Transient global amnesia

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Introduction

Overview

Transient global amnesia represents an episode of acute onset of transient global anterograde amnesia, with a variable degree of impairment of retrograde memory, which is not associated with any other major neurologic signs or symptoms. Resolution is gradual, with subjective recovery occurring in two thirds of patients within 2 to 12 hours and, in almost all, within 24 hours. In this article, the author explains that the etiology is still controversial and could be explained by an ischemic event due to arterial thromboembolic ischemia in a subgroup of patients with increased vascular risk factors. PET studies usually show hypometabolism in the hippocampi and mesial temporal lobes. An acute effect on hippocampal cornu ammonis neurons has been proposed as the functional correlate of amnesia, reflecting a transient disruption in the hippocampus memory circuits. It has been suggested that not only is memory affected, but executive functions are diminished as well.

Key points

- Transient global amnesia is characterized by acute onset of transient global anterograde amnesia that is not associated with any other major neurologic signs or symptoms.
- Amnesia resolves gradually, usually within about 2 to 12 hours.
- Recurrence is low, about 2.5% to 5% per year.
- In a significant percentage of cases, a precipitant factor (physical or psychological) can be identified.

Historical note and terminology

Fisher and Adams coined the term "transient global amnesia," but this syndrome was first described in 1956 by Bender as the "syndrome of [an] isolated episode of confusion with amnesia" and by Guyotat and Courjon as "les ictus amnesiques" (Bender 1956; Guyotat and Courjon 1956; Fisher and Adams 1958). Probably before 1950 it was interpreted either as a psychogenic amnesia or as an amnesia occurring after an emotional shock (Gil et al 2010). The essential features are an episode of acute onset of transient global anterograde amnesia, with a variable degree of impairment of retrograde memory, which is not associated with any other major neurologic signs or symptoms (Bender 1956). Since this syndrome's recognition, controversy has surrounded its pathogenesis, treatment, and prognosis.

Clinical manifestations

Presentation and course

Typically, the onset is abrupt, and anterograde memory is profoundly impaired. Patients are disoriented in time and often in place but never to person. Particulars are forgotten even after repeated practice, resulting in ideational and motor perseveration. Patients recognize their memory deficits and repeatedly ask orienting questions and also, "Why can't I remember?" (Bender 1956). Retrograde memory is variably disturbed, lasting hours to years. Patients often do not recognize acquaintances but can usually recall their own name and recognize close relatives. Immediate memory, as demonstrated by the patient's ability to immediately repeat several digits or words, and procedural memory, as demonstrated by the patient's ability to do complex tasks (eg, driving), are preserved (Evers et al 2002). Raised level of anxiety and a depressed mood are observed (Hainselin et al 2012). Patients appear confused, tending to get lost once outside familiar surroundings. Alertness is normal. General knowledge and ability to perform complex tasks, such as arithmetic, reading, writing, driving a car, and even performing a challenging musical concert (Thakur and Ropper 2011) are usually unaffected. During the attack, approximately 10% complain of a headache (Hodges and Warlow

1990a; Zorzon et al 1995). Transient oculomotor abnormalities may be present (Yang et al 2009). No other major neurologic symptoms, signs, or overt seizure manifestations are present. Resolution is gradual, with subjective recovery occurring in two thirds of patients within 2 to 12 hours and, in almost all, within 24 hours.

Detailed neuropsychological testing has been performed during attacks of transient global amnesia. An almost complete loss of short-term memory occurs, and a striking retrograde amnesia for both verbal and nonverbal facts is present, although the extent of the retrograde amnesia is variable, with more distant memories usually being spared. A defect in dating past memories exists. Immediate memory (ie, digit span) is spared. The impairment of anterograde memory is global, affecting verbal and nonverbal memory to a similar degree, and it is not material specific (Kritchevsky et al 1997). Jia and colleagues studied 3 patients with transient global amnesia using the Mini-Mental State Examination (MMSE), revised Wechsler memory scale (WMS-R), and MRI scans. Using (18)F-labeled deoxyglucose as the tracer, patients were given a PET examination at different periods during recovery. No obvious abnormality was found in MMSE and MRI scans in the 3 patients. However, WMS-R examination and cerebral PET imaging displayed cognitive dysfunction of various degrees and low metabolism in local areas related to memory in 2 of 3 patients. It was concluded that in transient global amnesia patients, cognitive function and cerebral metabolic levels are closely correlated with duration of symptoms (Jia et al 2002).

Personality and complex cognition, such as abstract thinking, problem solving, and language, are preserved. Memory of material required to give meaning and continuity to sensory experience is normal. During recovery, distant memories tend to return before more recent ones (Hodges and Ward 1989). Significant impairments of both anterograde and retrograde episodic memory during the acute phase, with a relative preservation of personal and conceptual semantic knowledge, are generally found. Retrograde amnesia recovers before the anterograde amnesia and anterograde episodic memory recovers gradually (Guillery-Girard et al 2004). Guillery and colleagues report 3 patients who were tested during a transient global amnesia attack, 2 in the early recovery phase and the third during the acute phase, with a semantic priming task involving a restructuring process of conceptual knowledge (Guillery et al 2001). During transient global amnesia, all patients demonstrated priming effects. Results obtained the day after the episode with the same task showed that these effects persisted at least 1 day. The authors concluded that episodic memory does not seem necessary for the acquisition of semantic information. Noël and colleagues found that mild episodic memory disorders can be detected even several months after the transient global amnesia episode (Noël et al 2011).

Quinette and colleagues analyzed working memory and executive functions during transient global amnesia episodes. They showed that subcomponents of working memory, such as the phonological loop and visuospatial sketch pad, were spared in transient global amnesia patients (Quinette et al 2003). Specific executive functions that entailed inhibitory control, dual task performance, updating, and shifting mechanisms were also found to be normal. However, the researchers found that transient global amnesia patients were significantly impaired in the recollection of their episodic memories. They also made reduced numbers of “remember” compared with “know” judgments in the episodic memory test several days after transient global amnesia. They suppose that the selective deficit in recollective episodic memories observed in transient global amnesia may be principally related to medial temporal lobe abnormalities that have been reported in this syndrome. Impairments in frontal/executive functions have also been reported by other authors (Na et al 2013).

A meta-analysis on 152 effect sizes (effect size –d- provides information about how much change is evident across all studies and for subsets of studies) from 25 studies showed that transient global amnesia is characterized by a significant reduction of anterograde (d = 1.89) and a milder reduction of retrograde (d = 1.28) episodic long-term memory. Furthermore, it was found that not only memory is affected, but also executive functions are diminished (d=0.79), although to a lesser degree (Jager et al 2009). Episodic long-term memory and executive function slowly recover.

It was believed that the memory impairment associated with transient global amnesia resolved completely within 24 hours; although it was recognized that memory did not recover for the period during the attack and for a period of 30 minutes to 2 hours just before the onset of the attack (Hodges and Ward 1989). Based on comparisons of patients who have had transient global amnesia with age- and IQ-matched control subjects, neuropsychological evidence shows a mild persistent impairment of both anterograde and retrograde memory after an attack (probably due to the attack itself) although a preexistent deficit cannot be excluded (Hodges and Oxbury 1990; Stillhard et al 1990). These deficits in antegrade and retrograde memory improve slowly, sometimes over a period of several months, usually to within the

normal range (Hodges and Oxbury 1990). Kessler and colleagues analyzed 14 patients with transient global amnesia and observed impairments in both verbal and nonverbal long-term memory and verbal fluency 3 to 4 days after the end of their transient global amnesia (Kessler et al 2001). Caffarra and colleagues have also noted that even at 6 months, verbal memory may still be significantly impaired after an attack of transient global amnesia (Caffarra et al 1981). Long-term difficulties in memory retrieval of both recent semantic and episodic information has been reported (Guillery-Girard 2006). Reduction of categorical learning, attention, and qualitative alterations of spatial strategies suggestive of a planning defect has also been suggested after clinical recovery (Le Pira et al 2005).

Recognized precipitating events include strenuous exercise, intense emotion, sexual intercourse (Bucuk et al 2004), pain, temperature extremes (eg, those produced by swimming in cold water or taking a hot bath), cervical manipulation, coughing spells, and medical procedures (eg, cerebral and cardiac angiography) (Hodges and Warlow 1990a; Minuk et al 1990; Zorzon et al 1995; Benke et al 2005). Such precipitants are present in 33% to 84% of attacks (Frederiks 1993; Zorzon et al 1995). Using a logistic regression analysis, Agosti and colleagues observed that an increased number of trigger events was associated with a higher probability of recurrence of transient global amnesia (Agosti et al 2006). Savitz and Caplan reported a case of transient global amnesia after sildenafil (Viagra) use (Savitz and Caplan 2002). About 50% of the patients report Valsalva-like activities preceding transient global amnesia (Sander et al 2000), and close to 20% experience emotional and psychological stress episodes directly before the transient global amnesia event (Döhring et al 2014). Transient global amnesia has also been reported to be associated with bilateral vertebral artery dissection (Michel et al 2004) and aortic dissection (Mondon et al 2007) and has been reported following the use of ergotamine and dihydroergotamine to treat migraine (Gil-Martinez and Galiano 2004). Hippocampal resection for therapeutic purposes in some epileptic patients is another factor suggested as a precipitant for transient global amnesia (Dupont et al 2008). Noteworthy, the onset of transient global amnesia has also been significantly associated with lower daily, monthly, and seasonal temperature. Using a series of 223 patients, Akkawi and colleagues found that most cases were observed when the temperature was less than 6.9 degrees C, whereas the frequency of transient global amnesia was minimal when it was more than 24 degrees C (Akkawi et al 2006).

Quinette and colleagues analyzed 1353 cases reported in the literature between June 1990 and May 2005 and 142 of their own cases collected at the Caen University Hospital (France) (Quinette et al 2006). In their own cases, 106 EEGs were conducted during or after the episode. Eighty-five (80%) were unremarkable. The remaining 26 revealed minor abnormalities but with no epileptic features. One hundred and two brain CT scans were obtained. Eight (7.8%) revealed minor abnormalities. Forty out of 41 Doppler scans of the supra-aortic vessels were normal. Taking together their own cases with those reported in the literature, the authors present the following general conclusions: (1) differences in the gender ratio are observed when comparing different reports; risk factors may be different in men and women; (2) the vast majority of attacks occur between the ages of 50 and 80; (3) although recurrences have been reported, in most patients, transient global amnesia occurs only once; (4) the only factor significantly associated with an increased risk of transient global amnesia –particularly in younger patients, is migraine; (5) psychological and emotional instability history is frequently found in transient global amnesia patients; these patients may be particularly sensitive to psychological stress; (6) precipitating events (observed in more than 50% of the cases) include emotional stress, physical effort, water contact (temperature change), and sexual intercourse; (7) associated symptoms (more than 70% of the cases) include headache, nausea, and dizziness; (8) more frequently (more than 50% of the cases) the episode begins in the morning; duration is usually 1 to 9 hours; (9) a hierarchical cluster analysis revealed different subgroups of patients; in women, episodes are mainly associated with an emotional precipitating event and certain personality traits, whereas in men, they are usually more frequently associated with physical precipitating events. In younger patients, a history of migraine represents an important risk factor. The authors suggest that transient global amnesia may represent a single manifestation of several physiopathological phenomena. In a retrospective case-control study comparing 293 patients with transient global amnesia, 632 patients with transient ischemic attack, and 293 normal controls, it was found that transient global amnesia patients had a significantly higher prevalence of hyperlipidemia, previous ischemic stroke, and ischemic heart disease (Jang et al 2014).

Prognosis and complications

Prognosis is usually excellent. Patients usually make a good recovery from the event, except for amnesia during and around the event, with little or no risk for cerebrovascular disease (Guidotti et al 1989; Mueller 1989; Gandolfo et al 1992). Gandolfo and colleagues followed 102 patients with transient global amnesia, whose mean age was 62.8 years, for a mean of 82 months (range of 12 to 241 months). There was no difference in the death rate between those with transient global amnesia and sex- and age-matched controls from the general population. Approximately 20% (19 of

102 cases) had recurrent attacks of transient global amnesia. Only 4 patients (4%) later developed a stroke (Gandolfo et al 1992). Mueller reported that within a mean period of observation of 5 years, a first recurrence was followed by 1 further amnesic attack in one fifth and by 2 or more attacks in one tenth of patients. Compared to patients diagnosed with migraine or seizure, patients with transient global amnesia do not seem to face a heightened risk of stroke (Mangla et al 2014). Others have reported a lower rate of recurrence, 2.5% to 5% per year for at least 5 years after the first event (Zorzon et al 1995; Kritchevsky et al 1997). The incidence of subsequent epilepsy is also low. Interestingly, it has been suggested that transient global amnesia represents a risk factor for mild cognitive impairment (Borroni et al 2004).

Clinical vignette

A 67-year-old teacher suddenly became amnestic after walking her dog. Her husband noted that she was oriented to person and knew the names of close friends; however, she was disoriented to time and place and seemed perplexed. She could follow complex commands but was unable to recall something she had been told 5 minutes before. The episode resolved after 10 hours, although she remained largely amnestic about the event. She had migraine without aura, but the episode of amnesia was not associated with headache. Her mother had a similar event after a traumatic experience. During and after the event, neurologic examination was normal. Computerized tomographic brain imaging, Doppler ultrasound of the extracranial cervical vessels, and electroencephalography were normal.

Biological basis

Etiology and pathogenesis

The etiology is unknown. Suggested causes have included a transient ischemic attack (Shuttleworth and Wise 1973; Guidotti et al 1989; Felix et al 2005; Webb and Rothwell 2013), migraine (Yamane et al 1989; Hodges and Warlow 1990a; Lin et al 2014), epilepsy (Fisher and Adams 1964), vein thrombosis (Solheim and Skeidsvoll 2005), central nervous system tumors (Dinca et al 2011), saline-contrast transthoracic echocardiography (Venkatraman and Bauerschmidt 2011), drug intoxication (Ardila and Moreno 1991) or other toxic and metabolic disturbances (Merriam et al 1992), and hysteria (Hodges and Ward 1989). None of these proposed etiologies have gained full acceptance.

A transient ischemic attack that affects the hippocampi and associated mesial structures was thought to be a leading cause of transient global amnesia (Shuttleworth and Wise 1973; Guidotti et al 1989; Li and Hu 2013), although many contest this view (Ghidoni et al 1988; Hodges and Warlow 1990). Supporting evidence includes PET and SPECT studies that show hypoperfusion and hypometabolism in the hippocampi and associated mesial structures during an attack with resolution following the attack (Stillhard et al 1990; Tanabe et al 1991; Liang et al 2009; Ahn et al 2011; Auyeung et al 2011). Furthermore, transient global amnesia may result in permanent hippocampal changes (Scheel et al 2012; Kim et al 2014). Using high-resolution, T2-reversed MRI, Nakada and colleagues observed that the incidence of hippocampal cavities increased with normal aging up to about 40% (Nakada et al 2005). Cavities, however, were found in all the patients who recovered from an episode of transient global amnesia. The authors concluded that hippocampal neuronal loss represents an important sequelae of transient global amnesia. Park and colleagues found in 80 patients that 51% revealed MRI hippocampal cavities, but there were no differences in the clinical factors between the patients with and without such as cavities; by the same token, diffusion-weighted imaging revealed that 24% of the studied cases exhibited high signal intensity in the hippocampus, but again, there were no differences in the clinical factors between the patients with and without high signal intensities in the hippocampus on diffusion-weighted imaging (Park et al 2015). The authors concluded that significant structural differences in the limbic areas between patients with transient global amnesia and the controls could be found.

Matsui and colleagues observed a patient with pure transient global amnesia whose MRI demonstrated a small region of increased signal intensity in the right hippocampus on diffusion-weighted imaging Matsui et al 2002). Functional changes in temporal lobe activity, particularly the temporolimbic circuits, during transient global amnesia have been reported (LaBar et al 2002; Westmacott et al 2008). Interestingly, sometimes the changes have been reported in the right (Matsui et al 2002), other times in the left, hippocampus (Inamura et al 2002), and sometimes bilaterally (Liang et al 2009). Guillery and colleagues reported the concomitant neuropsychological and PET assessment of 2 patients (Guillery et al 2002). Episodic disturbance was characterized by a storage disturbance for 1 case and an incapacity to learn episodic associations in the other, illustrating cognitive heterogeneity despite similar neurologic presentation. PET findings disclosed mild but significant changes in the amygdala (right or left) and left posterior hippocampus, which could account for both the storage disturbance and the inability to associate episodic components. Tiny

hippocampal lesions have been associated with transient global amnesia (Jeong et al 2003). Takeuchi and colleagues studied the areas involved in episodes of transient global amnesia by calculation of cerebral blood flow (Takeuchi et al 2004). Single-photon emission tomography was performed during and after transient global amnesia attacks in 8 patients. The SPET images were anatomically standardized and grouped into 12 segments (callosomarginal, precentral, central, parietal, angular, temporal, posterior cerebral, pericallosal, lenticular nucleus, thalamus, hippocampus, and cerebellum). For the control, SPET was performed on 8 subjects and repeated within 1 month. The correlation between the first and second CBF values of each of the 12 segments was evaluated in the same way for patients with transient global amnesia. Excellent reproducibility between the 2 CBF values was found in all 12 segments of the control subjects. However, a significant correlation between intra-episodic and postepisodic CBF was not shown in the thalamus or angular segments of transient global amnesia patients. The present study suggested that thalamus and angular regions are closely involved in the symptoms of transient global amnesia. Using brain perfusion SPECT, Lampl and colleagues found decreased perfusion in 16 cases during the acute stage. SPECT was normal 3 months later in 13 patients who had a first transient global amnesia episode. However, in 3 patients with recurrent transient global amnesia episodes, the brain perfusion remained abnormal after 1 year (Lampl et al 2004).

Possible explanations for the transient ischemic attack have included thromboembolic occlusion including paradoxical embolus through a patent foramen ovale (Shuttleworth and Wise 1973; Klotzsch et al 1996), vasospasm, hemodynamic mechanisms (Guidotti et al 1989; Zorzon et al 1995), and acute infarcts in the left mesial temporal lobe (Greer et al 2001). A case of acute amnesia resembling transient global amnesia after insertion of a coil into a posterior circulation aneurysm, suggesting an ischemia in the posterior circulation, has been reported (Graff-Radford et al 2013). However, the hypothesis of arterial vasoconstriction as a pathogenic factor in transient global amnesia has been controversial (Baracchini et al 2015).

Some studies noted a high prevalence of vascular risk factors among patients with transient global amnesia, evidence that was said to support a vascular hypothesis and a possible thromboembolic basis. Arterial hypertension, cardiovascular disease, migraine headache, and thyroid disorders had been reported in patients with transient global amnesia (Pai and Yang 1999; Santos et al 2000). Winbeck and colleagues suggested that 2 different conditions could be distinguished in transient global amnesia. The etiology of transient global amnesia could be explained by an ischemic event due to arterial thromboembolic ischemia in 1 subgroup of patients (those with increased vascular risk factors) but due to venous ischemia in another subgroup (with Valsalva-like activities before symptom onset) (Winbeck et al 2005).

An underlying impairment of cerebral venous outflow has been suggested in some patients (Chung et al 2006). At times, the cerebral computerized tomography and single photon emission CT are abnormal; however, against a vascular hypothesis, patients with transient global amnesia tend to have fewer infarcts on cerebral CT than those with transient ischemic attacks (Guidotti et al 1989). Prospective case-controlled studies have also cast significant doubt on the vascular hypothesis because stroke risk factors and vascular morbidity and mortality are no more common in patients with transient global amnesia than normal controls (Guidotti et al 1989; Hodges and Warlow 1990a; Zorzon et al 1995). Thus, ischemia in the posterior cerebral artery is not the usual cause of transient global amnesia, although it can occasionally cause transient dysmnesia and other findings such as a visual field defect. Huber and colleagues performed diffusion-weighted imaging in 10 patients with typical transient global amnesia at an average delay of 18 hours between onset of symptoms and MRI. Cerebrovascular studies (electrocardiography, echocardiography, and extra/transcranial Doppler-sonographic and duplex-ultrasonic investigation) and EEG were normal in all patients. Diffusion-weighted MRI sequences were normal in all patients. Conventional T2-weighted MRI in 3 out of 10 patients showed microangiopathic subcortical changes and lacunar strokes of older origin. The authors conclude that transient global amnesia does not result from a vascular ischemic etiology in the majority of cases (Huber et al 2002).

Bartsch and colleagues analyzed the topography and time course of hippocampal lesions by means of diffusion-weighted imaging in a sample of 41 patients (Bartsch et al 2006). Twenty-nine patients showed lesions in the hippocampus within a time window of 48 hours after onset. Most lesions (94%) were found in the CA-1 sector of the hippocampal cornu ammonis. A follow-up study 4 to 6 months after the event did not find evidence for residual structural lesions. Episodic verbal memory defects in the acute phase were correlated with lesions of the left hemisphere, whereas visuospatial memory deficits were associated with lesions of the right hemisphere. Nonetheless, long-term neuropsychological impairments were not detected 4 to 6 months after the transient global amnesia episode. An acute effect on hippocampal cornu ammonis neurons was suggested by the authors as the functional correlate of amnesia, reflecting a transient disruption of the hippocampus memory circuits (Bartsch et al 2008). Using

diffusion-weighted imaging, Weon and associates found at 3 days post onset that 13 out of 16 patients had single or multiple punctate hyperintense lesions; all of them (except one) were located in the hippocampus (Weon et al 2008). Toledo and colleagues observed a high frequency of punctate diffusion-weighted imaging lesions 12 to 72 hours post onset (in 88% of the studied patients), but no pathological findings were observed at 30 days (Toledo et al 2008). In general, detection rates of hippocampal lesions increase when MRI is performed 2 days after transient global amnesia symptom onset and high-resolution diffusion-weighted imaging is used (Choi et al 2012; Scheel et al 2012; Kim et al 2014). Interestingly, psychometric testing has not revealed long-term differences in cognitive performance between patients with and without hippocampal lesions, as well as compared to healthy subjects (Uttner et al 2012). However, in those patients with lesions in CA1 field of the hippocampus autobiographical memory can be significantly impaired (Bartsch et al 2011).

A diversity of brain abnormalities may be found in a minority of transient global amnesia patients. In a series of 130 cases, structural brain neuroimaging lesions were found in 10% of the cases; however, they were heterogeneous: 9 patients had leptomeningeal cysts, 2 falx meningiomas, 1 cerebellum hemangioma, and 1 white matter parieto-temporal hyperintensities (Agosti et al 2008a). A case of transient global amnesia associated with a unilateral infarction of the fornix was reported (Gupta et al 2015).

Interestingly, transient global amnesia patients have fewer vascular risk factors than transient ischemic attack patients (Maalikjy et al 2003). Comparing transient global amnesia and transient ischemic attack, it has been found that transient global amnesia more frequently has a history of psychiatric conditions and alcohol use and less frequently a history of cardiac or peripheral artery disease (Pantoni et al 2005).

In several case-controlled studies, patients with transient global amnesia have a significantly higher occurrence of migraine than normal and transient ischemic attack control subjects, suggesting that migraine may cause or predispose toward transient global amnesia (Hodges and Warlow 1990a; Zorzon et al 1995; Lin et al 2014). Maggioni and colleagues described twin monozygotic brothers, both presenting episodes of transitory global amnesia observed only during episodes of migraine without aura; this clinical observation may suggest a common genetic trait in both conditions (Maggioni et al 2011). Also, patients have had episodes of transient global amnesia after typical attacks of basilar migraine (Yamane et al 1989; Pradalier et al 2000). Leao spreading depression in the hippocampus has been proposed as a mechanism by which migraine might cause hypoperfusion and hypometabolism in the mesial temporal lobes and thereby cause transient global amnesia (Olesen and Jorgensen 1986; Gorji 2001). However, only a quarter of patients with transient global amnesia have migraine (Zorzon et al 1995), suggesting that migraine is not the only explanation. Also, transient global amnesia tends to be a singular event, whereas migraine is a recurrent disorder, further suggesting that this is not the entire explanation. Potential trigger factors, such as intense emotions or pain, have been identified in patients with transient global amnesia (Zorzon et al 1995). It has been suggested that powerful sensory input may cause a migraine-related spreading depression in the hippocampus or a vasomotor response causing memory dysfunction. Nonetheless, transient global amnesia that occurs during a migraine attack is rare; Donnet found 6 cases of transient global amnesia occurring during a migraine attack among 8821 patients (Donnet 2015).

Epilepsy has been found to cause transient global amnesia in 0% to 4.5% of patients in a prospective series (Guidotti et al 1989; Melo et al 1994; Zorzon et al 1995) and in 7% of patients in a retrospective series (Hodges and Warlow 1990b). Attacks that are brief and repetitive are said to be more likely to be due to epilepsy (Zorzon et al 1995). The lack of altered awareness or cortical dysfunction other than amnesia and the rare findings of epileptiform activity on electroencephalography during attacks suggest that an epileptic basis is untenable in the majority of patients (Giotto et al 1989; Melo et al 1992).

Hodges and Warlow suggest a familial predisposition, in that 2% (2 of 114 cases) of their patients had a family history of transient global amnesia. They also point out that a number of other authors have reported a positive family history of transient global amnesia (Hodges and Warlow 1990b). Consequently, a genetic predisposition has also been suggested (Segers-van Rijn and de Brujin 2010; Davies and Larner 2012). However, Agosti and colleagues did not find evidence of genetic background (Agosti et al 2008b).

Potential risk factors for transient global amnesia are still controversial. Maalikjy and colleagues selected 138 subjects; these included 48 patients with transient global amnesia, 42 age-matched patients with transient ischemic attack, and 48 controls (Maalikjy et al 2003). Patent foramen ovale was studied by contrast transcranial duplex sonography. Retrograde jugular venous flow was tested with air contrast ultrasound venography. This study found that transient

global amnesia patients and controls showed a lower prevalence for vascular risk factors than transient ischemic attack patients. No statistical difference was found between the 3 groups with regard to patent foramen ovale. Air contrast ultrasound venography detected jugular valve incompetence in 72.9% of transient global amnesia participants, 35.7% of the transient ischemic attack group, and 39.5% of controls. It was concluded that transient global amnesia patients have fewer vascular risk factors than transient ischemic attack patients. Although jugular valve incompetence is commonly described (Cejas et al 2010), its contributing role in its pathogenesis is not clearly understood. Agosti and colleagues argue that only in some cases is transient global amnesia associated with Valsalva-like maneuvers and emotional stress, supporting the venous blood congestion hypothesis; in other cases, a different vascular basis unrelated to venous congestion should be assumed (Agosti et al 2010). In young people, it has been reportedly associated with migraine and mild head injuries (eg, while playing football) (Ardila 1989; Tosi and Righetti 1997; Nilsson et al 2005). A case of recurrent transient global amnesia associated with high altitude, and consequently reduced oxygen availability, has been reported (Bucuk et al 2008); another case relates it with prolonged underwater swimming (Jeong e tal 2010); in another reported case, transient global amnesia is observed after prolonged and abnormal head posture (Borelli et al 2011); and also, there is at least 1 case report of marijuana-induced transient global amnesia (Mansour et al 2014).

The pathogenesis of transient global amnesia is unclear. Anterograde and retrograde memory defects in transient global amnesia may be due to an interruption in the transfer of data into and out of long-term storage (Hodges and Ward 1989). It has also been suggested that transient global amnesia is related to a functional disturbance in the brain episodic-memory network (Peer et al 2014).

Amnestic states are well known to correlate with damage to components of the limbic system such as the hippocampi and other mesial temporal structures. SPECT and PET studies during transient global amnesia show hypoperfusion, and PET studies show hypometabolism in the hippocampi and mesial temporal lobes (Stillhard et al 1990; Goldenberg et al 1991; Tanabe et al 1991). Chung and colleagues reported in 7 patients, while they were still symptomatic, a significantly decreased regional cerebral blood flow (rCBF) on their SPECT scans in the inferior and middle frontal gyrus bilaterally, with more prominent left-sided reductions in the superior temporal, precentral, and postcentral gyri, as well as increased rCBF primarily in the right hemisphere within the middle temporal, superior temporal, and inferior frontal gyri, cerebellum, and thalamus (Chung et al 2009).

A study using diffusion-weighted MRI of 10 patients with transient global amnesia (almost all of whom had attacks within the preceding 48 hours) found that 7 had signal change in the left hippocampus, 3 with concomitant changes in the right hippocampus (Strupp et al 1998). The increased signal in the hippocampi on diffusion-weighted MRI likely corresponds to cellular edema in the temporal lobes. Follow-up MRI studies were normal. This study lends strong support to temporal lobe dysfunction, particularly of the dominant lobe, in transient global amnesia. Other SPECT and PET studies performed during or immediately after the period of amnesia have shown unilateral or bilateral alterations in perfusion or metabolism in the thalamic regions, basal ganglia, and various areas of the neocortex (Stillhard et al 1990; Goldenberg et al 1991; Eustache et al 1999). Eustache and colleagues, in a PET study performed during the period of transient global amnesia, showed no change in the hippocampi but did show reduced cerebral blood flow and metabolism in the frontal and temporal cortices (especially inferior temporal cortex), with a mild reduction in cerebral blood flow and normal metabolism in the occipital cortex (Eustache et al 1999). This suggests that, at least in some patients, neocortical involvement may predominate in the pathogenesis of transient global amnesia. This study has also been interpreted as lending support to the hypothesis that transient global amnesia is due to the spreading wave of depression of Leao (Lauritzen 1994). Jovin and colleagues performed follow-up SPECT studies in a patient with transient global amnesia during the episode, 24 hours after the episode, and 3 months after the episode. The initial study showed bilateral mesial temporal lobe hypoperfusion that partially resolved after 24 hours and returned to normal at 3 months. Resolution of the SPECT scan abnormalities correlated well with resolution of memory loss (Jovin et al 2000). The authors suggest that a process causing decreased local metabolism, such as cortical spreading depression, constitutes the primary pathophysiologic mechanism in this case. Jimenez-Caballero and colleagues reported on a transcranial Doppler study carried out in a female patient during the acute phase of the amnesia, which showed no evidence of hemodynamic alterations or significant asymmetries (Jimenez-Caballero et al 2003). Repeating the test after clinical recovery offered values that were similar to those of the previous study. The authors concluded that the basis of this process would not be related to ischemia but instead to a mechanism enabling spreading neurogenic depression that is similar to that which takes place during a migraine attack.

Tikhonova and colleagues analyzed 27 patients with transitory global amnesia in the acute and late (from 7 days)

periods and 31 patients with dyscirculatory encephalopathy and subjective memory impairments (control group) (Tikhonova et al 2003). EEG data and assessment of the P300 cognitive-evoked potential wave established differences in the nature of beta1 activity between these groups. The extent of beta1 activity on the EEG showed different relationships with the latent period of the P300 wave. In the control group, there were increases in beta1 activity with increases in the latent period, but beta1 activity in transient global amnesia decreased with increases in latent period. These changes were most marked in the frontocentral areas. The authors believe that these patterns of changes in EEG and cognitive-evoked potentials provide evidence of the functional nature of transient global amnesia syndrome, which is not related to any damaged brain structure.

A fascinating observation by Merriam and colleagues hints at the molecular mechanisms underlying transient global amnesia. They have suggested that transient global amnesia triggered by intense emotion is likely linked to the benzodiazepine system, as benzodiazepine-induced amnesia in humans causes a profound impairment of antegrade memory but spares retrograde memory. Also, benzodiazepine receptors are linked to GABA(A) receptors and occur in high density in the human hippocampus, an area known to be affected in transient global amnesia (Merriam et al 1992). Danek and colleagues have suggested an association between transient global amnesia and endogenous benzodiazepines (Danek et al 2002). Melo and colleagues also attempt to link transient global amnesia with a disturbance in various neurotransmitter systems. They note that intense effort, emotion, or stress in a patient prone to migraine headaches may alter the activity of unstable serotonergic systems, which may lead to transient global amnesia by 2 possible mechanisms: (1) vasospasm of vessels supplying memory related areas or (2) an inhibitory effect on hippocampal cortex (similar to the spreading wave of depression of Leao) (Melo et al 1992).

Epidemiology"

Onset is usually after 50 years of age, and the mean age of onset is approximately 60 years of age (Zorzon et al 1995). In most studies, either no difference in incidence between sexes (Hodges and Warlow 1990a; Melo et al 1992) or a slight female predominance is noted (Gandolfo et al 1992; Zorzon et al 1995). The incidence has been estimated between 3.4 and 6.8 per 100,000 per annum (Hodges and Warlow 1990a; Berli et al 2009). An annual incidence rate of 6.4 per 100,000 was found in a community-based study in Merano, Italy (Brigo et al 2014). The estimated incidence in persons over 50 years of age is 23.5 to 32 per 100,000 per year (Kritchevsky et al 1997). Most attacks are singular; the rate of recurrence is 2.5% to 5% per year for at least 5 years after the first event (Zorzon et al 1995). At least one third of attacks have an identifiable physical or psychological precipitant (Kritchevsky et al 1997).

Prevention

Unless attacks recur, prophylactic treatment is not recommended. For those who have recurrent attacks, a careful search for possible underlying causes is required. In those with a history of migraine, particularly basilar migraine, and recurrent episodes of transient global amnesia, it is reasonable to begin prophylactic antimigraine treatment such as flunarizine hydrochloride, propranolol, valproic acid, or amitriptyline hydrochloride. Patients with recurrent transient global amnesia and risk factors for cerebral ischemia, such as hypertension and smoking, may be best treated by attending to these factors. The rare case with a clear-cut etiology, such as epilepsy, thromboembolism, or brain tumor, should be specifically treated for these disorders.

Differential diagnosis

The differential diagnosis for transient global amnesia includes head injury, nonconvulsive epilepsy, hysterical amnesia, Korsakoff psychosis, and various causes of acute confusional states such as dementia, drug or alcohol intoxication, and hypoglycemia. Clinical history and examination will often clarify the diagnosis.

Complex partial seizures and transient epileptic amnesia can usually be differentiated from transient global amnesia on clinical grounds, as they are associated with altered consciousness, automatisms, and impaired ability to perform complex tasks (Nicastro et al 2014). Moreover, seizures are briefer and tend to recur more frequently than transient global amnesia. Electroencephalography is the investigative method of choice.

An acute confusional episode differs from transient global amnesia in that the former is characterized by clouding of consciousness, impaired attention, poor clarity of thinking, and distorted perception. In dementia, recurrent confusional episodes with memory impairment are common, but between attacks, memory does not return to normal.

Transient global amnesia may be mistaken for hysterical amnesia as both are frequently precipitated by intense emotional experiences (Hodges and Warlow 1990a). However, unlike transient global amnesia, patients with hysterical amnesia cannot remember their names, addresses, occupations, personal histories, or any fact or event that might shed light on their identities. Also, no ideational preservation takes place; the patients do not appear worried about their condition, and after recovery, recall for events during the attack is often preserved (Bender 1956). Other indicators of hysterical (psychogenic) amnesia include insignificant anterograde amnesia, episodes of amnesia that may last weeks to years, retrograde amnesia that extends over a precisely identifiable time period or that may be material-specific, memory that often returns abruptly (as opposed to the gradual return following transient global amnesia), a poor premorbid personality, a past history of psychosis or attempted suicide, identifiable precipitants and gains, and inconsistent behavior (Hodges and Ward 1989; Kritchevsky et al 1997).

Diagnostic workup

This should start with a search for precipitants, such as sexual intercourse or intense emotional stress, in the hours prior to the attack. Neurologic examination should look for any abnormal neurologic signs, but should be particularly directed toward signs that might arise from vertebrobasilar ischemia. Brain imaging, either CT or MRI, is valuable in cases with any focal neurologic deficit, as the occasional patient will have an underlying brain tumor (Dinca et al 2011); typically, however, no abnormality is found in patients with true transient global amnesia.

Electroencephalography is usually normal after an attack of transient global amnesia; activation procedures, sleep, and 24-hour ambulatory studies are of no additional value to the standard recordings (Fisher and Adams 1964). Electroencephalography is particularly indicated for attacks that are associated with altered consciousness or impaired ability to perform complex tasks. Focal dysfunction (focal theta or delta) may be present over the temporal or temporoparietal regions (Rowan and Protass 1979). Temporal spikes have been reported infrequently, the morphology of which overlaps with benign epileptiform transients of sleep and spike discharges seen in partial seizures (Rowan and Protass 1979).

Management

No specific treatment is available for an episode of transient global amnesia. Following the attack, a discussion with the patient regarding the overall good prognosis does much to alleviate anxiety.

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**References especially recommended by the author or editor for general reading.

Former authors

Vladimir C Hachinski MD and John Maher MD (original authors)

ICD and OMIM codes

ICD codes

ICD-9:
Transient global amnesia: 437.7

ICD-10:
Transient global amnesia: G45.4

Profile

Age range of presentation

13-18 years
19-44 years
45-64 years
65+ years

Sex preponderance

male=female

Family history

family history may be obtained

Heredity

none

Population groups selectively affected

none selectively affected

Occupation groups selectively affected

none selectively affected

Differential diagnosis list

head injury
nonconvulsive epilepsy
hysterical (psychogenic) amnesia
Korsakoff psychosis
various causes of acute confusional states
dementia
drug intoxication
alcohol intoxication
hypoglycemia
complex partial seizures
acute confusional episode

Associated disorders

Basilar migraine
Epilepsy
Migraine
Patent foramen ovale
Thromboembolism
Transient ischemic attack

Other topics to consider

Drug-induced memory disturbance
Epilepsy
Late-life migrainous accompaniments
Memory loss
Migraine

Mountain sickness: neurologic aspects
Patent foramen ovale