ED Evaluation of Transient Global Amnesia

Jeremy Brown, MB BS

From the Department of Emergency Medicine, Boston Medical Center, Boston, MA.

Received for publication December 23, 1996. Revision received March 6, 1997. Accepted for publication March 13, 1997.

Transient global amnesia is an unusual syndrome involving a transient memory loss and inability to form new memories, without affecting other cognitive functions. Although the patient often lacks insight into the problem, the syndrome is very frightening for family members, who frequently present to the ED. The evaluation of the syndrome is the subject of some controversy. This review presents current understanding about the causes of transient global amnesia and an approach to the ED evaluation of the syndrome.

[Brown J: ED evaluation of transient global amnesia. *Ann Emerg Med* October 1997;30:522-526.]

INTRODUCTION

Transient global amnesia (TGA) is a well-described but unusual clinical syndrome involving the self-limited, sudden loss of memory of recent events and transient inability to retain new information.[1] It has an annual incidence of 3.4 to 5.2 per 100,000 each year, increasing to 23.5 per 100,000 in people 50 years and older.[2,3] Although more than 1,000 case reports have been published,[4] wide differences of opinion still remain as to the appropriate evaluation and work up of patients who present with TGA. This problem is further compounded by the lack of universally accepted diagnostic criteria or sound epidemiologic studies, and the inclusion of patients in studies of TGA in whom the true diagnosis is unclear.[5] Because the syndrome is unusual, many physicians have never encountered it, and even when TGA is the diagnosis the ED evaluation of the patient is controversial, with some advocating intensive laboratory and radiologic testing[4,6] and others supporting a more conservative approach.[1-3] In an attempt to help formulate a rational approach to this problem, I present here a review of the literature and a suggested outline of the emergency evaluation of patients with TGA.

The syndrome of TGA was first described by Bender in 1956,[7] but the term was first coined by Fisher and Adams and thoroughly described in their seminal paper published

in 1964.[8] The syndrome consists of the abrupt onset of a temporary, severe anterograde amnesia (the inability to form new memories), usually accompanied by repetitive questioning, in the absence of any focal neurologic features.[9] Behavior is otherwise normal; the patient remains alert and cognition is not impaired, but he or she is often disoriented to time and place.[4,9] The vast majority of attacks last between 1 and 8 hours, with a mean duration of 4.2 hours.[9] After the attack the patient's the ability to form new memories gradually returns, although he or she remains amnestic to events that took place during the episode.

CRITERIA FOR DIAGNOSING TGA

Unfortunately, the term "transient global ischemia" has been applied to several different clinical situations featuring unusually profound memory loss. Some authors of case reports and studies have included patients with unwitnessed attacks, focal neurologic findings, or traumatic head injury, whereas others have excluded such cases.[5] Most investigators now use criteria proposed by Caplan[10] and Hodges and Warlow.[3]

The following criteria from these authors' work should be used in the ED evaluation of TGA: An attack must be witnessed by an observer who can provide additional information. Anterograde amnesia must be present. Clouding of consciousness or loss of personal identity has not occurred (ie, patients know their names). Cognitive impairment is limited to amnesia (ie, no apraxia or aphasia). The patient can have had no recent history of head trauma, and no history of seizures in the preceding 2 years. There are no focal neurologic signs, and no epileptic features.

Another criterion for TGA is resolution of the attack within 24 hours, but the emergency physician will not find this characteristic useful in evaluating an acute episode.

THE CLINICAL SYNDROME

Most cases of TGA occur in people aged 50 years and older.[11] In approximately one third of cases TGA is precipitated by an emotional experience, intense pain or cold, or strenuous physical activity.[11] Well-described precipitating factors include sexual intercourse, swimming in cold water, and emotionally taxing episodes such as being robbed, hearing bad news, or experiencing painful medical procedures.[2,5,11]

Patients may feel "something is wrong," but in many cases there is a profound lack of insight and the patient may have had to be coaxed by a worried observer into coming to the ED.[4] All attacks are characterized by a triad of acute impairment of memory, namely the inability to form new memories of anything occurring during the episode; a temporary long-ranging retrograde amnesia, with more recently acquired memories more at risk; and a relatively short permanent retrograde amnesia, of up to 8 hours, of the most recent memories.[4,11] This short retrograde amnesia gradually shrinks until it remains only for the period between the onset of the attack and full recovery.[12] Subjects are disoriented to time and place, and 60% to 90% exhibit repetitive questioning, which may last throughout the attack[5,10,11] Although they are described as confused by nonmedical personnel, patients do not exhibit the features of a true confusional state. They are attentive, can follow complex commands, and do not confabulate.[4,5,8] Detailed neuropsychologic examination of patients during an attack of TGA shows that personality, complex cognition, problem-solving, semantic knowledge, language, and visuospatial function remain intact.[9] Patients can learn a list of words and retain them when they are able to rehearse but rapidly forget when distracted. Most patients can copy a complex drawing but are unable to recall it properly.[9] Although distant memories tend to be preserved, semantic memory (long-term memory responsible for the storage and integrity of knowledge about the world, including the meaning of words and objects)[13] and "metamemory" (the awareness of what one should know) are usually preserved.[4,9,14] The cause or causes of TGA remain unclear. Some suggest it is a variant of epilepsy[8,11] but there is no good evidence of this.[9] Others have suggested a cerebrovascular origin,[6,15] migraine,[16] or a functional ablation in the hippocampus caused by glutamate release in response to painful or emotional experiences.[17]

DIFFERENTIAL DIAGNOSIS

One of the most remarkable clinical features of TGA is the unusual purity of the way in which it presents. It is a unique phenomenon, and when diagnostic criteria are properly applied, it will become apparent that no other clinical or pathological entity mimics TGA. It is for this reason that a true differential diagnosis is difficult to describe. A differential diagnosis is "a list of alternative explanations for a given sign, symptom, or laboratory test, arranged in descending order of probability"[18] If properly understood, no entity can cause the syndrome of pure TGA. However, several common disorders may be misdiagnosed as TGA.

Acute confusional state is the disorder most commonly misdiagnosed as TGA.[4] Toxin-induced memory loss from alcohol or benzodiazepines is usually evident from a good history, and toxic ingestions causing memory loss are usually accompanied by other clinical stigmata.[19] Careful neurologic examination will usually show these patients to be inattentive and unable to sustain a coherent stream of

thought. Patients with TGA are able to maintain a coherent stream of thought, although disorientation to time may be present in both states. Attention is often reduced in acute confusional states, so that the ability to perform serial sevens or spell "world" backward is impaired.[20] These abilities are not normally affected in TGA. Unlike TGA vicitms, patients in an acute confusional state are often able to learn new data if sufficient time for encoding is allowed.[4]

Transient complex partial seizures may present in the postictal state, with a clinical syndrome not unlike that of TGA. TGA should only be diagnosed if a witness has observed the patient. In this way the likelihood of having missed other expressions of a complex partial seizure are markedly reduced. Transient amnesia is known to occur as a rare manifestation of temporal lobe epilepsy, but such epileptic amnesia can usually be distinguished form TGA by the presence of different clinical features, including absence of repetitive questioning and a perplexed anxious state, the occurrence of amnestic episodes on waking or first thing in the morning, the brief duration of some of the episodes of memory dysfunction, and evidence of seizures on occasions other than those of transient memory loss.[21] The diagnosis should be made with extreme caution, if at all, in a patient with a known history of epilepsy.

Psychogenic amnesia usually occurs in a young population in the presence of a known psychiatric stressor. It is accompanied by personality changes, as well as memory loss for personal identification, and there is no anterograde amnesia or amnestic gap during the episode.[4]

ED EVALUATION

The syndrome of pure TGA is so specific when correctly applied that the diagnosis may safely be made on the basis of physical findings alone. There has been much debate in the literature about the extent to which patients with TGA should be evaluated in the emergency setting. Sandson and Price[4] recently recommended an evaluation including but not limited to a toxicology screen, magnetic resonance imaging of the brain, electroencephalography, Holter monitoring, echocardiography (including a bubble study), and "vascular workup that is probably best done with MR angiography of both the posterior and anterior circulations." Very little evidence supports such an aggressive work up, on an emergency or elective basis. Indeed, the syndrome is benign and, once recognized in its true form, requires little further testing (Table).

Alcohol and a wide variety of toxins have been documented to produce a spectrum of changes in mental status ranging from subtle changes to coma. In a case-control study of 114 patients, no evidence of acute or chronic alcoholism was noted as a causative agent.[5] Because alcohol and the agents detected in routine toxicology screens produce a toxidrome that is usually recognizable and distinct from TGA, there seems to be no role for the routine use of these tests.

Metabolic and electrolyte abnormalities may often present with a change in mental status but do not cause the purity of symptoms seen in true TGA. In a careful case-control study of 18 patients with TGA, no abnormalities of serum glucose, electrolytes, liver chemistries, or coagulation

Table.
Emergency laboratory and radiologic testing for suspected TGA.

Clinical Test	Possible Cause of Change in Mental Status	Overall Logic for Use	Recommendation
Alcohol level determination	Well described	No evidence of causative relationship[5]	Not useful; alcohol intoxication or withdrawal usually apparent and does not cause symptoms of TGA
Toxicology screen	Well described	Needed to exclude toxic causes; recommended by some[4]	No evidence for any toxin producing pure TGA
Hemoglobin/ hematocrit, electrolytes, liver-function tests	Anoxia, metabolic abnormalities	No abnormalities revealed in case-control studies[6]	Not helpful in the absence of other clinical abnormalities
Cerebrospinal fluid	Infection	No abnormalities in 15 of 15 case-control patients[6]	Not helpful in the absence of other clinical abnormalities
Head CT	Space-occupying lesions, bleeding	No evidence of abnormalities in case-control studies using strict definitions[5]	Some case reports of space-occupying lesions found in those with recurrent TGA or secondary focal findings;[22,23] overall, not recommended for first episode
EEG	Atypical epileptic activity	No abnormalities in case-control study;[6] some evidence for mild temporal lobe abnormalities[24]	May be useful in atypically brief or recurrent TGA to rule out epilepsy;[4] overall, not useful

times were seen, and no blood dyscrasias were identified.[6] Overall these tests are not useful in the emergency setting unless there are other clinical indications for them.

A sample of cerebrospinal fluid is always required in suspected central nervous system (CNS) infections unless intracranial pressure is increased. CNS infections do not present with the specific symptoms seen in pure TGA. In 15 cases of pure TGA in which CSF was obtained during the episode, no abnormalities were detected.[6] A lumbar puncture is not recommended unless a CNS infection is suspected.

Intracranial space-occupying lesions and bleeding may cause acute changes in mental status. In one case-control series, 13 patients underwent computed tomography (CT) of the head, 10 within 48 hours of the attack and the other 3 within 3 weeks. Twelve of the scans were contrast enhanced. Five of the 13 scans were interpreted as abnormal; one showed a small thalamic lacuna and another a small posterior thalamic hemorrhagic infarct. A third patient showed old encephalomalacia involving the posterior temporal lobe, and another patient had changes consistent with prior temporal and cerebellar infarction. The fifth patient showed marked temporal and occipital atrophy without focal abnormalities.[6] Although CT abnormalities were identified more frequently in TGA patients than in controls, this study showed no significant difference. In a larger study by Hodges and Warlow,[5] 95 patients with TGA underwent noncontrast CT of the head an average of 40 days after the attack. There were no cases of cerebral tumor; 12% had small lacunar lesions, none of which involved the known memory structures of the medial thalamus and temporal lobe. Compared with the non-TGA group, the proportion of cases with small deep white-matter lesions or atrophy was not significantly different than that in the TGA group, leading the authors of this large study to recommend that routine head CT not be undertaken after a single attack of true TGA.

Space-occupying lesions have been found in patients presenting with TGA. In one case, TGA was reported to be the result of a left temporal hemorrhage, but in the description the patient was reported to have a broad-based gait and an abnormal Romberg test result.[22] These focal deficits mean that a true case of TGA was not reported. In another report,[23] aphasia and a right hemiparesis developed 3 months after the initial transient amnesia, and CT done at that time showed a large mass lesion in the right hemisphere. The authors of this report concluded that in patients with TGA a careful examination should be made to exclude a tumor. This is a sound recommendation, but in the absence of a causative relationship between intracranial tumors and TGA, and against the background of well-performed case-control studies, this search should be based on clinical examination rather than on early CT scanning. In the absence of focal neurologic deficits, CT is not indicated.

Electroencephalography is not routinely performed in the ED, but it is included here because patients or their families may request such a test. One study of EEG findings in TGA patients comprised 10 cases, only one of which involving a patient studied during an attack.[24] The other nine were undertaken 1 to 10 days after the ictus. The EEG was normal in 6 of the 10 patients, and of the other four two had mild temporal-lobe abnormalities, one had bitemporal delta-wave activity with rare sharp waves, and another had occipital theta activity. However, it is not possible from this study to be sure whether the changes occurred after or before the amnestic attacks, although resolution of temporal spike foci in one TGA patient has been reported,[25] indicating that in that patient, at least, the EEG changes were probably caused by the same process underlying TGA. Eighteen patients in a case-control study underwent EEG, and abnormalities were detected in only four (right temporal sharp spikes, left asymmetrical alpha depression, and intermittent rhythmic slowing in two patients).[6] EEG remains a research tool in the study of TGA and should only be undertaken in cases of atypically brief or recurrent TGA to rule out epilepsy.

If a patient presents with all of the features of TGA outlined earlier, there is little evidence that any of these tests is indicated or helpful in obtaining a diagnosis, even if the attack is still active. Although the transient nature of the amnesia is one of its defining features, patients with TGA demonstrate all the other features (eg, lack of neurologic focality and clear mentation), so that the emergency physician can make the diagnosis and reassure the patient and family that the attack will end within 24 hours. Close follow-up should be made in cases in which the attack has not yet ended, but ongoing TGA is no more a matter for concern than resolved TGA. In any case of doubt about the diagnosis, early neurologic consultation should be sought, and on discharge all patients with TGA should have neurologic follow-up.

OUTCOME OF TGA

Given the alarming features of TGA, it is useful to understand the natural history of the attacks. Patients with TGA have a mortality from vascular death approximately nine times *less* than that for their non-TGA counterparts.[5] Rates of later development of epilepsy are no greater in TGA patients than in controls, but in the subgroup of patients presenting with more than one attack of TGA a significantly greater proportion of patients go on to experience epilepsy.[5] It therefore seems appropriate to give patients with recur-

rent attacks of TGA a more guarded prognosis in terms of the later development of epilepsy, and some have suggested cautioning this subgroup of TGA patients against driving for 12 months.[5] The stroke morbidity of TGA patients does not differ from that of the general population,[1] and the risk of a recurrent attack within 5 years is 3% to 20%.[1,5]

SUMMARY

Despite its initial appearance and alarming presentation, a careful review of the literature shows that TGA is a benign syndrome with a low risk of subsequent neurologic or vascular disease. Although some authors have suggested an extensive emergency work-up for these patients,[4,6] there is little evidence to substantiate these recommendations, and elaborate diagnostic procedures are not needed.[1,2,5] The emergency physician should remain aware that these recommendations do not apply to patients with TGA and focal neurologic manifestations, in whom an extensive emergency neurologic investigation remains the standard of care.

REFERERENCES

1. Hinge H-H, Jensen TS, Kjaer M, et al: The prognosis of transient global amnesia: Results of a multicenter study. *Arch Neurol* 1986;43:673-676.

2. Miller JW, Petersen RC, Metter EJ, et al: Transient global amnesia: Clinical characteristics and prognosis. *Neurology* 1987;37:733-737.

3. Hodges JR, Warlow CP: The aetiology of transient global amnesia: A case-control study of 114 cases with prospective follow-up. *Brain* 1990;113:639-657.

4. Sandson TA, Price BH: Transient global amnesia. *Semin Neurol* 1995;15:183-187.

5. Hodges JR, Warlow CP: Syndromes of transient amnesia: Towards a classification: A study of 153 cases. *J Neurol Neurosurg Psychiatry* 1990;53:834-843.

6. Kushner MJ, Hauser WA: Transient global amnesia: A case control study. *Ann Neurol* 1985; 18:684-691.

7. Bender MB: Single episode of confusion with amnesia. *J Hillside Hospital* 1956;5:212-215.

8. Fisher CM, Adams RD: Transient global amnesia. *Acta Neurol Scand* 1964;40(suppl 9):1- 83.

9. Hodges JR,Ward CD: Observations during transient global amnesia: A behavioural and neuropsychological study of five cases. *Brain* 1989;112:595-620.

10. Caplan LR: Transient global amnesia, in Vinken PJ, Bruyn GW, Klawans HL (eds): *Handbook of Clinical Neurology.* Amsterdam: Elsevier Science Publishers, 1985:205-218.

11. Fisher CM: Transient global amnesia: Precipitating activities and other observations. *Arch Neurol* 1982;39:605-608.

12. Croft PB, Heathfield KWG, Swash M: Differential diagnosis of transient amnesia. *BMJ* 1973; 4:593-596.

13. Hodges JR: Semantic memory and frontal executive function during transient global amnesia. *J Neurol Neurosurg Psychiatry* 1994;57:605-608.

14. Evans J, Wilson B, Wraight EP, et al: Neuropsychological and SPECT findings during and after transient global amnesia: Evidence for the differential impairment of remote episodic memory. *J Neurol Neurosurg Psychiatry* 1993;56:1227-1230.

15. Mathew N, Meyer J: Pathogenesis and natural history of transient global amnesia. *Stroke* 1974;5:303-311.

16. Caplan L, Chedru F, Lhermitte F, et al: Transient global amnesia and migraine. *Neurology* 1981;31:1167-1170.

17. Olsen J, Balslev J: Leao's spreading depression in the hippocampus explains transient global amnesia: A hypothesis. *Acta Neurol Scand* 1986;73:219-220.

18. Sapira JD: *The Art and Science of Bedside Diagnosis.* Baltimore, MD: Williams & Wilkins, 1990.

19. Huff J, Plunkett HG: Anterograde amnesia following triazolam use in two emergency physicians. *J Emerg Med* 1989;7:153-155.

20. Shneider S: Organic brain syndrome, in Harwood-Nuss AL, Linden CH, Luten RC (eds): *Clinical Practice of Emergency Medicine.* Philadelphia: Lipincott-Raven, 1996:852-856.

21. Kapur N: Transient epileptic amnesia: A clinical update and reformulation. *J Neurol Neurosurg Psychiatry* 1993;56:1184-1199.

22. Landi G, Giusti MC, Guidotti M: Transient global amnesia due to left temporal haemorrhage. *J Neurol Neurosurg Psychiatry* 1982;45:1062-1063.

23. Lisak RP, Zimmerman RA: Transient global amnesia due to a dominant hemisphere tumor. *Arch Neurol* 1977;34:317-318.

24. Rowan AJ, Protass LM: Transient global amnesia: Clinical and electroencephalographic findings in 10 cases. *Neurology* 1979;29:869-872.

25. Tharp B: The electroencephalogram in tansient global amnesia. *Electroencephalogr Clin Neurophysiol* 1969;26:96-99.

Reprint no. **47/1/84484**

Reprints not available from the author.