = 64)	p-value
Females	29 (87.9)	57 (89.1)	0.862
Age (years)	55.61 ± 9.21	52.56 ± 7.73	0.089
Lesion size (mm)	3.04 ± 1.03	2.85 ± 0.97	0.372
Lesion number			
1	24 (72.7)	54 (84.4)	0.250
2	9 (27.3)	8 (12.5)	
3	0 (0)	1 (1.6)	
4	0 (0)	1 (1.6)	
Multiple lesions (>2)	9 (27.3)	10 (15.6)	0.171
Lesion side			
Left	17 (51.5)	28 (43.8)	0.761
Right	14 (42.4)	31 (48.4)	
Bilateral	2 (6.1)	5 (7.8)	
FLAIR old lesion	7 (21.2)	2 (3.1)	0.007
BG old lesion	6 (18.2)	1 (1.6)	0.006
SVD grade			
0	21 (63.6)	44 (68.8)	0.816
1	11 (33.3)	19 (29.7)	
2	1 (3.0)	1 (1.6)	
Smoking	7 (21.2)	17 (26.6)	0.563
Alcohol	15 (45.5)	23 (35.9)	0.363
Hypertension	6 (18.2)	9 (14.1)	0.595
Diabetes	3 (9.1)	1 (1.6)	0.113
HbA1c level	5.72 ± 0.40	5.67 ± 0.38	0.609
Dyslipidemia	18 (54.5)	31 (48.4)	0.569
PFO	18 (58.1)	40 (63.5)	0.611
EEG abnormality	3 (9.1)	2 (3.2)	0.335
Stress	20 (62.5)	45 (70.3)	0.44
Headache	19 (57.6)	44 (69.8)	0.229
ICAS	2 (6.1)	5 (7.8)	1
ECAS	13 (39.4)	3 (4.7)	<0.001
Onset to initial DWI (h)	29.36 ± 23.21	12.14 ± 5.21	<0.001
Follow-up duration (years)	4.52 ± 1.06	4.88 ± 0.90	0.083
TGA recurrence	2 (6.1)	5 (7.8)	1

Data are presented as numbers (%) or means ± standard deviations.

DWI, diffusion-weighted imaging; PFO, patent foramen ovale; FLAIR, fluid-attenuated inversion recovery; BG, basal ganglia; SVD, small vessel disease; HbA1c, glycated hemoglobin; EEG, electroencephalography; ICAS, intracranial atherosclerosis; ECAS, extracranial atherosclerosis; TGA, transient global amnesia.

**Table 4. Univariate and multivariate analyses of the parameters associated with late diffusion-weighted imaging-positive lesions in patients with transient global amnesia.**

	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age (years)	0.956 (0.907–1.007)	0.092	0.980 (0.901–1.065)	0.629
FLAIR old lesion	0.120 (0.023–0.616)	0.011	0.052 (0.005–0.513)	0.011
Onset to initial DWI duration	0.827 (0.755–0.906)	<0.001	0.788 (0.703–0.884)	<0.001

OR, odds ratio; CI, confidence interval; DWI: diffusion-weighted imaging, FLAIR: fluid-attenuated inversion recovery.

visible PFO was not confirmed through TEE in all patients. This study also could not classify and evaluate high risk PFO such as large size (> 3 mm), hypermobility, and presence of an atrial septal aneurysm, which could be confirmed in TEE.

## 5. Conclusions

Although this study was retrospective and observational and had various biases, it examined the long-term recurrence of TGA or other vascular events. A hippocampal thin-section diffusion MRI was performed to confirm the detection of

small lesions on DWI. Additionally, because of the follow-up MRI conducted for patients who initially presented DWI-negative findings, more patients with lesions on DWI were identified. This had not been done in previous studies. These facts that MRI lesions were more frequently observed in TGA patients with PFO and they had less traditional vascular risk factors than TGA patients without PFO suggested that the paraxial embolus through PFO could be one factor causing TGA. If a large-scale prospective study based on these relevant results is conducted, the prognosis for various causes of TGA can be evaluated.

## Abbreviations

DWI, diffusion-weighted imaging; EEG, electroencephalography; FLAIR, Fluid-attenuated inversion recovery; HSI, high signal intensity; MRI, magnetic resonance imaging; PFO, patent foramen ovale; SPSS, Statistical Product and Service Solutions; TCD, Transcranial doppler ultrasound; TGA, transient global amnesia.

## Author contributions

HGK and SMN designed the research study. HGK and SMN collected and analyzed the data. SMN performed computational studies and was involved in manuscript writing. HGK provided advice and helped in manuscript revision. All authors have read and approved the final manuscript.

## Ethics approval and consent to participate

This study was conducted with the approval of the institutional review board of St. Vincent's Hospital (VC21RASI0056). The requirement for informed consent was waived owing to the retrospective nature of the study.

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## Conflict of interest

The authors declare no conflict of interest.

## Supplementary material

Supplementary material associated with this article can be found, in the online version, at <https://jin.imrpress.com/E N/10.31083/j.jin2003077>.

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