

Transient Global Amnesia: An Uncommon Differential Diagnosis of Transient Ischemic Attack

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Transient global amnesia (TGA) is defined as an acute episode of short-term memory loss that occurs in the absence of other neurologic signs or symptoms and resolves within 24 hours.¹ TGA is an uncommon occurrence, with an incidence of 5 to 11 cases per 100,000 persons per year. The mean age of onset is approximately 60 years, and women are more commonly affected.² TGA is considered to be a relatively benign condition that infrequently recurs (12%–19% of cases).^{3,4} However, there are several other disorders that have varying prognoses with which TGA may be confused. Most notably, TGA is included in the differential diagnosis for transient ischemic attack (TIA), a syndrome that must be ruled out prior to conferring the diagnosis of TGA. This article reports 4 cases demonstrating a spectrum of TGA presentations from 2 high-volume, community-based teaching hospitals. In addition, the etiology, pathogenesis, clinical features, and prognosis of TGA are reviewed.

CASE PRESENTATIONS

Case 1

A 76-year-old woman was brought to the emergency department (ED) by her husband because she experienced an episode of acute confusion and memory loss that occurred a few hours prior to admission. According to her husband, she went to the toilet for a bowel movement around noon, and when she returned she appeared to be confused. She was unable to recollect the date or time, did not recall the events of that morning, and did not remember what she had cooked for dinner the previous night. The episode lasted for approximately 1 hour and resolved spontaneously. No seizure-like activity was witnessed, and there was no recent head trauma. The patient had no significant past medical history. She denied smoking and drank alcohol only occasionally.

When interviewed in the ED, the patient had no

recollection of events that occurred during the episode. Physical and neurologic examinations were completely normal. Computed tomography (CT) scan of her brain revealed no acute hemorrhage or mass, whereas magnetic resonance imaging (MRI) showed periventricular white matter changes suggestive of small vessel disease. Carotid Doppler ultrasound scans were unremarkable. Results of complete blood count (CBC) and blood chemistries were within normal limits, with the exception of serum cholesterol (235 mg/dL [borderline, 200–239 mg/dL]) and low-density lipoprotein (160 mg/dL [normal, <160 mg/dL]) levels. Following overnight observation, the patient was discharged with no memory impairment except for the amnesia of the episode.

Case 2

A 64-year-old woman was brought to the ED due to acute onset of short-term memory impairment. Four hours prior to admission, she developed a “squeezing” headache while she was watching television. Shortly thereafter, she developed right-sided chest pain. The patient subsequently called paramedics and asked a friend to accompany her to the ED. When the patient arrived at the hospital, she did not recollect any of the prior events and denied having chest pain. The patient had a past medical history significant for hypertension, atrial fibrillation, diabetes mellitus type 2, hyperlipidemia, and obesity. Her medications included amiodarone, atenolol, folate, and multivitamins. She denied use of tobacco, alcohol, or intravenous drugs.

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On physical examination, the patient's vital signs were stable, and her only neurologic deficit was impaired memory for the recent events. Results of a Mini-Mental State Examination (MMSE) were normal indicating that the amnesic episode had resolved. CBC and blood chemistry panels were unremarkable. MRI of the brain demonstrated small vessel ischemia with no acute pathology. During the course of her 2-day hospital stay, no cardiac or pulmonary etiology for her chest pain was identified.

Case 3

A 65-year-old woman who was a regular swimmer and diver presented to the ED following acute onset memory loss that apparently developed after swimming, 3 hours prior to admission. As the patient stepped out of the pool, a friend noticed that the patient seemed confused and did not recognize her friend. In the ED, the patient persistently asked questions such as "Why am I here?" and "What happened?" Her memory for remote events in the past was intact. The patient had a past medical history significant for hypertension and hypothyroidism, which were controlled with enalapril and levothyroxine, respectively. Physical examination revealed an elevated blood pressure (152/90 mm Hg), left carotid bruit, and a MMSE score of 27 out of 30. Missed questions on the MMSE exclusively dealt with amnesic components of the examination. She had no other neurologic deficits.

CBC and blood chemistry panels revealed no abnormalities. CT scan and MRI of the brain were normal. The patient's memory loss improved the next day, as did her MMSE score (30/30). Left carotid Doppler ultrasound scans revealed 80% stenosis, for which she underwent left carotid endarterectomy. Two days postsurgery, the patient experienced cardiac arrest following asystole, which was attributed to carotid sinus hypersensitivity following surgery. However, she recovered and had an uneventful hospital stay thereafter, with no residual memory loss. She was discharged after 8 days.

Case 4

A 65-year-old man was brought to the ED by his wife because of sudden-onset memory loss. He did not remember what he had done earlier in the morning, such as shoveling snow from the driveway of their house. He recognized his wife but could not recall the name of the president of United States. As he was agitated and frustrated by his inability to remember things, his wife called the paramedics. She did not witness any seizures or change in consciousness, and the patient denied any other neurologic symptoms. The

Table. Diagnostic Criteria for Transient Global Amnesia

Attacks must be witnessed, and information must be available from a capable observer who was present for most of the attack
There must be clear-cut anterograde amnesia during the attack
Clouding of consciousness and loss of personal identity must be absent, and the cognitive impairment must be limited to amnesia (eg, no aphasia, apraxia)
There should be no accompanying focal neurologic symptoms during the attack and no significant neurologic signs afterwards
Epileptic features must be absent
Attacks must resolve within 24 hr
Patients with recent head injury or active epilepsy (ie, currently on medication or at least 1 seizure in the past 2 yr) are excluded

Data from Hodges JR, Warlow CP. Syndromes of transient amnesia: towards a classification. A study of 153 cases. *J Neurol Neurosurg Psychiatry* 1990;53:834–43.

patient had a past medical history of hypertension, hyperlipidemia, and osteoarthritis, which were all well controlled with irbesartan, atorvastatin, and naproxen, respectively. He never smoked and only occasionally consumed alcohol.

Both the physical and neurologic examinations were unremarkable, as was CT scan of his brain. Approximately 4 hours after onset, the patient regained his memory but had complete amnesia for the morning's events that occurred at home and in the ED. CBC and blood chemistry panels, brain MRI scan, and carotid Duplex ultrasound scan showed no abnormalities.

TRANSIENT GLOBAL AMNESIA

Fisher and Adams first coined the term TGA in 1958.¹ Since then, various authors have described the clinical features of this disorder (**Table**).^{2,3,5,6} TGA is characterized by anterograde and retrograde amnesia.¹ *Anterograde amnesia* refers to impaired memory for events occurring after the onset of amnesia and/or an acute inability to learn new information, whereas *retrograde amnesia* refers to the inability to recall events that occurred before the actual onset of amnesia. The patient retains knowledge of his or her identity and does not lose consciousness. Active epilepsy, recent head trauma, and focal neurologic symptoms (eg, visual disturbances or motor or sensory deficits) are absent both during and after the episode. The amnesic episode resolves within 1 to 24 hours.¹

Etiology and Pathogenesis

Although TGA is a clinically well-defined disorder, its etiology and pathogenesis remain poorly understood. TGA is characterized by a dysfunction of

episodic memory,⁷ which involves the medial temporal lobes of the brain. Many investigators have confirmed that the anatomic site of involvement in TGA is the medial temporal lobe, specifically the hippocampus.¹ One theory that has been proposed to explain the phenomenon involves events that trigger TGA, including Valsalva maneuver (as in case 1), exercise, emotional stress, sexual intercourse, immersion in cold water (as in case 3), painful stimuli, and severe exertion that includes activities such as digging or shoveling (as in case 4).^{5,6} Theoretically, these activities may increase intrathoracic pressure, leading to decreased cerebral venous return from the superior vena cava and increased cerebral venous pressure, thereby causing venous ischemia in the medial temporal lobes due to venous congestion.⁷ An increased prevalence of jugular venous insufficiency in patients with TGA has further supported these findings.^{8,9}

Other hypotheses that link TGA to migraine and epilepsy have not been proven conclusively. Although some patients with epilepsy may have episodes resembling TGA, there is little evidence to suggest that epilepsy causes TGA.⁷ Schmidtke and Ehmsen¹⁰ conducted a case-control study to determine whether TGA represented a migraine aura or migraine equivalent but found no association between TGA and migraine. Also, the late-age distribution of TGA, unusual precipitating triggers, and recent MRI findings argue against the migraine hypothesis.¹¹

Several studies have sought to determine whether arterial ischemia causes TGA. One retrospective study that compared TGA patients with TIA patients observed that TGA did not appear to have arteriosclerotic pathology.⁴ In a recent prospective study with 7 years of follow-up, it was noted that patients with TGA had a more favorable vascular risk profile than those with TIA and a significantly lower risk of combined stroke, myocardial infarction, or death.¹² Another study that used magnetic resonance diffusion-weighted imaging (MR-DWI) to determine whether TGA had an arterial thromboembolic ischemic origin found no evidence to support this theory.¹³ However, Winbeck et al¹⁴ prospectively analyzed MR-DWI signal intensity changes in TIA and TGA patients and compared the clinical characteristics and risk factors of both groups. MR-DWI signal intensity changes were comparable in 36% (10/28) of TGA patients and 28% (21/74) of TIA patients. Overall, TIA patients had a higher prevalence of vascular risk factors as compared with TGA patients. In the TGA group, patients with abnormal MR-DWI significantly more frequently had carotid atherosclerosis. Based on these findings, the authors suggested that

the etiology of TGA could be explained by an ischemic event: arterial thromboembolic ischemia in patients with increased vascular risk factors, and venous ischemia in patients who performed Valsalva-like activities before symptom onset.

Clinical Evaluation

The diagnosis of TGA primarily is a clinical one, and the most widely used diagnostic criteria are those proposed by Caplan et al² and modified by Hodges and Warlow^{5,6} (Table). On presentation, a witness may report that the patient had performed a precipitating activity (eg, Valsalva maneuver) before the episode began. During the episode, the patients repeatedly ask questions despite being answered, and they usually become frustrated because of their intact insight of memory loss. Patients are generally disoriented to time and place during the episode. The MMSE deficits are limited to the amnesic components, and there are no changes in consciousness, no loss of self-awareness, and no focal neurologic deficits. In fact, the presence of neurologic deficits excludes the diagnosis of TGA.¹⁵

TGA is a diagnosis of exclusion. The differential diagnosis includes acute confusional states, complex partial seizures, transient epileptic amnesia, psychogenic amnesia, and, more commonly, TIA.¹⁵ Clinically, it is important to differentiate TGA from TIA because of the excellent prognosis of TGA, which is evident from several studies.^{2,4,12} A basic metabolic panel should be ordered to exclude electrolyte imbalance, which is a common cause of acute mental status changes. If meningoencephalitis is suspected, a lumbar puncture should be performed promptly. Electroencephalogram may be performed to exclude seizures. In regards to imaging, CT scan of the brain is useful to rule out any intracranial hemorrhage or mass lesions. MRI and magnetic resonance angiography scans of the brain are crucial to rule out an acute ischemic event. Although there have been contradictory findings regarding high-signal abnormalities visualized on MR-DWI, recent studies have revealed lesions in the hippocampus.^{1,11} Interestingly, these lesions consistently appeared 48 hours after the acute amnesic episode.¹⁶ However, the diagnostic utility of these lesions still remains unproven, given that such lesions also may be observed in patients with TIA.

Management

TGA is a benign, self-limiting condition, and no specific medical treatment is recommended, other than reassuring the patient. Thrombolytic or antiplatelet therapy is not recommended unless the patient has

cerebrovascular risk factors.⁴ Follow-up neurologic assessments should be performed to identify any worsening of the symptoms or development of any new neurologic deficits, as these abnormalities rule out TGA and may be indicative of a more serious condition.

Prognosis

Most patients with TGA recover without any neurologic or cognitive deficits. In a long-term follow-up study by Gandolfo et al,³ there was no difference in the death rate between patients with TGA and age- and sex-matched patients. Lampl and colleagues¹⁷ recently conducted the largest single photon emission CT study of patients with TGA (N = 16), which revealed that cerebral blood perfusion returned to normal within 3 months of the attack in patients with a first episode of TGA. However, patients with recurrent TGA attacks had abnormal perfusion at 3 months and at 1-year follow-up. Patients who experience recurrent attacks may represent a subset of patients with a non-benign TGA. Recently, there have been concerns about impairment of cognitive function in TGA patients. When compared with age-matched controls after at least 1 year of follow-up, patients with TGA had lower scores on tests evaluating verbal and nonverbal long-term memory and attention.¹⁸

CONCLUSION

TGA is a benign clinical entity with an unclear etiology. Although TGA is not seen commonly, it is important to recognize its clinical characteristics and differentiate it from TIA, which has different prognostic implications. **HP**

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