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Update on Transient Global Amnesia (TGA): Current Theories Underlying the Etiology, Diagnosis, Prognosis, and Management of TGA

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Abstract

Purpose of review This review discusses a condition known as Transient Global Amnesia (TGA). We discuss the most up-to-date theories related to etiology and risk factors, as well as its correlations to other conditions such as Takotsubo cardiomyopathy and reversible cerebral vasoconstriction syndrome (RCVS).

Recent findings In these other conditions, there appears to be an involvement in a mind-brain-body connection, potentially through a sympathetic surge leading to cerebral vasoconstriction and hypoperfusion. Although TGA is thought to be a seemingly benign condition, it can mimic other neurological emergencies such as stroke and seizure. A more thorough understanding of TGA is necessary for appropriate patient counseling.

Summary The etiology of TGA is still unclear but initial diagnosis and management should focus on ruling out conditions, such as seizure and stroke, that require more urgent treatment and monitoring. Overall prognosis of TGA is favorable since it is associated with high likelihood of symptom resolution and a low recurrence risk.

Introduction

Transient Global Amnesia (TGA) was first characterized in 1958 by Miller and Adams [1], and by 1964, they had observed 17 patients who suffered attacks of sudden memory loss without loss of consciousness or any other neurologic deficits [2]. During the attacks, patients would stereotypically repeat questions, often with regards to their location or other orientation questions. Over the course of minutes to hours, these symptoms would eventually self-resolve, lasting no longer than 24 h. A formal set of diagnostic criteria were defined in 1990 by Hodges and Warlow [3]. After studying 153 cases, the diagnosis required that the attack be witnessed, include definitive signs of anterograde amnesia, without loss of consciousness or other neurologic deficits, without epileptic features, and must resolve within 24 h. Although no clear trigger had been identified, either a significant physical or emotional stressor [1] frequently precedes an event. Case reports of TGA have been associated with sexual intercourse [4] as well as after procedures such as carotid artery stenting [5]. Current incidence is suspected to be about 3 to 10 persons per 100,000 population [6] with increased prevalence in people over the age of 50 years [7].

Common symptoms associated with TGA include headache (10%), nausea and/or vomiting (10%) in patients immediately after the attack [3]. Anxiety was also present, and in the day preceding the event, approximately 14% of patients recalled an emotionally stressful episode that had occurred [3]. TGA is a diagnosis of exclusion, and patients should undergo assessment and evaluation for acute ischemic stroke, seizure, toxin ingestion, substance use, psychological conditions, functional disorder, or malingering when clinically appropriate. Several theories have been explored regarding etiologies related to TGA, including vascular causes, epileptic triggers, as well as a type of cortical spreading depolarization seen in migraine. Cortical spreading depolarization (CSD) can depolarize cells and suppress spontaneous activity of neurons, which induces hypoxic stress on neuronal metabolism [8]. Neither cell death nor permanent damage typically occur, as long as normal metabolism can be restored. This is often achieved through dilation of cerebral vasculature to provide additional blood flow. No definitive etiology of TGA has been determined, and this is an area of active future research.

During a 12-year follow-up of 221 TGA patients by the Mayo Clinic [6], there was a similar prevalence of vascular risk factors (hypertension, dyslipidemia, peripheral vascular disease, smoking history), as well as seizures or epilepsy. However, the prevalence of migraine was higher in TGA patients compared to healthy controls. Recurrence rate was found to be 5.4%, and there was no increased risk of subsequent dementia, stroke, or seizure [6]. It is unknown if this recurrence rate is skewed by patients not re-presenting to the emergency department given prior reassurance. Overall, the diagnosis of TGA is thought to have a good prognosis. There were no lasting memory issues in TGA patients, as well as no association between TGA recurrence and cognitive impairment [6].

A neurologist in 2021 published a personal encounter of a TGA episode, which took place during a video conference call. This involved a "dream-like" sense of awareness with sudden onset loss of memory. The episode lasted 50 min and there was no recollection by the neurologist of what happened during this time period. No loss of consciousness or seizure activity was seen on video recording afterwards. MRI obtained 71 h after event demonstrated DWI hyperintensity in left hippocampus, which was not present on MRI 5 h after event. EEG was normal. No known vascular risk factors or history of epilepsy. The lesion was not present on repeat imaging 2 months afterwards [9].

Diagnostic evaluation

A thorough evaluation, preferably by a neurologist, is important in making the correct diagnosis of TGA and ruling out more worrisome mimics. History must be carefully obtained to determine whether the event aligns with the diagnostic features of TGA as systematized in 1990 by Hodges and Warlow

[3]. These include that an episode be witnessed by a reliable bystander, involve signs of anterograde amnesia during the episode, with no other signs of alteration in consciousness or loss of personal identity, no other neurologic deficits, no features concerning for epilepsy, and that the episode must resolve within 24 h. For most patients, the episode last between 1 to 8 h. If the episode appeared to be triggered by an emotional or physical stressor, such as sexual intercourse [4], death of a family member, or temperature changes [10], this further raises suspicion for a TGA episode. In several of these reports, procedural memory notably was spared, such as in one episode that took place during a professional cello concert [11]. The neurologic exam is also very important – positive exam findings or lack thereof are crucial to the diagnosis of TGA or its mimics.

TGA is a clinical diagnosis with multiple key features. Memory loss, namely prominent anterograde amnesia, is often what triggers presentation to the emergency room. Retrograde amnesia can be present as well, though it is not officially part of the diagnostic criteria. Many patients have been shown to repeat similar questions, often with regards to location or what brought them for evaluation. They are typically not aware they are repeating the same questions (often described as being a "broken record"). No other aspects of cognition, such as speech or level of arousal, and no other neurologic deficits involving speech, motor, sensation or coordination are usually noted. The typical patient is between 50 and 70 years old, rarely younger [12]. A slight male predominance at 55% has been noted, both with monophasic and recurrent TGA. This difference was not statistically significant, however [13•].

Additional tests can be performed to exclude other diagnoses. It is prudent to obtain brain magnetic resonance imaging (MRI) or computed tomography (CT) even if description of events is stereotypic of TGA, mainly to rule out mimics. Some patients will have high-signal foci in their hippocampi on magnetic resonance diffusion-weighted imaging (DWI) (Fig. 1). In one study of 10 TGA patients, unilateral DWI-positive lesions were found in 3 patients (30%). No patients had bilateral hippocampal lesions [14]. Among the 3 patients, 2 had lesions in the left hippocampus and 1 had a lesion in the right hippocampus. The specific location is often in the cornu ammonis (CA1) field of the hippocampus [10], which is a region particularly susceptible to hypoxia and cellular stress [15]. Interestingly, these imaging findings appear 24–48 h from initial TGA symptoms, in contrast to diffusion-weighted findings seen in acute ischemia [16]. Many patients will have no imaging abnormalities on their MRI. When DWI changes occur in the hippocampi, repeat imaging often shows resolution of prior findings on diffusion restriction or fluid-attenuated inversion recovery (FLAIR) sequences [17]. This further supports a non-ischemic etiology, which typically demonstrates persistent FLAIR changes. This suggests that there may be transient dysfunction in either the hippocampal system or its connection within the Papez circuit. If there are no red flags with examination or history and no other lesions on DWI, the typical stroke work-up, including vessel imaging, echocardiography, and a hypercoagulability work-up, is sometimes not pursued. Again, the diagnosis of TGA is a diagnosis of exclusion. The use of antiplatelets will be discussed later.

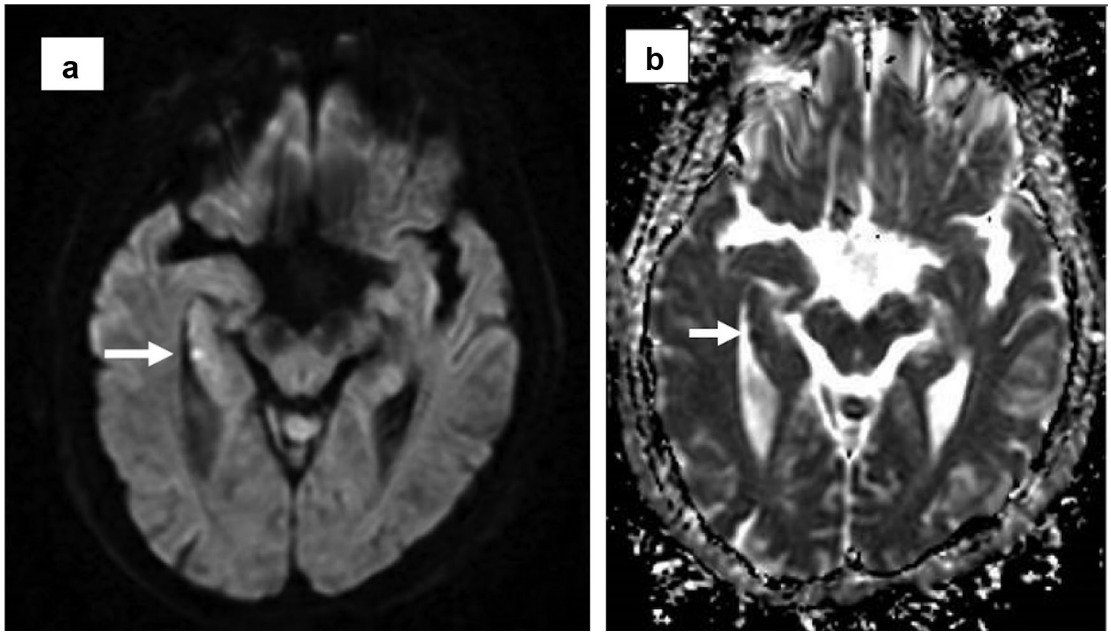

Fig. 1 Example of acute focal diffusion restriction in the right hippocampal body of a patient with history most consistent of transient global amnesia. **a** hyperintensity present on DWI and **b** hypointensity present on ADC sequences.

Transcranial doppler sonography (TCD) of internal jugular veins, basal veins of Rosenthal, and great vein of Galen in TGA patients has been studied to evaluate patients for venous congestion [18]. Although an increase of internal jugular valve insufficiency was seen in TGA patients compared to healthy controls; this did not correspond to intracranial venous reflux. The flow velocities of cerebral veins of patients did not differ significantly from control subjects either at rest or during prolonged Valsalva-associated maneuvers, casting doubts on this hypothesis. TCD, therefore, is not recommended to evaluate patients suspected of having TGA. Perfusion imaging has also been studied in TGA patients and there is some evidence for reduced regional cerebral blood flow (CBF) and regional cerebral blood volume (CBV) in TGA patients compared to control subjects [19].

The utility of electroencephalography (EEG) has also been studied in TGA patients and is consistently unremarkable [20]. In cases where the diagnosis is uncertain, however, EEG may be useful in differentiating from transient epileptic amnesia (TEA), which is usually shorter in duration and accompanied by olfactory auras or oral automatisms, or ruling out other ictal or post ictal presentations.

Depending on the clinical context, other differential diagnoses should be considered such as hypoglycemia, substance use intoxication, herpes simplex encephalitis, or infection leading to toxic-metabolic delirium. Especially for older patients, who are the typical demographic for TGA, medications such as benzodiazepines can cause transient memory loss as a side effect [21].

Mind-brain-body connection

More recent theories have highlighted the interconnection between the brain and body by relating TGA to Takotsubo cardiomyopathy (TTC) or "broken heart" syndrome. Takotsubo cardiomyopathy is a reversible cardiac condition, involving apical ballooning and left ventricular dysfunction, often triggered by a physical or emotional stressor. This can mimic an acute myocardial infarction, although cardiac catheterization reveals absence of obstructive coronary artery disease. Similarly, TGA is a reversible neurologic disorder involving anterograde amnesia, also thought to involve similar triggers. There are even case reports of TTC and TGA co-occurring [22•]. This is thought to involve the "neuro-cardiac axis," which includes the prefrontal cortex, amygdala, insular anterior cingulate cortex and brainstem. It is possible that a catecholamine surge plays a role in both conditions. The increased sympathetic tone leads to elevated central venous return and increased cerebral venous pressure. Theoretical venous congestion of the hippocampi can cause transient disruption in the formation of memories and retrieval of information [23].

Another intriguing theory is a potential overlap between Reversible Cerebral Vasoconstriction Syndrome (RCVS) and TGA ("broken brain" syndrome) [22•]. As the name implies, RCVS is often reversible, and it can be triggered by sympathomimetic agents such as cocaine or by physical or emotional stress. One case report involved a 62-year-old woman who presented with concurrent RCVS and TGA with a previous history of TTC [24]. A 2022 case study found an increasing co-occurrence between RCVS and TGA, with already 7 reported cases linking the two together [25•]. Although more robust studies are needed, this suggests a possible overlap amongst these conditions. In all TTC, RCVS, and TGA, transient organ dysfunction is thought to be triggered by sympathetic hyperactivity, and specifically in RCVS and TGA, vasoconstriction occurs with subsequent hypoperfusion. This theory would explain the transient hippocampal DWI hyperintensities seen in TGA. Of note, RCVS can result in ischemic and hemorrhagic stroke and subarachnoid hemorrhage [26]. Similarly, TTC is not always reversible and can lead to permanent cardiomyopathy [27].

Current treatment/management approaches

Patient counseling

There are no clear guidelines with regards to the treatment of TGA. Since physical and/or emotional stress can precede an episode of TGA, general counseling of patients should include lifestyle guidance regarding stress and emotion management. With all of these conditions, including TTC, RCVS, and TGA, the recurrence is low. For RCVS, recurrence rate was 5.4% [28], and for TTC recurrence rate was about 5% at 6 years [29]. Recurrence rate for TGA was also approximately 5.4% [6]. These conditions also serve as remarkable

reminders of the brain-body connection and the physical manifestation of extreme stress on our bodies.

When counselling patients on risk of recurrence of TGA, there is evidence that younger age of onset (< 60 years) and lack of cerebral microangiography both increase risk of recurrence [30•]. The mean latency to recurrence was 3 years with a mean standard deviation of approximately 2 years after the first episode. A subgroup analysis of this population showed a recurrence risk of 11.3% [30•]. A large meta-analysis found an increased risk of recurrence with a history of migraine, depression, and with sexual intercourse as the inciting trigger of the event [31•]. In this analysis, no association with risk of recurrence was found with patient's sex, age, history of vascular risk factors (hypertension, hyperlipidemia, diabetes, smoking), atrial fibrillation, or other inciting triggers including exercise, showering, vomiting, or coughing [31•].

Use of medications

Currently, there is no evidence that supports the use of antiplatelets or statins in TGA, despite early concerns that diffusion restriction on imaging could be related to ischemia. Importantly, there was no increased risk of ischemic stroke seen in long-term 12-year follow-up at the Mayo clinic [6]. Minimizing polypharmacy may be beneficial, especially avoiding or minimizing benzodiazepines, which have been associated with side effects of transient memory loss [21]. The Beers Criteria [32] provides helpful guidelines for medications to avoid to prevent signs of dementia or cognitive impairment in elderly individuals.

A 2021 study showed that TGA patients are often hypertensive on presentation [30•], likely reflecting acute dysregulation, but do not have higher levels of chronic hypertension. As a result, there is no indication for blood pressure medications at the time of diagnosis. As compared to acute ischemic stroke patients, TGA patients have lower levels of cerebral microangiopathy, lower C-reactive protein levels, and lower blood glucose levels [30•].

Need for follow-up

Patients can follow-up with their primary care provider or a neurologist, who can provide guidance on general healthy lifestyle habits. This includes healthy weight management, stress regulation techniques, smoking cessation, nutrition, as well as proper sleep hygiene. With a completed appropriate work-up, detailed neurologic exam, and history, there is no evidence for activity restriction, including driving [12]. As most learned tasks, such as driving, are unaffected during a TGA event, there is less of a risk of patients putting themselves and others in danger while operating equipment. In addition, there is usually no loss of consciousness associated with the acute memory loss. Counseling regarding the patient's own risk fo recurrence may be helpful. If memory issues persist, follow-up with a neurologist is recommended and further testing, such as lumbar puncture and repeat imaging, may be needed (Table 1).

Table 1. Work up and management of transient global amnesia

Work Up and Management of Transient Global Amnesia	
History	Key features • Sudden onset of anterograde amnesia • Lack of other cognitive and neurological symptoms • Recent physical and/or emotional stressor • Duration of less than 24 h • No loss of personal identity • Lack of recent medication changes • No significant underlying memory deficits
Physical Examination	Vital Signs • Fever would raise suspicion for infectious process, i.e. encephalitis • Patients may be hypertensive and/or tachycardic Neurologic Exam, a detailed neurologic exam with particular attention to the following • Mental status exam: orientation, attention, praxis, language, memory • Visual fields and extraocular movements • Gait examination
Initial Work Up	Lab work • CBC • BMP • Urine toxicology screen Imaging • MRI brain with DWI sequences, ± contrast based on suspicion of malignancy or infection Further testing • Consider EEG if symptoms are episodic or associated with other transient neurologic symptoms
Treatment	• Medication management: minimize polypharmacy, with particular attention to the Beers criteria • No role for the use of antiplatelets if other diagnoses like stroke have been ruled out
Prognosis and Follow Up	• Reassurance • Counseling regarding possible recurrence in higher risk population • Counseling on stress, emotion management, nutrition, weight management, and sleep hygiene • Follow up with primary care doctor and/or neurologist • If symptoms recur, consider repeat imaging and EEG

TGA transient global amnesia, *CBC* complete blood count, *BMP* basic metabolic panel, *MRI* magnetic resonance imaging, *DWI* diffuse weighted imaging, *EEG* electroencephalogram

Conclusion

Although the exact etiology of TGA remains unknown, more recent evidence suggests that there may be similar pathophysiology to conditions such as RCVS and Takotsubo cardiomyopathy. Difference remain amongst the three conditions, namely RCVS is diagnosed by imaging and involves multiple suspected causes, TTC is based on echocardiography and also related to a variety of

triggers, and TGA is less stereotypical without specific imaging biomarkers. As MRI technology advances, it is possible that new imaging results will emerge that will elucidate a clearer etiology. Although our evidence is currently limited to case series, it is possible that TGA, RCVS, and TM exist on a common spectrum and are reflective of a shared mind-brain-body pathophysiology with different end organ presentations. Further studies are needed to explore this relationship, including studies with adequate representation of minority demographics and with longitudinal data over longer timeframes.

Compliance with Ethical Standards

Conflict of Interest
Nara Miriam Michaelson, Sarah A. Friedman and Judy H. Ch'ang have no conflict of interest to disclose.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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