Pathogenesis and Natural History of Transient Global Amnesia

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Abstract: Pathogenesis and Natural History of Transient Global Amnesia

Fourteen patients aged between 49 and 92 years who had suffered from one or more attacks of transient global amnesia (TGA) have been followed for a mean interval of 30 months. Thirteen patients had one or more risk factors for cerebrovascular disease, such as hypertension, cardiac abnormalities, diabetes and hyperlipidemia. Clinical evidence for vertebrobasilar arterial insufficiency was demonstrated in 11 cases. EEG examination revealed bitemporal or bioccipital slow wave activity. Four-vessel arteriography showed atherosclerotic, stenotic, or occlusive lesions predominantly in the vertebrobasilar and posterior cerebral arterial systems. Five patients without recurrence of TGA showed no permanent impairment of memory, whereas eight who had recurrent attacks of TGA showed permanent memory impairment as well as mild visual-spatial or visual-motor dyspraxia as judged by neuropsychological tests on follow-up visits. "Amnesic stroke" with permanent and gross memory defect and dyspraxia occurred in two patients.

It is concluded that the majority of transient global amnesic episodes in the elderly or in those with the risk factors listed above result from cerebrovascular insufficiency particularly in the territory of vertebrobasilar and posterior cerebral arterial systems (which supply major portions of the ascending reticular activating system, parahippocampal-fornical-mamillary system, inferomedial aspects of the temporal lobe and occipital lobe). Repeated attacks of TGA are not rare and with each attack the likelihood increases of permanent memory deficits and progressive dementia. A rarer outcome is cerebral infarction in the territory of posterior cerebral arteries commonly referred to as "amnesic stroke."

Additional Key Words
dementia
vertebrobasilar insufficiency
amnesic stroke
posterior cerebral arteries

The transient global amnesia syndrome (TGA) may be defined as the sudden onset of episodes of loss of memory for recent events and inability to recall recently learned information associated with retrograde amnesia. During these amnesic episodes, patients appear alert and retain much of their personal identity but are confused, and usually become upset and concerned about their memory loss, frequently repeating the same questions. Earlier publications on this subject have mainly dealt with purely clinical descriptions of this amnesic syndrome in order to establish the organic nature of the condition and to differentiate it from hysterical or motivated amnesia. Because it is a transient cerebral disorder usually with recovery, epilepsy, migraine, hypoglycemia and transient cerebral ischemia have all been considered as possible etiological factors. Review of the literature reveals that the majority of opinion concedes that in the elderly, TGA are usually due to episodes of transient cerebral ischemia. This opinion was based on consideration of such factors as the age at onset and lack of history and clinical features usually seen in patients with epilepsy, migraine or hypoglycemia. Nevertheless, adequate substantiation of the cerebrovascular etiology has not been available in the majority of reports, and we know...
of no prospective study to determine the natural history of TGA. The present communication reports a prospective study of 14 patients with TGA with special reference to the pathogenesis and natural history of the condition.

Case Material

A group of 14 patients have been followed for a mean interval of 30 months following an episode (or episodes) of TGA. Thirteen patients were admitted to the inpatient service of the Baylor-Methodist Center for Cerebrovascular Research and one patient requested that the investigation be limited to outpatient visits. A detailed general medical and neurological history, with special regard to risk factors for cerebrovascular disease, was obtained in all cases. Careful inquiry of prior medical problems was made in order to rule out the possibility of epilepsy, migraine, hypoglycemia and/or psychiatric illness. Other points routinely investigated in the history-taking were: (1) number of TGA episodes, (2) other transient neurological symptoms which might have occurred during or between attacks of TGA, and (3) occurrence of any permanent neurological or neuropsychological deficit with special reference to permanent change in memory function. All patients had detailed general medical and neurological examinations, which were documented initially and at regular intervals thereafter. Ten patients also were evaluated by a cardiologist during hospital admission.

Laboratory examinations included fasting blood sugar, glucose tolerance test (in seven cases), BUN, creatinine, serum cholesterol, triglycerides, serum lipoprotein electrophoresis, complete blood count, sedimentation rate and urinalysis. Chest x-ray, EKG and brain scan were performed in all cases. Thirteen had serial electroencephalograms during the follow-up period. EEG was accomplished at varying periods of time after an episode of TGA, the closest interval being 12 hours. A four-vessel cerebral arteriogram was obtained in 12 patients, and five had measurements of regional cerebral blood flow (rCBF) using the gamma camera and intracarotid injection of $^{133}$Xe as the indicator. Detailed neuropsychological testing was carried out in eight patients at the time of initial admission and periodically during follow-up admissions. The battery of psychological tests administered is shown in table 1.

Results

The average follow-up was 30 months. The age of the patients ranged from 49 to 92 years. There were six males and eight females (fig. 1). Thirteen of the 14 patients studied (92%) had one or more risk factors for cerebrovascular disease, as defined by the Stroke Council of the American Heart Association. Eleven patients (78%) were found to have various combinations of coronary heart disease, cardiac enlargement by x-ray, left ventricular hypertrophy by
EKG, cardiac dysrhythmia or congestive heart failure. Nine (64%) had essential hypertension with blood pressures of 160/95 mm Hg or greater; there were four cases (28%) with diabetes mellitus and four cases (28%) with hyperlipidemia.

**ASSOCIATION OF SIGNS AND SYMPTOMS OF VERTEBROBASILAR INSUFFICIENCY**

Eleven of 14 patients (78%) exhibited one or more signs or symptoms which are generally considered to be due to ischemia within the vertebrobasilar territory (fig. 3). These signs and symptoms of vertebrobasilar insufficiency mainly occurred between episodes of TGA, although various combinations of light-headedness, bilateral blurring of vision, ataxia and occipital headache actually occurred during the TGA attack itself in four patients.

**ASSOCIATION OF SIGNS AND SYMPTOMS OF CAROTID INSUFFICIENCY**

Only two patients (14%) showed clinical evidence of ischemia in the territory of the internal carotid artery. One case complained of an attack of amaurosis fugax with mild hemiparesis and the other complained of an attack of mild dysphasia with hemiparesis. These occurred between the episodes of TGA in the case with amaurosis fugax and three months prior to the episode of TGA in the case with dysphasia.

**EEG**

Pertinent EEG findings in the series of cases are summarized in table 2. In ten patients, the EEG was considered abnormal. Bitemporal and bioccipital slow waves, often paroxysmal in nature, were the most common abnormalities. They were often asymmetrical with left temporal areas showing more prominent slow waves in four of six cases. In one patient, a recording of the EEG 12 hours after the TGA attack showed bitemporal sharp wave activity which eventually disappeared. None of these patients showed spike activity or well-defined epileptiform activity in any of the serial EEGs performed.
SIGNs AND SYMPTOMS OF VERTEBROBASILAR INSUFFICIENCY IN PATIENTS WITH TGA

Drop Attacks
Ataxia
Vertigo, Nausea, Vomiting
Nystagmus
Dizziness or Lightheadedness
Syncope
Diplopia
Oscillopsia
Unilateral or bilateral, or altering paresthesia or weakness.
Circumoral Paresthesia
Tremor
Cortical Blindness
Episodic Bilateral Blurred Vision
Occipital Headache
One or more of the above

NUMBER OF PATIENTS

FIGURE 3

Incidence of signs and symptoms of vertebrobasilar insufficiency in patients with TGA.

TABLE 2

EEG in Transient Global Amnesia

<table>
<thead>
<tr>
<th>Type of abnormality</th>
<th>No. of patients</th>
<th>Symmetrical</th>
<th>Asymmetrical</th>
<th>Predominant right</th>
<th>Predominant left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bitemporal slow waves</td>
<td>6</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Occipital slow waves</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Bifrontal slow waves</td>
<td>2</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Diffusely slow waves</td>
<td>1</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
NEUROPSYCHOLOGICAL TESTING

The subsequent course of the disorder is summarized for the 14 patients in table 4. In five patients no further episodes of TGA were observed in the follow-up interval and none showed impaired memory or other mental functions during the follow-up interval. One case (no. 14) presented eventually with the acute onset of an “amnesic stroke” characterized by sudden loss of memory, right homonymous hemianopia, visual agnosia, color agnosia, alexia and anomic aphasia which has persisted for several months. Recurrence of TGA attacks was observed in eight patients during the follow-up period. The frequency of recurrence ranged from one to numerous later attacks. All cases with recurrent attacks of TGA developed permanent memory loss documented by poor performance in the Wechsler Memory Scale. These cases also had impairment of visual-spatial and visual-motor functions without lateralization to the right hemisphere. One patient (case no. 2), who had seven prior episodes of TGA and subsequent dementia, eventually developed an “amnesic stroke” (similar to case no. 14). In addition to the sudden onset of global amnesia, the patient had a right homonymous hemianopia, anomic aphasia, visual agnosia, difficulty in naming colors and mild transient hemiparesis. Brain scan showed an increased uptake of technetium(99m) consistent with infarction of the left occipital area.

Discussion

For clinical purposes, memory may be conveniently divided into three subdivisions: immediate, recent, and remote. According to the clinical studies of Symonds,11 the neural substrate for memory consists of memory units registered in a vast number of neurons. As in all biological systems, this storage has a tendency to decay but is believed to be reinforced by the limbic system, which functions as a strong activating system. If the activating system is destroyed, the ability to store new memory is lost and stored memory decays. According to this theory, recently stored memory is the first to be lost since it is reinforced the least. If this hypothesis is correct, it seems reasonable to conclude that transient global amnesia results from temporary inactivation of the limbic system.

Previous clinicopathological studies of Victor et al.,12 Scoville and Milner,13 and Gless and Griffith14 emphasize that amnesic disorders in man arise from bilateral lesions of the hippocampal formation (gyrus dentatus, hippocampus and parahippocampal gyrus), whereas they are not seen with more anterior lesions (of the uncus, the amygdaloid body and extreme...
Retrograde right brachial arteriogram showing stenosis of right posterior cerebral artery (arrow) and irregular atherosclerotic lesions at the origin of both posterior cerebral arteries (patient no. 4).

Anterior portion of the hippocampus. Bilateral occlusion of the posterior cerebral arteries produces ischemia and infarction in the inferomedial portion of the temporal lobes and related structures (specifically in the hippocampal formation, fornix and mamillary body) and results in permanent loss of recent memory. Nine cases of “amnesic stroke” reported in the important study of Benson et al. confirm the importance of the territory supplied by both posterior cerebral arteries in relation to memory.
In the first series of TGA to be reported by Fisher and Adams, two patients had symptoms of brain stem and occipital lobe dysfunction, which may be assumed to be secondary to ischemia from embolization and bilateral occlusion of the posterior cerebral arteries, although there was no confirmatory pathological or arteriographical evidence. Surprisingly, while Fisher and Adams considered transient cerebral ischemia as a cause of TGA, they rejected it as unlikely because of the absence of other evidence of cerebral ischemia or infarction and because patients with cerebral infarction usually do not have transient amnesia. Nevertheless, Poser and Ziegler, in a series of case reports concerned with seven patients with TGA, used cogent clinical arguments to establish cerebrovascular insufficiency as the cause of TGA, although they could provide no information concerning any regional area of cerebral ischemia responsible for amnesia. A valuable contribution concerning this point was made by Steinmetz and Vroom, who reported four ad-
Table 4

<table>
<thead>
<tr>
<th>Case no.</th>
<th>No. of episodes</th>
<th>No change in mental status</th>
<th>Dementia</th>
<th>Amnesic stroke</th>
<th>Mean rCBF (ml/100 gm/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>7</td>
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<td>34.8</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>+ + +</td>
<td></td>
<td></td>
<td>31.5</td>
</tr>
<tr>
<td>4</td>
<td>Numerous</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td>1</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
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<td>9</td>
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<td></td>
</tr>
<tr>
<td>14</td>
<td>1</td>
<td>+</td>
<td>+</td>
<td></td>
<td>34.2</td>
</tr>
</tbody>
</table>

Additional cases of TGA, two of whom showed clinical evidence of vertebrobasilar ischemia. These authors favored posterior cerebral artery ischemia as the etiology based on the presence of bitemporal EEG abnormalities and neuropsychological deficits indicating bitemporal lesions. Likewise, Shuttleworth and Wise reported two cases of TGA due to presumed arterial embolism of the posterior cerebral arterial systems occurring as a complication of cardiogenic angiography. The present authors have seen in consultation two cases of transient cortical blindness with transient amnesia followed by complete recovery in 24 hours as a rare complication of selective vertebral angiography.

Transient ischemia affecting the inferomedial portion of the temporal lobes and related structures is within the terminal territory supplied by the posterior cerebral arteries and appears to be a logical explanation for the pathogenesis of TGA as evidenced by the present series of cases as well as individual case reports cited in the literature. The frequent onset of symptoms during the sixth to eighth decades, the absence of a history of epilepsy or EEG evidence of convulsive disorders, together with the absence of hypoglycemia, migraine, brain tumor, alcoholism or psychiatric illness in the present series of patients, support transient ischemia as the pathogenic factor in TGA. The associated high incidence of risk factors for cardiovascular disease such as cardiac abnormalities, hypertension, diabetes, and hyperlipidemia lends further support to their vascular nature. The association of transient ischemia with vertebrobasilar insufficiency in 11 of 14 patients during or between attacks of TGA strengthens the argument that they are due to ischemia in the vertebrobasilar system. Bitemporal and bioccipital EEG abnormalities and, above all, arteriographical evidence of stenotic or occlusive arteriosclerotic lesions seen in the vertebrobasilar and posterior cerebral arterial systems has been confirmed in the majority of our patients. Finally, regional cerebral blood flow measurements showed focal reduction in rCBF values in the mid and posterior temporal regions.

Recurrence of TGA was a striking feature in our series, whereas Fisher and Adams found recurrence in only one patient out of 17. Their study, however, did not include a prospective follow-up. Steinmetz and Vroom also reported multiple attacks of TGA, and Poser and Ziegler documented numerous episodes in four of their seven cases. These experiences suggest that recurrence of TGA is not uncommon and indeed appears to be a striking feature in the natural history of the disease.

Furthermore, the present series indicates that permanent memory deficits and progressive dementia are likely to follow repeated episodes of TGA. This was evident from the clinical course in eight of our patients who developed various degrees of dementia during the follow-up (Table 4). Each of the eight patients had more than one attack of TGA, whereas the other six patients in our series who showed no change in mental status had only one episode. The predominant defects were in the Wechsler Memory Scale and visual-spatial discrimination with relative sparing of other higher functions, in agreement with the hypothesis that eventually irreversible damage occurs to inferior medial temporal lobes and neighboring related structures. Table 4 suggests that development of permanent memory impairment and dementia is to some extent predictable and occurs predominantly in patients who have more than one attack of TGA. It may be noted that permanent memory loss was reported by Steinmetz and Vroom in one of their patients who had multiple episodes of TGA.

Two of our patients developed "amnesic stroke,"
TRANSIENT GLOBAL AMNESIA

with clinical signs of acute infarction in the distribution of the posterior cerebral artery. One (case no. 14) had one episode of TGA and the other (case no. 2) had seven episodes of TGA, and consequently moderate dementia prior to the “amnesic stroke.” Both patients showed homonymous field defects, visual agnosia, difficulty in recognizing colors, alexia and anomia. Four-vessel arteriography confirmed occlusive stenotic disease of both posterior cerebral arteries in case no. 14, and the brain scan was positive in the left occipital area for case no. 2.

Conclusion

It thus appears not only from our own experience but also from cases reviewed in the literature that most TGA episodes in the elderly result from transient ischemia in the territory of the vertebrobasilar-posterior cerebral arterial system which supplies major portions of the ascending reticular activating system, the parahippocampal-fornical-mamillary system, inferomedial portions of the temporal lobe, and the occipital lobe. Recurrence of TGA is not uncommon, and repeated attacks may result in permanent loss of memory. A smaller number of patients may eventually develop clinically detectable infarction referred to as “amnesic stroke.” According to these views, even in established cases of senile or arteriosclerotic dementia, a detailed history may reveal previous episodes of TGA. The study thus has important clinical implications in that early recognition of TGA, proper control of hypertension, diabetes, hyperlipidemia and cardiac dysrhythmia as well as treatment with cerebral vasodilators and agents which prevent platelet aggregation in cases where embolism is suspected from atherosclerotic plaques, may reduce the incidence of permanent memory deficits and dementia.

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Stroke. 1974;5:303-311
doi: 10.1161/01.STR.5.3.303

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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