The aptly named transient global amnesia (TGA) syndrome was initially described more than a century ago by Ribot and later in 2 independent case series. It came to official recognition as a named syndrome after a large series described by Fisher and Adams. Although the clinical syndrome is easily recognized and highly consistent in its characteristic features, the underlying pathophysiology has remained elusive. Proposed mechanisms include focal ischemic lesions, either related to arterial or venous dysfunction, paroxysmal neuronal discharges or epileptic phenomena, or local nonischemic energy failures of other causes. None of these, however, has been clearly demonstrated, although some evidence has been shown for all of these mechanisms. In the past, all investigations of these patients were normal, including brain imaging and electroencephalogram (EEG). With improvements and MRI technology, diffusion-weighted imaging (DWI) has been able to demonstrate focal areas of restricted diffusion, which seem entirely restricted to the CA1 sector of the hippocampus. Nonetheless, the mechanism of this diffusion restriction is uncertain and does not necessarily indicate ischemia, leaving the exact nature of this seemingly benign disorder in doubt after many decades of study. The goal of this review is to summarize the pertinent clinical features, proposed pathophysiology, epidemiology, imaging, and future directions in understanding TGA.

CLINICAL FEATURES AND BASIC APPROACH

The definition of TGA includes an anterograde and retrograde amnesia lasting less than 24 hours, although significant variations from this time frame have been reported. The clinical features are highly characteristic, but if this disorder is not considered, it can cause considerable diagnostic confusion. The usual presentation is a middle-aged patient brought in by family members concerned about stroke or other devastating brain disease. Most clinicians familiar with this syndrome agree that there is frequently a social or physical stress around the time of onset, but this has been difficult to prove in epidemiologic studies. Proposed precipitating events...
include social events such as family gatherings, travel, strenuous activity, pain, sexual intercourse, and even water contact or temperature change. The most characteristic feature is the tendency to repeat the same questions, and often forgetting conversations within just minutes. This can cause difficulty in explaining the diagnosis to patients, in that they often have insight into the fact that something is wrong and are frequently frightened. Reassuring these patients is a challenge because they readily forget that they have just had the condition explained.

The diagnosis of TGA requires that a patient is alert and otherwise seems well. Any encephalopathic patient should be presumed to have an underlying acute condition until proved otherwise. Language function is normal in TGA, as is the remainder of the neurologic examination, with the only deficit being isolated to anterograde memory, with lesser involvement of retrograde memory. Registration is generally preserved, but even brief delays before testing recall reveal dramatic impairment of anterograde memory. Associated symptoms may include headache, a vague sense of dizziness, nausea, fear of dying, and chills or flushes. Many patients are anxious, because they quickly realize that something is wrong, at least partly because of the family’s reaction to their behavior. Bizarre behavior out of character for a patient, loss of self-identity, forgetting names of family members, and dramatic retrograde memory impairment, however, are not characteristic of TGA and may be suggestive of a factitious memory disorder.

Basic investigations in an emergency department should include routine hematology and chemistry, glucose, screening for infection when indicated, and EEG and MRI when there is any doubt about the diagnosis. When the syndrome is clear, EEG and MRI need not be performed urgently, but MRI and EEG should be offered at least on a follow-up basis. In many cases, reassurance to the family and patient allows for discharge home in the care of family members with the patient can be observed until symptoms resolve. Hospital admission is always reasonable, however, to ensure resolution of symptoms and provide a safe environment for the patient, in general leading to the discharge of a healthy patient the following day. As symptoms clear, the period of time for which a patient is amnestic may decrease, but in general there is always some period of time that is never remembered. The prognosis is generally excellent, although some have suggested that long-term deficits in memory may persist in a subclinical fashion. Borroni and colleagues subjected 55 patients who had suffered a TGA episode to standardized neuropsychological testing at least 1 year after the attack and found that they performed significantly worse on tests of memory compared with matched controls, whereas other cognitive domains were comparable.

Diagnostic criteria have been proposed, including: Witnessed anterograde amnesia, absence of encephalopathic symptoms or loss of personal identity, absence of cognitive deficits beyond amnesia, absence of focal neurologic deficits or symptoms of seizures, absence of recent head trauma, and resolution within 24 hours. These criteria can be further summarized to simply state that a patient must have isolated transient amnesia, with normal consciousness and other faculties intact, and rapid improvement. The duration criteria may be generous, because the mean duration of attacks is probably between 4 and 6 hours.

Differential diagnostic possibilities are listed in Box 1. Consideration of seizures is important, especially in diabetic patients, because hypoglycemic seizures can produce an essentially identical transient amnestic syndrome in the postictal period. This probably relates to selective metabolic stress to the CA1 region of the hippocampus in hypoglycaemia and seizures, the same region thought to be affected in TGA. In young patients with apparent TGA, the history should always include questions of myalgias, tongue trauma, and nocturnal incontinence. Other
temporal lobe seizures may also present with isolated postictal amnesia, but this is less common in other disorders, such as mesial temporal sclerosis, compared with hypoglycemic seizures. A careful drug history is always advisable, specifically with respect to benzodiazepines, anticholinergics, and narcotics. Finally, factitious disorders should be considered when this classic description is not seen. Personal identity and recognition of family members are always intact in TGA.

In elderly patients, differential diagnosis should always include stroke, usually of the posterior cerebral artery, which supplies the medial temporal lobe and hippocampal regions. Isolated amnesia as a result of posterior cerebral artery stroke is uncommon, however, and careful assessment for hemianopia suggesting occipital lobe involvement is often revealing. Strategic infarcts of the medial or anterior thalamus or fornix can also produce isolated amnestic syndromes. Thiamine deficiency should be considered in alcoholic patients, those with malabsorption syndromes, or those who have undergone abdominal surgeries that could affect nutritional status. Although this is generally considered a less acute problem, Wernicke encephalopathy certainly can present fulminantly, and consciousness may be relatively preserved. A variety of ocular motility disorders and gait impairment may be associated, but the safest approach is to administer thiamine intravenously if there is any doubt. MRI findings in Wernicke encephalopathy include abnormal signal or DWI changes in the medial thalami, mammillary bodies, periaqueductal region, and tectal plate and less commonly in the cerebellar hemispheres.

**EPIDEMIOLOGY**

The majority of TGA attacks occur in people between the ages of 50 and 70, and it is rarely encountered in young patients; thus, more extensive investigations and hospital admission should be strongly considered in any patient younger than 40, even in otherwise classic cases. The reported incidence rate varies between 3 and 8 per 100,000 people per year. There is no strong gender bias, with various investigators reporting higher prevalence in either gender. Recurrences are relatively uncommon but may be as frequent as 6% to 10% per year. Among 51 patients who were followed for 7 years, the recurrence rate was 8%. Risk factors for a first attack or for recurrent TGA are not well defined, although there have been several valiant attempts. Factors that have been considered include hypertension, dyslipidemia, diabetes, seizures, and migraine, but none of these has consistent evidence of association, although migraine may be a risk factor in younger patients with TGA. Personality

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**Box 1**

**Differential diagnosis of TGA**

- Stroke involving mesial temporal area, thalamus, or fornix
- Delirium (often metabolic or infectious)
- Wernicke encephalopathy/Korsakoff syndrome (thiamine deficiency)
- Psychiatric disorder, dissociative fugue, conversion disorder
- Migraine
- Transient epileptic amnesia
- Nonconvulsive status epilepticus
- Hypoglycemic seizures
- Drug overdose or toxicity
traits may predispose patients to the development of TGA, with one study showing that 82% of 51 patients demonstrated pathologic avoidance behavior toward potentially fearful situations, such as crowded stores, seeing blood, or crossing a bridge. A family history of psychiatric disorders may be a risk factor.

**PATHOPHYSIOLOGY**

The localization of TGA has always been presumed to involve the mesial temporal structures or specifically the hippocampus. The physiologic mechanisms remain difficult to explain in full, however, because investigations (until recently) have been invariably negative, including EEG and neuroimaging. As discussed previously, there is no definite increased risk of transient ischemic attack (TIA) or stroke, seizures, or migraine among patients with TGA, although each of these has been weakly associated in some studies. Abnormalities of venous flow have been investigated recently but without convincing evidence of a primary role for this mechanism in causing focal hippocampal dysfunction. As with any studies using ultrasound, including those proposing venous abnormalities in multiple sclerosis, operator dependence remains problematic in attaining objective results. In addition, the high variability of normal venous anatomy makes interpretation difficult.

The age of onset and sudden deficit are suggestive of ischemic mechanisms, but the prompt resolution of symptoms in all cases makes stroke less likely. Compared with patients with TIA, patients with TGA are less likely to suffer a stroke in the future. Magnetic resonance angiography studies do not demonstrate abnormalities of the intracranial vessels, and perfusion-weighted imaging has also been normal, even during acute attacks. Winbeck and coworkers found that carotid atherosclerosis was more likely to be found among TGA patients with DWI changes compared with controls, using ultrasound examinations. They concluded that a subgroup of TGA patients may have symptoms resulting from ischemia, but this remains a loose association, and other vascular risk factors were not common in this group compared with TIA patients who served as controls. TGA patients did not show increased frequency of microvascular ischemic changes on MRI, again arguing against a primary arterial etiology.

The evidence for an association with migraine is complex. Without any definite causal association, migraine is associated with innumerable disorders, including epilepsy, stroke, patent foramen ovale, high antiphospholipid antibody titers, depression, arterial dissection, fibromyalgia, and dementia, to name a few. The ubiquity of the syndrome makes any association studies difficult to interpret. In the TGA population, some investigators have found a strong association with migraine, whereas others have refuted this. Nonetheless, a migrainous phenomenon is a reasonable candidate to explain TGA based on its well-described mechanisms of paroxysmal neuronal dysfunction with a comparable time course. Cortical spreading depression (CSD) of Leão is generally accepted as the pathophysiologic correlate of migraine with aura and is characterized by transient neuronal depolarization and hyperperfusion, followed by hyperpolarization, hypoperfusion, and neuronal dysfunction, which spreads across the cortex at a rate of 3 to 5 mm per minute. This process can be seen in animal models, including in the hippocampal region, even leading to hypoxic states in the CA1 fields. In 1986, Olesen and Jørgensen proposed CSD as a mechanism for explaining TGA, because induction of CSD in animals produces comparable amnestic behavior that resolves spontaneously. They also proposed that the high hippocampal glutamate concentrations might explain the tendency of TGA to follow emotional events, which could trigger glutamate release. Since then, laboratory data have confirmed a selective vulnerability of the CA1
region to various metabolic stressors, resulting in glutamate excitotoxicity and calcium influx. Experimentally, induction of hippocampal dysfunction is possible by initiating a stress response. True abnormalities of DWI have not been described in migraines unless associated with stroke—however, abnormalities of apparent diffusion coefficient maps have been reported in patients with prolonged aura. Although much of this experimental data does make CSD an attractive explanation, the epidemiology is not supportive because migraine aura is common in young individuals, but TGA is not. It might be hypothesized that in younger patients, compensatory mechanisms prevent the syndrome during CSD of the hippocampal regions. In addition, migraine headaches are generally not associated temporally with TGA attacks. Ultimately, a potential but weak association with migraine is all that is possible in regards to explaining the physiology of TGA.

Epileptic phenomena have been suggested as a cause of transient amnesia since proposed by Hughlings-Jackson in 1889. Quinette and colleagues conducted EEG studies in 106 patients during or soon after an attack of TGA and found that 80% were unremarkable, with the remaining records showing minor, nonepileptiform abnormalities. In 52 patients recorded during the attack, 87% were normal. These findings, which have been consistent in the literature, in combination with the low likelihood of developing epilepsy in TGA patients, eventually led to a search for other mechanisms. There has been a resurgence of interest, however, in so-called transient epileptic amnesia in recent years. Attacks of otherwise classic-appearing TGA associated with clear electrographic seizures have been reported but with considerably shorter time courses of 1 to 3 hours as opposed to 24 hours for typical TGA. Similar clinical features may also be seen after otherwise typical complex partial seizures, with unresponsiveness, automatism, or secondarily generalized seizures followed by an alert but amnestic state. In a few cases recorded during an attack of apparent TGA, nonconvulsive status epilepticus has been found. In one case, a temporal lobe tumor was presumed to have caused a 5-hour episode resembling TGA, with the EEG only showing wicket spikes (a benign variant). The investigators proposed a possible underlying epileptic phenomenon. This syndrome should be considered when there is a history of epilepsy, when attacks are recurrent, or when the duration is atypical. Because up to 70% of patients with TEA may have normal interictal EEG, continued surveillance may be necessary. Prolonged or ambulatory EEG studies in patients with TGA or TEA may be helpful in elucidating the nature of these attacks and better defining the frequency of TEA in a subgroup of patients.

NEUROIMAGING OF TGA

In the past, brain imaging was considered completely unrevealing for the vast majority of TGA cases. Over the last 2 decades, however, reports of DWI abnormalities suggesting ischemic injury have emerged. Other investigators found no DWI changes during attacks of TGA and recommended that if DWI changes are seen and thought to represent ischemic injury, a diagnosis of TGA should not be made. Since that time, there have been variable reports of DWI or apparent diffusion coefficient changes in TGA patients. Ahn and colleagues studied MRI scans of 203 cases of TGA over a 7-year period and found only 16 patients with DWI changes in the hippocampal region, among whom there were no apparent clinical differences. The overall mean time to MRI in this study was 6 hours, whereas those with DWI changes were studied at 9 hours ($P = .002$), suggesting that with careful timing of imaging, more abnormalities may be found. Supporting the importance of timing, Bartsch and coworkers studied the evolution of MRI changes in 29 patients with TGA and found 34 DWI

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lesions localized to the CA1 sector of the hippocampus when studied between 24 and 72 hours. DWI normalization was seen at approximately day 10, which is similar to the time course for ischemic lesions, leading the investigators to suggest a vascular origin for some TGA lesions. Optimal imaging protocols continue to be refined, but practical recommendations are available and include a 3-T magnet, acquisition between 24 and 72 hours after onset, and a 3-mm DWI slice thickness.

Further evidence for local dysfunction of CA1 neurons comes from MR spectroscopy studies of hippocampal DWI lesions, which have demonstrated a lactate peak. Positron emission tomography (PET) and single-photon emission CT (SPECT) studies have been conflicting but do generally support both hypoperfusion and hypometabolism of the hippocampal region. In many cases, however, dysfunction has been seen elsewhere, including the thalamic, frontal, cerebellar, and striatal regions. In most cases, resolution of these changes is expected, but in recurrent TGA, persistent hypoperfusion has been seen as late as 1 year after the initial attack. In general, PET and SPECT studies are congruent with the findings from MRI studies, suggesting metabolic dysfunction in the mesial temporal lobes, although abnormalities in other anatomic regions are commonly seen as well. Unfortunately, this offers little additional insight into underlying mechanisms because altered perfusion and metabolism are also seen in migraine and epilepsy.

**SUMMARY AND FUTURE DIRECTIONS**

With the emergence of advanced imaging and laboratory techniques, the long-held belief that TGA is related to focal hippocampal dysfunction is no longer just a hypothesis. Clearly, there is metabolic stress, mainly localizing to the CA1 sector. Nonetheless, the precise etiology remains unclear, as are the exact triggers of attacks. Is it coincidental that stressors seem to precipitate episodes of TGA? Could this suggest a supply and demand phenomenon, wherein a threshold of metabolic stress is achieved causing energy failure in a metabolically fragile hippocampus? The frequency of DWI changes in TGA patients has not been clearly defined because the optimal imaging parameters have only recently been elucidated and are not available uniformly. The results of such studies may lead to uncertainty regarding treatment—should all patients with DWI lesions be treated as stroke or TIA patients, with initiation of secondary prevention measures? The epidemiology suggests otherwise, but imaging findings of presumed stroke make this less clear. Autopsy studies have not been performed and may be useful in clarifying whether the dysfunction relates to focal ischemia or energy failure of other causes. Prolonged or ambulatory EEG may be useful in identifying a subgroup of patients with epileptic syndromes, which should be considered in recurrent cases or those with unusually short duration. Fortunately, the prognosis for most cases of TGA remains excellent, and the mainstay of management remains recognition and reassurance.

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