

Current Concepts of Cerebrovascular Disease — Stroke

Transient Global Amnesia

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TRANSIENT global amnesia (TGA) is a syndrome occurring in the middle-aged or older patient, manifested by the sudden transient loss of ability to lay down new memories with associated mild to moderate retrograde amnesia without other neurological signs. Bender first described a patient with this syndrome in 1956,¹ but it was Fisher and Adams in 1958 who defined the clinical picture in a series of patients and coined the term "transient global amnesia."^{2,3} Since that time more than 100 papers and case descriptions have been published in an attempt to categorize this puzzling entity.⁴⁻³² The purpose of this review is to examine the natural history, proposed pathogenesis, and prognosis of this syndrome.

TGA is not a rare illness. Although reported infrequently, there are surely numerous cases which do not come to medical attention, either because of its transient nature or its misdiagnosis. Most cases occur in the sixth and seventh decades (age range 21 to 92 years). There is no apparent sex difference. The patients are generally in good health without significant cardiac or cerebrovascular disease. At times the patient notices the abrupt onset and asks, "What's wrong? I'm not thinking well," but more often, only a close observer notes its manifestations. Pallor and anxiety are occasionally seen, but other systemic and focal neurological signs are conspicuously absent. Most striking is the patient's complete inability to learn new information coupled with apparently intact immediate recall. There is always some degree of retrograde amnesia which tends to be maximum at the beginning of an attack and rapidly recedes over time, leaving a short period (usually hours) of total or near total amnesia. Patients often repeat phrases over and over, such as, "Where am I, and what day is today?" A typical episode lasts minutes to hours but no longer than a day. After recovery there is amnesia only for the involved time of the attack. The patient is otherwise again normal.

Numerous case histories have been recorded. Perhaps the most eloquent are those by Fisher and Adams.^{2,3} A representative history is offered from our files:

O.T. was a 69-year-old farmer with a history of hypertension. On the morning of January 28, 1982, he was feeling well when he went outside at 8:00 AM to

begin his chores. The temperature was 0°F. After feeding the cattle, he drove the tractor to the barn where he and his wife moved a large amount of hay. At about 10:00 AM she returned to the house and 15 minutes later heard her husband drive the tractor to the front of the house and leave it running. When she greeted him at the doorway, he first asked what time it was, then what day. He had no complaints at all, and his wife noticed nothing abnormal. He was concerned as to the whereabouts of the tractor and the necessity to move the hay. She assured him that they had just finished working with the hay and that the tractor was waiting outside. Within two or three minutes he asked the same questions again, and on three occasions he went to the front window to view the tractor. Finally, he went out and drove the tractor into the barn only to arrive back in the house and ask her where the tractor was!

Throughout this time he had no complaints of weakness, nor had his wife noticed convulsive movements, agitated behavior, or loss of consciousness. As his wife drove him to the emergency room at 12:30 PM, he asked her what had become of his fingers on his left hand, evidently not remembering that they had been traumatically amputated by farm machinery four months earlier. When they drove past his sister's home, he was able to identify it correctly but could not remember the names of several members of his wife's family. On arrival at the emergency room 30 minutes later, his physical examination was normal, and his memory was beginning to return. A serum glucose was normal, and he was discharged home. Since then his only deficit is persistent, near total, amnesia for a three-hour period from 9:30 to 12:30 that morning.

The above description is quite typical for the majority of patients with TGA. TGA has been associated with a number of other disorders including migraine,^{4,7} intracerebral tumor,^{5,6} diazepam overdose,⁷ cardiac arrhythmia,⁸ presumed embolism during coronary angiography,⁹ cerebral infarction,^{10,11} dissecting aortic aneurysm,¹² myxomatous degeneration of the mitral valve,²⁶ and polycythemia rubra vera.²⁶ Precipitating factors or events occurring in proximity to the onset of the amnesia have included swimming in cold water,³ driving an automobile, participating in strenuous sports,³² and sexual intercourse.^{13,26} Medical illnesses common to patients with TGA have included hypertension, ischemic heart disease, and, on occasion, hyperlipidemia and diabetes. In the pure form of TGA, the neurological examination is normal. Several authors have reported TGA in association with other neurological deficits, but this probably represents a different syndrome with a different natural history.^{14,15}

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globin, hematocrit, serum electrolytes, and fasting blood sugar have been normal. Abnormalities, if present, tend to occur in angiographic and encephalographic examinations. Angiography has been performed in a number of cases, and while some authors have found a propensity for significant cerebrovascular disease (particularly of the vertebrobasilar circulation),¹⁴ others have not. Electroencephalographic abnormalities have been noted anywhere from 0 to 80% of the time. In earlier studies only routine awake tracings using standard electrodes were performed. Often the EEG was performed days to weeks after the episode. Not surprisingly, few abnormalities were seen.^{16, 17} More recently, however, several groups have reported a higher frequency of changes with the use of sleep deprivation and nasopharyngeal electrodes.^{18, 19} The most common abnormalities have been frontotemporal slow waves with or without mesial temporal spikes and sharp transients. Most abnormalities clear over several days, but there are reports of persistent slowing. Computerized tomography (CT) of patients with TGA has shown no abnormality or only atrophy in about half of the patients studied.²⁰ The most common abnormalities are hypodense lesions in the temporal or occipital regions. Thalamic lesions have also been noted. These hypodense lesions, presumably infarctions, are most often left-sided but occasionally bilateral.

Before discussing the proposed theories of pathogenesis, a brief review of memory and its proposed anatomical correlates would be helpful.²¹ Memory can be broken down into three major areas: (1) immediate recall or the ability to reproduce after at most a few minutes a given set of information, (2) remote memory, i.e., the ability to retrieve previously learned material from the past, and finally, (3) recent memory or the ability to learn new information. It is the last type that is almost exclusively and totally affected in TGA. Certainly, there is not a clear demarcation between recent and remote memory, and in fact, a striking retrograde amnesia is almost always seen in TGA. The exact anatomical site of memory is not known. Certain areas of the brain, if damaged, will show memory loss, including the hippocampus, mammillary bodies, fornix, medial temporal lobes, and possibly the dorsomedial nucleus of the thalamus. For the most part these are paired structures, and it is of note that except in rare instances unilateral destruction will not result in significant memory loss. An episode of transient global amnesia is felt to represent a dysfunction in all or part of these areas.

The known causes of amnesia are limited.²¹ Trauma, drug intoxication, alcoholism, most metabolic changes, and CNS infections are quickly excluded by the history, physical, and routine studies. Hypoglycemia and migraine are more difficult to disprove but certainly must not be common. However, migraine has been shown by one group to occur frequently in their series of patients with TGA.^{4, 22, 23} The two theories proposed most often are epileptogenic and cerebrovascular (ischemic) causes. In their original description

Fisher and Adams felt that this syndrome was more likely epileptogenic in origin. The abruptness of onset, brevity, and reversibility of the episodes, coupled with the occasional abnormalities in the EEG led them to suspect a form of epilepsy. Indeed, more recent work by other investigators has shown a striking increase in EEG abnormalities with more refined techniques. Although the epileptic theory is almost impossible to disprove, other features of the disease, such as the length of the attack (hours, not minutes), the otherwise clear faculties of the patient, the lack of generalized convulsion or even convulsive movements during or subsequent to the attacks, and its general lack of recurrence, make epilepsy less appealing.

Most authors feel that TGA represents a form of ischemia to structures of the deep limbic system on the basis of thromboembolic cerebrovascular disease. Amnesic strokes (infarctions) usually occur in the distribution of the posterior cerebral arteries, often with other neurological signs. Certainly, transient ischemic attacks (TIA's) could occur in the same distribution. The benign course of TGA is especially difficult to explain. Recurrent episodes of TGA are uncommon, and progression to more widespread posterior circulation TIA's and stroke is even more uncommon. Furthermore, why are other symptoms and signs so uncommon in a circulation so prone to multiple symptomatology? Perhaps this is not a posterior circulation event at all but instead related to anterior circulation ischemia, such as the recurrent artery of Heubner, as has been suggested by Bender. Or perhaps this is not an atherosclerotic embolus at all but another type of lacuna.

Whichever theory one chooses, it must incorporate in its structure an explanation for the benign nature of this disorder. By far, the most common presentation is that of a single episode of amnesia without recurrence. In the initial series by Bender and by Fisher and Adams, there were no recurrences in an average follow-up of three months. The incidence of TIA and stroke is minimally (if at all) increased over that of the general population. In some series, however, the incidence of recurrence has been as high as 50 to 60% and the occurrence of stroke and TIA much higher. These studies consisted of patients with a higher incidence of initial neurological abnormalities than the original studies and most subsequent ones. It would seem more reasonable to classify these patients as a different subgroup more prone to suffer long-term sequelae. Although initial observations indicated that there were no persistent memory changes, more recent studies have suggested a persistent decrease in verbal long-term memory and verbal IQ can occur after even one episode of TGA.²⁵ Other studies have documented an even more profound change with recurrent episodes.²⁴ However, it would seem that striking changes in memory or personality with a single episode of TGA are quite uncommon.

In summary, transient global amnesia may be defined as the abrupt onset of the inability to store new memories, almost always associated with transient,

although at times striking, retrograde amnesia without other neurological signs, lasting less than 24 hours. The subsequent course is benign, with recurrence uncommon and TIA and stroke rare. The etiology is presumed to be ischemia of the medial temporal lobes, particularly the hippocampus, mammillary bodies, fornix, and the thalamus. The occurrence of TGA in association with other neurological symptoms may represent more severe involvement by the same pathological process, or it may be an entirely different illness. It would appear that long-term memory changes do occur, but the relative frequency and severity are not clear. At this time the benign prognosis does not warrant vigorous treatment.

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