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ORIGINAL COMMUNICATION

Interaction between the heart and the brain in transient global amnesia

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Abstract

Background To analyse whether patients with transient global amnesia (TGA) have concomitant cardiac injury by assessing clinical symptoms, as well as blood and cardiologic test results.

Methods In this retrospective observational study, we analysed 202 consecutive patients presenting with isolated TGA and treated at our institution between March 2010 and December 2018. We examined the incidence of high-sensitivity cardiac troponin I (hs-cTNI) level elevation, electrocardiogram (ECG) findings, and data on clinical management.

Results Among the TGA patients, 17 (8.4%) exhibited elevated levels of hs-cTNI. Although none of the patients had ST elevation, 12 (6.7%) showed QTc prolongation and 11 (6.1%) an inverted T wave on ECG. No typical clinical symptoms suggestive of myocardial infarction were present in any of the cases, however, 17 (8.4%) patients complained of mild somatic symptoms. Patients with hs-cTNI level elevation had a significantly greater likelihood of a history of coronary heart disease ($p = 0.03$) and a significantly shorter TGA duration at presentation ($p < 0.01$). Of the 17 patients with hs-cTNI elevation, Takotsubo syndrome was diagnosed in 2, while in the remaining 15 hs-cTNI level elevation remained unresolved. A literature review indicated the female predominance for the occurrence of cardiac involvement in TGA.

Conclusions Although the in-hospital outcomes appear favourable in all cases reported thus far, we believe that all patients with TGA should be carefully evaluated for potential underlying cardiac involvement and comorbidity. Further research on cardiac vulnerability in TGA should attempt to develop a diagnostic algorithm and assess the potential causes of cardiac injury in TGA.

Keywords TGA · Transient global amnesia · High-sensitivity cardiac troponin I · MRI

Introduction

Transient global amnesia (TGA) is a clinically defined syndrome characterized by a sudden and severe disturbance of memory that interferes with learning novel information but usually resolves within hours [49]. Studies have proposed different pathophysiological mechanisms underlying TGA, although there is no definitive evidence of a specific aetiology thus far. The only consistent finding in TGA patients is the presence of small lesions in the hippocampus on diffusion-weighted magnetic resonance images (DW MRI) 24–48 h after the onset of TGA, although the aetiology of these lesions remains uncertain [2, 45]. Up to 90% of reported TGA cases report a precipitating event causing physical, emotional, or behavioural stress prior to the amnestic episode, which suggests that stress triggers TGA [40]. Recent individual case reports indicated the coincidence

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of TGA with Takotsubo syndrome (TTS), which led to the hypothesis that the two disorders represent two clinical facets of a single pathology, especially because they share the same stress-related triggers [3, 13, 15, 39]. Other studies reported other cardiac findings and abnormalities in acute TGA, such as arrhythmias, myocardial infarction, or elevated troponin levels [6, 26]. A recent case–control study found cardiac troponin level elevation in one of four patients with TGA [11].

Based on these findings, we aimed to analyse the incidence of possible heart muscle injury based on high-sensitivity cardiac troponin I (hs-cTNI) level elevation and ECG findings, to study the relationship between neurological and cardiac factors and hs-cTNI level elevation, and to report the clinical management in those with abnormal hs-cTNI levels.

Materials and methods

Study population

From our prospectively collected database of > 400 patients with TGA, we analysed a subset of 202 consecutive patients admitted with a diagnosis of TGA between March 2010 and December 2018. In this database demographic, clinical and MRI data of patients with isolated, clinically defined TGA, according to diagnostic criteria at presentation, and confirmation of the diagnosis at discharge, are collected. We chose March 2010 as the beginning of the study period since hs-cTNI testing was introduced in our hospital at that time and was routinely performed in all patients presenting to our interdisciplinary emergency department (IED).

Standard protocol approvals

The study was approved by the Ethics Committee of the Medical Faculty Mannheim, Heidelberg University and conformed to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 6th revision, 2008).

Neurological assessment

All patients were examined by a neurologist in the IED. TGA was diagnosed according to the Hodges and Warlow criteria, indicating that clouding of consciousness, a focal neurological deficit, or a history of epilepsy or trauma was not present in any of the patients [23]. In all the cases, anterograde amnesia was documented by the IED neurologist or a capable witness. Patients and family were questioned regarding potential stressful events preceding the onset of TGA. These were documented and classified either as an immediately preceding physical or emotional stressor or as a remote or ongoing emotional stressor in the days or weeks before the episode. Spontaneously reported somatic symptoms accompanying TGA were documented. All patients, except those with a contraindication, underwent cranial MRI within the first 3 days of hospitalisation, including DW MRI parallel to the long axis of the hippocampus. These images were analysed for the presence and location of typical hippocampal hyperintense lesions. The presence of additional extrahippocampal diffusion-weighted (DW) MRI abnormalities was also documented.

Cardiac investigations

In all the patients, the following data were collected retrospectively from IED forms: initial blood pressure and heart rate, serum hs-cTNI values, and medical history of hypertension, diabetes, coronary heart disease, atrial fibrillation, cancer, mental illness, and stroke. An elevation of serum hs-cTNI levels was defined as a concentration of > 0.045 ng/ml [46, 51]. All patients underwent 12-lead ECG at admission. These ECGs were interpreted by a cardiologist as abnormal if ≥ 1 of the following was present: cardiac arrhythmia, bundle branch block, conduction delay, signs of right or left ventricular hypertrophy or left atrial enlargement, prolonged QT interval, or ST elevation or T wave inversion. Corrected QT intervals (QTc) were calculated according to heart rate using either Bazett's or Fridericia's formula and defined as prolonged if the QTc in lead V2-3 was ≥ 460 ms in women and ≥ 450 ms in men [41].

Statistical analysis

Group comparisons for continuous variables were calculated using Student's *t* test for independent samples. To detect group differences in the distribution of categorical variables, Chi square test or Fisher's exact test (as applicable) were used. As this study is a first attempt to detect possible associations between cardiac injury and TGA, we refrained from adjusting the alpha-level of statistical significance testing to avoid an alpha error accumulation by multiple testing.

Results

A total of 202 TGA patients were included in the analysis, with a mean age of 66.7 ± 8.6 years (128 female patients, 63.4%). During the study period, 7 patients (3.5%) experienced multiple TGA episodes. According to the medical records, 6 patients (3.0%) had a history of TGA, whereas 1 patient (0.5%) had previously experienced TTS.

Neurological characteristics

All 202 patients met the clinical criteria for TGA. In 155 cases (76.7%), an ongoing episode of TGA was documented by the IED neurologist. In a subset of 130 (64.4%) patients with a witnessed onset of the amnestic episode, the mean duration of the amnestic attack at presentation was 3.82 ± 3.74 h. A potential stress trigger was identified in 133 patients (65.8%), including 101 (50%) with emotional or physical stress immediately preceding the episode and the remaining 32 with remote triggers (defined as triggers within the last week or triggers that had persisted for several previous weeks). In 17 (8.4%) cases, spontaneously reported associated somatic symptoms on the IED forms were as follows: dyspnoea/shortness of breath in 2, dizziness in 10, chest tightness in 1, and fear/agitation in 4. In all cases, the clinical symptoms of amnesia resolved within 24 h. Thirty-three patients had contraindications for MRI. Of the other 169 patients, 127 (75.1%) exhibited a total of 1–5 typical hippocampal DWI lesions in either hippocampus, whereas 42 (24.9%) had no hippocampal lesions. In 7 cases (4.1%), additional small and clinically silent, multiple embolic lesions were detected outside the hippocampus on DWI.

Cardiologic assessment

The mean heart rate in our cohort, measured in the IED, was 77.8 ± 17.1 beats per minute. The mean systolic blood pressure was 165.6 ± 28.3 mmHg and mean diastolic blood pressure was 89.9 ± 16.7 mmHg; the initial systolic blood pressure measured in the IED was > 180 mmHg in 54 (26.7%) patients. ECG data were available for 179 patients, and abnormal findings were noted in 27 (15.1%) cases. With regard to specific ECG abnormalities, QTc prolongation was detected in 12 (6.7%) and an inverted T wave was detected in 11 patients (6.1%). Based on the medical history, the following comorbidities or illnesses were reported: hypertension in 116 patients (57.4%), diabetes in 11 patients (5.4%), cardiac heart disease in 23 patients (11.4%), atrial fibrillation in 12 patients (5.9%), cancer in 13 patients (6.4%), mental illness in 20 patients (11%), and a history of stroke in only 2 patients (0.1%). Heart failure was not reported in the medical history of any the patients of this series.

Incidence of hs-cTNI level elevation and patient management

A hs-cTNI level elevation was detected in 17 patients (8.4%). Patients with hs-cTNI level elevation were significantly more likely to have a history of coronary heart disease ($p = 0.03$), and also had a significantly shorter TGA symptom duration on IED presentation ($p < 0.01$) (Table 1). All patients with an elevated hs-cTNI level were immediately examined by a cardiologist in the IED; no typical clinical symptoms suggestive of myocardial infarction were present in any of the cases. Diagnostic and therapeutic decisions were based on the discretion of the treating physician and are listed in Table 2. Three patients received aspirin/heparin loading in the IED, and four patients were monitored in the intensive care unit. Transthoracic or transoesophageal echocardiography was conducted in seven patients and additional coronary angiography was performed in five of these patients. Of the 17 patients with hs-cTNI elevation, TTS was diagnosed in 2. The first patient was asymptomatic, had a normal ECG and received complete cardiac assessment (transthoracic echocardiography and coronary angiography with left ventriculography). She was diagnosed with midventricular type TTS and had bilateral hippocampal DWI lesions on follow-up MRI performed on day 1 (Fig. 1). The second patient reported slight shortness of breath—this, together with hs-cTNI-elevation and ECG finding of a bundle branch block at presentation lead to further cardiac examinations. After left ventricle cardiac thrombus formation was detected using echocardiography, cerebral MRI was ordered showing small cortical embolic lesions. Regional wall motion abnormalities on echocardiography and cardiac MRI confirmed TTS (Fig. 2). Follow-up MRI of the hippocampus was not performed due to continuous monitoring in the intensive care unit. Cardiac assessment was unrevealing in another two patients using echocardiography, and in three patients, using coronary angiography, while in the remaining ten patients, no further investigations were prompted, mostly as hs-cTNI level elevation was asymptomatic. In one case, coronary angiogram was declined by the patient. Of the seven patients with asymptomatic embolic DWI lesions, two showed hs-cTNI level elevation.

Discussion

Among our cohort of 202 patients who presented with isolated and clinically diagnosed TGA, 8.4% had elevated levels of hs-cTNI indicating myocardial injury, but none complained of pronounced symptoms suggestive of acute coronary syndrome. Mild somatic symptoms reported during TGA were documented in 8.4% of patients. Patients with hs-cTNI level elevation had a significantly greater likelihood of a history of coronary heart disease ($p = 0.03$) and had a significantly shorter amnestic symptom duration at the time of presentation ($p < 0.01$). QTc prolongation was detected in 9% of patients and an inverted T wave was detected in 7.1% of patients. Of the 17 patients with hs-cTNI elevation, TTS was diagnosed in 2. In ten patients, no further investigations were prompted as patients were asymptomatic, and the finding remained unresolved.

Table 1 Characteristics of the study group

Variable	High-sensitivity cardiac troponin I		*p* value
	Elevated ($n=17$)	Non-elevated ($n=185$)	
Age, years	69.0 ± 10.0	66.6 ± 8.5	ns
Male	3 (17.6)	71 (38.4)	ns
TGA conditions			
Preceding trigger identified	7 (77.8)	94 (75.8)	ns
Overall trigger identified	9 (52.9)	124 (67.0)	ns
Duration of TGA at IED presentation (h)	1.5 ± 1.1	4.0 ± 3.9	**< 0.01**
DW MRI of the brain			
Hippocampal lesion identified	12 (85.7)	115 (74.2)	ns
Right hippocampus involved	6 (42.9)	72 (46.5)	ns
Left hippocampus involved	11 (78.6)	85 (54.8)	ns
Number of overall lesions	1.5 ± 1.2	1.23 ± 1.0	ns
At presentation to the IED			
Heart rate, beats per minute	81.6 ± 14.8	77.5 ± 17.3	ns
Systolic blood pressure (mm/Hg)	163.9 ± 25.1	165.7 ± 28.7	ns
ECG findings			
Abnormal ECG	4 (25.0)	23 (14.1)	ns
QTc prolongation	1 (6.3)	11 (6.7)	ns
Inverted T wave	2 (12.5)	9 (5.5)	ns
History of			
Hypertension	12 (70.6)	104 (56.2)	ns
Diabetes mellitus	1 (5.9)	10 (5.4)	ns
Coronary heart disease	5 (29.4)	18 (9.7)	**0.03**
Atrial fibrillation	1 (5.9)	11 (5.9)	ns
Cancer	3 (17.6)	10 (5.4)	ns
Mental illness	2 (14.3)	18 (10.7)	ns
Stroke	0 (0)	2 (1.1)	ns

Variables are presented as mean ± standard deviation or number (%)

TGA transient global amnesia, *IED* interdisciplinary emergency department, *DW MRI* diffusion-weighted MRI, *ECG* electrocardiogram

Although clinical criteria do not indicate any focal neurological signs in TGA cases, accompanying somatic symptoms have very well been described in the literature and include dizziness, nausea, chills/flushes, fear of dying, paraesthesia, or cold extremities and emotionalism [40]. In some cases, symptoms resembling a panic attack have also been reported [24]. These somatic symptoms have primarily been explained as related to the emotional stress, and TGA patients have been reported to have certain personality types with vulnerability to stress as well as enhanced cortisol secretion during acute TGA [22, 32]. However, it is unclear whether TGA is truly asymptomatic in this context. In several published cases, patients complained to relatives about symptoms indicating acute coronary syndrome at the beginning of amnesia, but did not remember or report these during the attack [4, 43].

In acute coronary syndrome, the electrocardiographic feature of acute myocardial infarction is ST elevation, which, however, is not be present in acute non-ST elevation myocardial infarction or in some cases of TTS. In TTS, after the resolution of initial ST segment elevation (if present), progressive T wave inversion and QT interval prolongation over several days may occur with subsequent gradual resolution of the T wave inversion and QT interval prolongation over days to weeks [16]. In our cohort, none of the patients exhibited ST elevation on initial ECG. Nevertheless, we found T wave inversion and QT interval prolongation in 9% and 7.1% of our patients, respectively, which is suggestive of cardiac injury. In patients with delayed presentation of TTS, these changes may be present on admission in the absence of ST segment elevation and may represent the only ECG changes [16].

Although the hs-cTNI level is informative in excluding myocardial infarction in patients with acute coronary syndrome, elevated cardiac troponin levels have also been described in other acute cardiac and non-cardiac conditions, as well as in chronic diseases reflecting myocardial injury of unknown origin [35]. In these cases, the elevation

Table 2 Clinical findings in patients with elevated hr-cTNI levels

No	Age (years)/ gender	Trigger	DW MRI lesion	Cardiac symptoms Clinical management Diagnosis
1	73/m	Physical (strenuous gardening)	Left hippocampal lesion	S: Asymptomatic M: No further investigation prompted Dx: Hs-cTNI level elevation of unclear significance
2	69/f	Emotional (family gathering)	Left hippocampal lesion	S: Asymptomatic M: Heparin and aspirin loading, TTE and coronary angiogram unremarkable Dx: Hs-cTNI level elevation of unclear significance
3	68/f	Emotional (at deathbed of husband)	Bilateral hippocampal lesion	S: Chest tightness M: Aspirin loading, ICU monitoring, TTE and coronary angiogram unremarkable Dx: Hs-cTNI level elevation of unclear significance
4	66/f	Emotional (argument with sister)	Left hippocampal lesion	S: Asymptomatic M: TTE and coronary angiogram unremarkable, patient started on aspirin Dx: Hs-cTNI level elevation of unclear significance
5	83/m	Emotional (beginning of vacation)	Left hippocampal lesion	S: Asymptomatic M: No further investigation prompted Dx: Hs-cTNI level elevation of unclear significance
6	37/m	Emotional (work stress)	Multiple embolic lesions, no follow-up hippocampal MRI performed	S: Shortness of breath M: ICU monitoring, TTE, coronary angiogram, cardiac MRI performed, anticoagulation initiated Dx: Takotsubo syndrome, intracardiac thrombus
7	73/f	Physical (strenuous gardening)	Bilateral hippocampal lesion	S: Asymptomatic M: No further investigation prompted Dx: Hs-cTNI level elevation of unclear significance
8	7/f	Emotional (argument with son)	Bilateral hippocampal lesion	S: Asymptomatic M: No further investigation prompted Dx: Hs-cTNI level elevation of unclear significance
9	66/f	Physical	Right hippocampal lesion	S: Asymptomatic M: No further investigation prompted Dx: Hs-cTNI level elevation of unclear significance
10	76/f	Physical	Right hippocampal lesion, Multiple embolic lesions	S: Asymptomatic M: Stroke Unit monitoring, TTE unremarkable, started on aspirin and statin therapy Dx: Hs-cTNI level elevation of unclear significance
11	73/f	None	Right hippocampal lesion	S: Asymptomatic M: No further investigation prompted Dx: Hs-cTNI level elevation of unclear significance
12	74/f	Emotional (argument with daughter)	Left hippocampal lesion	S: Shortness of breath M: ICU monitoring, TTE unremarkable, coronary angiogram declined by the patient, dual platelet and statin therapy Dx: Hs-cTNI level elevation of unclear significance

Table 2 (continued)

No	Age (years)/ gender	Trigger	DW MRI lesion	Cardiac symptoms Clinical management Diagnosis
13	72/f	None	None	S: Asymptomatic M: No further investigation prompted Dx: Hs-cTNI level elevation of unclear significance
14	75/f	Physical (painful dental treatment)	Left hippocampal lesion	S: Asymptomatic M: No further investigation prompted Dx: Hs-cTNI level elevation of unclear significance
15	58/f	Emotional (argument with husband)	Bilateral hippocampal lesion	S: Asymptomatic M: No further investigation prompted Dx: Hs-cTNI level elevation of unclear significance
16	63/f	None	Left hippocampal lesion	S: Asymptomatic M: No further investigation prompted Dx: Hs-cTNI level elevation of unclear significance
17	76/f	None	Bilateral hippocampal lesion	S: Asymptomatic M: ICU monitoring, TTE, coronary angiogram, cardiac MRI Dx: Takotsubo syndrome

f female, *m* male, *DW MRI* diffusion-weighted magnetic resonance imaging, *TTE* transthoracic echocardiography, *ICU* intensive care unit

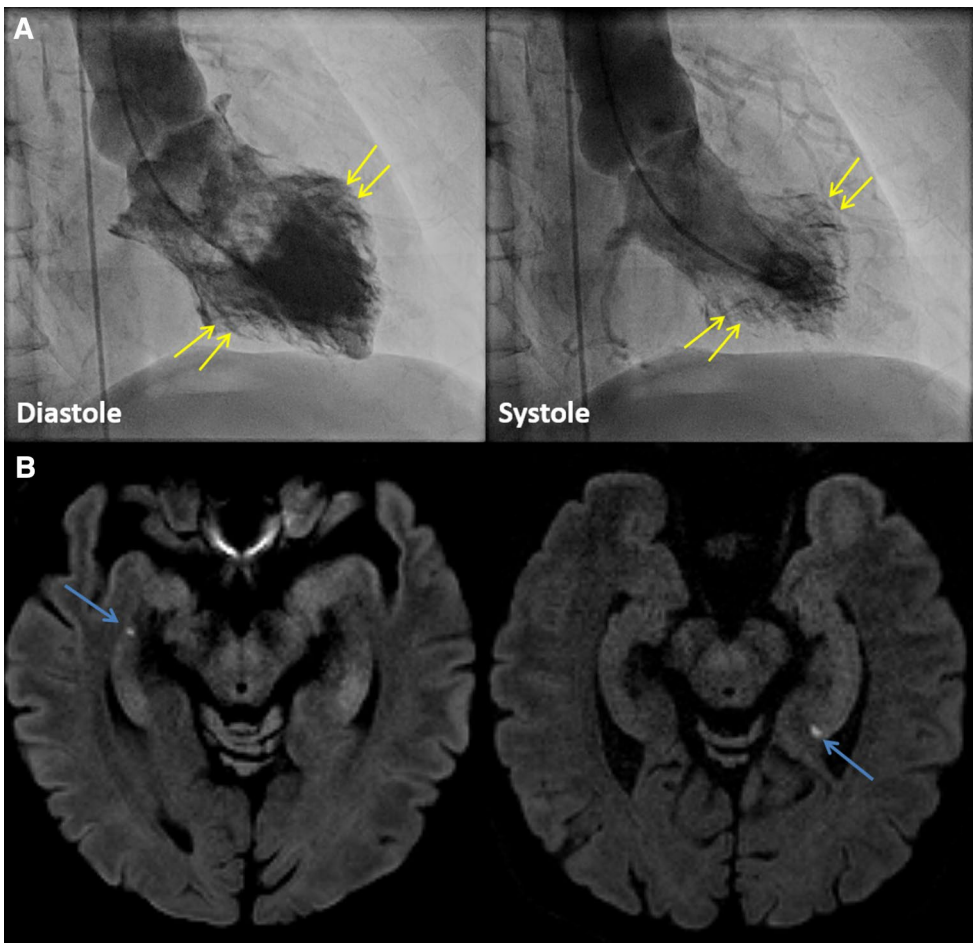

Fig. 1 Cardiologic and MRI findings in patient 17. Left laevocardiography (**a**) illustrates wall motion abnormality (yellow arrows) in midventricular type Takotsubo syndrome during diastole and systole in a 76-year-old woman without any symptoms suggestive of acute coronary syndrome and normal ECG findings, but with elevated high-sensitivity cardiac troponin I levels. Diffusion-weighted magnetic resonance imaging (MRI) of the brain (**b**) demonstrates small hyperintense lesions on day 1 after transient global amnesia

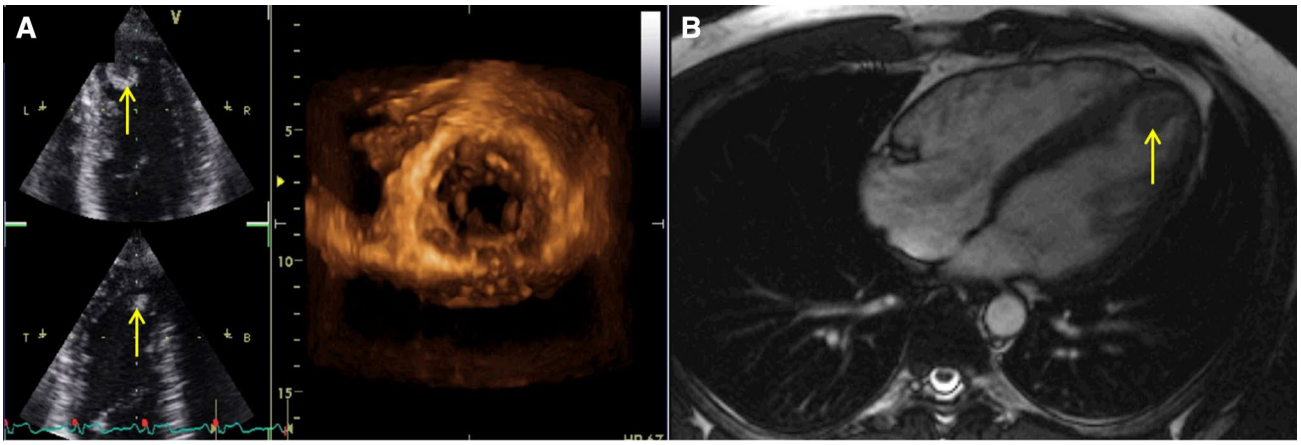

Fig. 2 Cardiologic findings in patient 6. Echocardiography (four and three chamber view) (**a**) and cardiac magnetic resonance imaging (MRI) (**b**) in a 37-year-old man with transient global amnesia show apical ballooning and a left ventricle thrombus formation (yellow arrow). Cardiac examinations were performed due to slight shortness of breath and elevated high-sensitivity cardiac troponin I levels. As the patient was monitored in the intensive care unit, follow-up MRI of the hippocampus was not performed

is believed to be multifactorial, including myocardial ischaemia, increased wall tension and ventricular strain, direct myocyte trauma, excess catecholamines, and possibly impaired renal clearance [18]. Such cardiac vulnerability is especially common in patients with ischemic stroke and has been hypothesized to be the consequence of concurrent cardiovascular disease or as a result of focal cerebral injury (such as in the right insular cortex) [5]. In particular, the insula is believed to regulate the autonomic nervous system and accentuate sympathetic activity when stimulated [33]. A recent study identified patients by searching the hospital administrative data for ICD-10 diagnoses of TGA, and found cardiac troponin level elevation in 25% of 113 patients with acute TGA [11]. An analysis of case files showed that none of the patients had clinical symptoms or ECG alterations indicating myocardial infarction, heart failure, TTS, or non-cardiac causes of troponin level elevation. Consistent with previously published data, elevated blood pressure at presentation was a prominent finding in our cohort, a finding that has also been linked to troponin level elevation in patients with no other explanation [18, 31]. The possibility of cardiac damage due to TGA has been proposed in recent years, and similar findings have been reported in other neurological disorders such as stroke or epilepsy [9, 34]. The recently published TRELAS study reported coronary angiographic findings in acute ischemic stroke patients with elevated cardiac troponin and found that coronary culprit lesions were significantly less frequent in stroke patients compared with age- and sex-matched patients with non-ST elevation acute coronary syndrome despite similar baseline cTn levels [29].

TTS—another acute cardiac condition leading to troponin level elevation—is a transient wall motion abnormality of the left ventricle that has common features with acute coronary syndrome, including symptoms, ECG abnormalities, biomarker elevations, and complication rates [15]. The risk of thromboembolic events and adverse rhythm disorders has been well described in TTS patients [10]. TTS shares its characteristic association with a preceding stressful event involving emotional trauma or physical stressors with TGA. Although TTS is most commonly accompanied by symptoms of acute myocardial infarction, it might be an incidental finding in certain other cases [15]. In a cross-sectional study of the national inpatient sample, Morris and co-workers reported the association between TTS and the acute neurological conditions subarachnoid haemorrhage, status epilepticus, seizures and TGA using discharge records defined by UCD-9-CM diagnosis codes [30]. Cardiovascular manifestations of neurologic disease due to proposed anatomic and physiological links between normal and abnormal functions of the two systems have been getting increasing amounts of interest in recent years [9, 34]. However, in contrast to stroke, the similarities between TGA and TTS may indicate a potential shared pathological mechanism, and thus offer an opportunity to improve our understanding of these disorders. One explanation may be the possible involvement of the insula in TGA. TGA is increasingly recognized not as an isolated hippocampal disorder, but as a complex network disorder of the brain; in fact, anatomical/functional connections have also been described between the hippocampus and the insula [17, 36]. For instance, connections of the hippocampus with the ventral anterior insula may play a role in the mediation of memory encoding with emotionally arousing information [7]. These effects are consistent with a finding that the insula is involved in representing states of awareness related to external threats and in representing internal states of arousal—both conditions being associated with TTS and TGA [8]. A very recent study on cerebral connectivity at rest found reduced functional connectivity

in TTS patients, relative to controls, in the hippocampus and the insula among other regions of the brain [50].

In case reports of TGA, a possible relationship between cardiac disorders has been discussed. Conditions such as long-standing atrial fibrillation or severe bradyarrhythmia have been hypothesized to cause cerebral hypoperfusion secondary to altered cardiac output and to thereby lead to TGA [14, 21]. We compared our findings with those of articles describing cases of TGA with subsequent or simultaneous cardiac comorbidity or injury published from 1970 to 2019. PubMed was searched using the terms "transient global amnesia" and "cardiac", "heart", or "takotsubo". We found a total of 18 cases that were documented in detail concerning neurological and cardiologic findings (Table 3). The cardiac comorbidities were as follows: cardiac arrhythmia in 1 case, troponin level elevation of unclear significance in 1 case, acute coronary syndrome

Table 3 Literature review of transient global amnesia and cardiac involvement

No	Authors	Year	*N*	Age (years)/ gender	Trigger	Cardiac symptoms/comorbidities	Cardiac diagnosis*
1	Greenlee et al. [21]	1975	1	54/m	No	None/hypertension	Cardiac arrhythmia and digitalis toxicity
2	Agosti et al. [1]	2006	1	72/m	No	None/hypertension, ischemic heart disease	Acute anterolateral myocardial infarction
3	Caramelli et al. [4]	2009	1	57/m	No	Chest pain/hypertension	Myocardial infarction
4	Courand et al. [6]	2014	1	63/m	No	Retrosternal pain/prostate cancer	Anterior ST segment elevation myocardial infarction
5	Saker et al. [44]	2018	1	69/f	Recent death of husband, stressful computer class	None/hypertension	Non-ST elevation myocardial infarction with severe left ventricular systolic dysfunction
6	Petrea et al. [37]	2008	1	72/f	Altercation	Left chest pressure/none	Takotsubo syndrome (laevocardiogram)
7	Stollberger et al. [48]	2010	1	77/f	Assault	None/hypertension, history of recent syncope	Takotsubo syndrome (TTE)
8	Grautoff et al. [20]	2012	1	69/f	No	None/none	Takotsubo syndrome (laevocardiogram) Complicated by AV-block Type 2 Temporary pacemaker
9	Bobinger et al. [3]	2013	1	62/f	Swimming	Chest pain, dyspnoea/hypothyroidism, TGA	Takotsubo syndrome (TTE)
10	Toussi et al. [52]	2014	1	66/f	Upon death of sister	Dyspnoea, crushing chest pain/hypertension	Takotsubo syndrome (TTE)
11	Jain et al. [25]	2015	1	73/f	Not reported	None/hypertension, type 2 diabetes	Takotsubo syndrome (laevocardiogram)
12	Quick et al. [39]	2015	1	57/f	Recent death of son	Typical symptoms of angina pectoris/none	Takotsubo syndrome (laevocardiogram)
13	Jalanko et al. [26]	2015	1	75/f	Upsetting phone call, recent death of brother	None/hypertension	Isolated troponin elevation
14	Sajeev et al. [43]	2017	1	60/f	Anniversary of the death of a loved one	Chest pain/hypertension	Takotsubo syndrome (laevocardiogram, TTE)
15	Pyle et al. [38]	2018	1	59/f	Anxiety attack, death of son 2 weeks earlier	Chest pressure/multiple sclerosis	Takotsubo syndrome (laevocardiogram)
16	Stollberger et al. [47]	2018	1	57/f	No	Chest pain/none	Takotsubo syndrome (TTE)
17	Finsterer et al. [12]	2019	1	64/m	Funeral of brother-in-law	None/arterial hypertension, history of myocarditis	Takotsubo syndrome (TTE)
18	Tso et al. [53]	2019	1	62/m	Subacute stressor (family court case)	Dull chest pain/TGA	Takotsubo syndrome (laevocardiogram)

Diffusion MRI was not performed except in case 8; this patient showed no hippocampal lesions

f female, *m* male, *TGA* transient global amnesia, *TTE* transthoracic echocardiography

*Procedure performed indicated in brackets

in 4 cases, and TTS in 12 cases. Of these 18 patients, 12 (66.7%) were women, 9 (50%) had symptoms suggestive of acute coronary syndrome, and 11 (61.1%) reported potential stressful triggers. Interestingly, in many of these cases, the diagnosis remained uncertain until invasive cardiologic tests with coronary angiography were performed, which proved apical ballooning as the key finding in TTS. Although all the reported cases of acute myocardial disease in TGA had favourable in-hospital outcomes, ICU monitoring and complications (arrhythmia/left ventricle thrombus) were also reported. This finding challenges the truly benign nature of TGA, and suggests that cardiac diagnostic procedures should potentially be considered in future routine workup of TGA patients—even if otherwise asymptomatic, including at least 1 ECG scan and 2 blood tests a few hours apart, as well as echocardiography in cases with cardiac troponin level elevation, as suggested previously [20, 27].

Finally, in seven cases (4.1%), MRI demonstrated additional small and clinically silent, multiple embolic lesions, a finding that has been previously described in case studies and small case series only and termed "ischemic amnesia" [19, 28, 42]. This finding, along with the main focus of our analysis, suggests that clinically typical, isolated TGA in rare cases might be accompanied by acute cardiac (or cerebral) injury or involvement.

In conclusion, patients with isolated TGA symptoms should be carefully evaluated for potential underlying cardiac comorbidities. Especially those patients with cardiac troponin elevation should be monitored for potential ECG abnormalities and receive a transthoracic echocardiogram. Further research on cardiac vulnerability in TGA should attempt to develop a diagnostic algorithm and assess the potential causes of cardiac injury in TGA.

Author contributions All the authors contributed to the study conception and design, material preparation, data collection and analysis. Kristina Szabo wrote the first draft of the manuscript and all the authors commented on previous versions of the manuscript. All the authors read and approved the final manuscript.

Compliance with ethical standards

Conflicts of interest On behalf of all the authors, the corresponding author states that there is no conflict of interest.

Ethical standard The study was approved by the Ethics Committee of the Medical Faculty Mannheim, Heidelberg University and conformed to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 6th revision, 2008).

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