

Title: Transient Global Amnesia

Authors

Christopher Butler, Academic Clinical Lecturer, Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK.

Adam Zeman, Professor of Cognitive and Behavioural Neurology, Department of Neurology, Peninsula Medical School, St Lukes' Campus, Magdalen Road, Exeter, EX1 2LU, UK.

Summary

Transient global amnesia (TGA) is a neurological syndrome characterised by a self-limiting episode of isolated memory impairment. The aetiology of TGA is unknown but it is widely thought not to be an epileptic phenomenon. Nevertheless, epileptic seizures can cause a very similar clinical picture – the syndrome of transient *epileptic* amnesia (TEA). It is important to distinguish between these two phenomena as their treatment and prognosis are different. In this chapter, we describe the principle clinical features of transient amnesic syndromes, highlighting those that help to distinguish TGA from TEA. We also discuss recent advances that are beginning to unravel the aetiology of TGA.

Keywords

Transient global amnesia; transient epileptic amnesia; memory; epilepsy; diffusion weighted imaging

Introduction

Transient global amnesia (TGA) is a striking clinical syndrome characterised by the occurrence, typically in middle or old age, of a sudden-onset, dense and isolated amnesia that lasts for a few hours before spontaneously resolving. In Gowers' time, transient episodes of amnesia were generally regarded as being of 'hysterical' origin (Hacking, 2002, Hodges, 1991, although see Gil *et al*, 2010 for an alternative view). However, the first description of a case similar to that which we now recognise as TGA appeared just two years after the publication of 'Borderland of epilepsy', in a paper intended to demonstrate cases of 'organic' (i.e. non-hysterical) amnesia (Benon, 1909). In this article, the French psychiatrist Benon described a 66 year old female patient who experienced four episodes of transient amnesia over a four year period. During the attacks, which resolved after a few hours, the patient was unable to remember recent events or retain new information in memory, and asked questions in a repetitive manner. No other neurological deficit was apparent. Despite Benon's report, the view that transient amnesia was of hysterical origin persisted into the mid 20th century (Kennedy and Neville, 1957). It was not until the independent publication of carefully observed cases by Bender (1960), Guyotat and Courjan (1956) and Fisher and Adams (1964) that TGA began to be recognised as a distinct neurological entity.

Since that time, there has been enthusiastic debate about the pathophysiological mechanisms underlying TGA. Several early authors suggested that it may be an epileptic phenomenon (Fisher and Adams, 1964, Gilbert, 1978, Lou, 1968). This idea then fell out of favour, given the tendency for TGA to occur only once and the lack of demonstrable epileptiform abnormalities on EEG. Discussion began to revolve around whether a vascular (Heathfield *et al.* , 1973) or migrainous (Caplan, 1981, Hodges, 1991) origin was more likely. The cause of TGA remains uncertain. However, in recent years, there has been growing recognition that a subgroup of patients presenting with recurrent episodes of transient amnesia do indeed have epilepsy. Such cases of transient *epileptic* amnesia (TEA) may be difficult to distinguish from those with a non-epileptic aetiology. In this chapter,

we describe the clinical, neuropsychological and radiological features of TGA, contrast them with those of TEA and summarise recent thought on the aetiological origins of this enigmatic neurological syndrome.

Transient global amnesia

Clinical features

The most widely accepted diagnostic criteria for TGA, introduced by Hodges and Warlow (Hodges and Warlow, 1990), are shown in box 1. The key feature is a transient impairment of new learning occurring in the absence of signs that would suggest an alternative diagnosis: focal neurological deficits, loss of personal identity (characteristic of 'psychogenic' amnesia), or antecedents of epilepsy or head injury.

Epidemiology

In the general population, the incidence of TGA is estimated to be between 3 and 8 per 100,000 people per year (Bartsch and Deuschl, 2010). The syndrome arises almost exclusively in individuals between the ages of 40 and 80 years, with the average age being about 60 years (Quinette *et al.* , 2006). In younger people, a similar phenomenon may occur following head injury (Haas and Ross, 1986), but such attacks are usually excluded from the rubric of TGA. A meta-analysis of 1333 published cases of TGA failed to find any significant difference in frequency between the sexes (Quinette *et al.* , 2006). There are no data available on the epidemiology of TGA in different racial groups.

Precipitants

TGA is often preceded by a period of intense emotional or physical stress. Frequently reported triggers include immersion in cold water, sexual intercourse, vigorous exercise, pain, a heated argument or the receipt of distressing news. Such events have been reported in 50 to 90% of TGA episodes (Quinette *et al.* , 2006). TGA-like attacks have also been reported to occur in many other circumstances including high altitude, cerebral angiography, upper

gastrointestinal tract endoscopy and the use of a variety of prescription and recreational drugs including sodium amobarbital, sildenafil, sibutramine, zolpidem, dobutamine, intrathecal baclofen and marijuana. Quinette et al. (2006) used a hierarchical cluster analysis to classify 63 patients into three groups according to their precipitating events and clinical characteristics. In men, TGA occurred more frequently after a strenuous physical event. In women, TGA was more closely associated with an emotional event such as arousal or anxiety. In patients younger than 56 years of age, TGA was associated with a past history of migraine.

Clinical features of the amnesic episode

Whilst the precipitating circumstances of TGA vary widely, its core clinical features are remarkably consistent and are illustrated by the following example.

A 63-year old, recently retired teacher was brought to the Accident and Emergency department by her husband. One hour earlier, she had telephoned him from a local gym where she had just finished her daily workout and said: "I don't know where I am. What's happening? Where am I?" Despite his reassurances, she had continued to repeat the same questions. On examination, she was disoriented in time and place, had no recollection for events of the previous week and was unable to retain new information – including the identity of the attending doctor. Besides the amnesia, there were no other neurological signs or symptoms. A CT scan of the head was normal. Over the following 6 hours, her memory deficit gradually resolved although she was left with a dense 'gap' for the episode of transient amnesia itself and for the preceding trip to the gym.

The key cognitive deficits involve the acquisition of new memories (anterograde amnesia) and retrieval of memories for past events (retrograde amnesia). The onset of TGA is usually heralded by repetitive questioning, often related to attempts at self-orientation: "What day is it?" or "What am I doing here?" Although a small amount of information can be retained for a few seconds, it is rapidly lost when the patient's attention shifts. The retrograde component is variable in its extent: patients are unable to report what they had been doing

when the attack began but may also have lost access to memories for events that occurred many years ago. Patients often appear bewildered by their circumstances and may be restless or agitated. Witnesses may describe the patient as 'confused', but careful examination reveals that there is no impairment of arousal or of other cognitive functions such as attention, language or perception. In contrast to psychogenic forms of amnesia (see below), knowledge of personal identity is always retained. Focal neurological deficits are ruled out by the diagnostic criteria, but non-specific symptoms are commonly associated with the amnesia and include headache (40%), dizziness (25%), nausea and vomiting (24%), chills or flushes (16%) and emotionalism (11%) (frequencies as reported by Quinette et al. (2006)).

The duration of TGA is difficult to measure accurately. Whilst the onset of the amnesia is usually abrupt, recovery is gradual and its completion indeterminate. If the end of the episode is taken to be when the patient is orientated in place and time and is able to explain the reasons for their hospitalisation, a mean duration of 6 to 8 hours is typically observed. The great majority of episodes lasts between 1 and 10 hours. After recovery, a dense amnesic gap persists for events that occurred during the attack itself but there is no clinically significant long-term cognitive impairment. In most patients, TGA occurs only once. Systematic, very long-term follow-up studies are lacking, but a recent review estimated an annual recurrence rate of about 6% (Quinette *et al.* , 2006). TGA is therefore widely regarded as a syndrome with a benign prognosis.

Neuropsychology

Formal neuropsychological testing during a TGA attack bears out the clinical impression. The patient is able to hold and manipulate information normally in working memory as tested, for example, by backwards digit span (Quinette *et al.*, 2003). However, on tests of long-term anterograde memory, such as delayed recall of a word list, story or complex figure, performance is at floor (Hodges, 1991). Interestingly, despite having no recollection of stimuli encountered during the attack, patients nonetheless demonstrate perceptual priming (Kapur *et al.* , 1996) suggesting that, as with more permanent amnesia from medial

temporal lobe or diencephalic damage, some forms of implicit learning remain intact.

During the episode, patients may also lose access to memories acquired prior to the onset of the attack. The initial acquisition of such memories is, of course, beyond the reach of experimental manipulation so assessment of retrograde amnesia can be difficult. In the acute and recovery phase of TGA, tests probing memory for both personal and public facts and events have revealed variable patterns of impairment across individuals. In general, accounts of personally experienced episodes are “curiously empty and lacking in colour, as if reduced to the bare bones of memory” (Hodges and Ward, 1989). They lack what has been called “autonoetic consciousness” – the feeling of having experienced the past episode oneself. Retrograde amnesia may affect memories from across the lifespan or from a more limited time period prior to the attack.

During the recovery phase, retrograde memory improves more rapidly than anterograde memory (Kapur *et al.*, 1998). In some cases, memories are recovered in chronological order whereas in others more salient, detailed memories return first no matter what age they are (Guillery-Girard *et al.*, 2004, Kapur *et al.*, 1998). Anterograde memory impairment may last much longer than is clinically apparent (Borroni *et al.*, 2004). Subtle deficits, particularly in story recall, can be demonstrated several days and, in some cases, several months later. Following recovery from TGA, patients are left with complete amnesia for events that occurred during the attack. There is also usually a short, permanent retrograde amnesia for events that occurred in the one to two hours leading up to the attack.

Investigations

In the vast majority of patients with TGA, the electroencephalogram (EEG), whether performed during or after the amnesic episodes, is unremarkable (Hodges, 1991). For example, of 106 EEGs performed by Quinette *et al.* (Quinette *et al.*, 2006), 85 were normal and the remaining 21 showed minor, non-specific abnormalities. There have, however, been several reports of TGA cases in which

the EEG has revealed abnormalities taken to suggest epilepsy (Deisenhammer, 1981, Jeong *et al.*, 2010, Lou, 1968). In some of these cases, the abnormalities may in fact have been benign (e.g. benign sporadic sleep spikes (BSSS) (Miller *et al.*, 1987)) or non-specific (e.g. subclinical rhythmic electrographic discharges of adults (SREDA) (Brigo *et al.*, 2010)). In others, the patient would now have met diagnostic criteria for TEA (Lou, 1968).

For many years, structural brain imaging was thought to be entirely normal in the majority of TGA cases. Recently, however, a number of studies have shown that, in the period immediately following a TGA attack (within 24 to 72 hours of onset), diffusion weighted (DWI) and T2 weighted magnetic resonance imaging (MRI) can detect small (1 to 5 mm), punctate hippocampal lesions, indicating areas of restricted diffusion, in up to 85% of patients (Bartsch and Deuschl, 2010). These lesions are most frequently found in the CA1 subfield of the hippocampus, a region known to be particularly sensitive to hypoxic injury, and may be unilateral or bilateral (see figure 1). The lesions resolve by about 10 days after the acute amnesic episode (Bartsch *et al.*, 2007). The pathophysiology of these abnormalities remains unclear. Magnetic resonance spectroscopy has revealed a distinct lactate peak at the site of the DWI lesions and not beyond (Bartsch *et al.*, 2008). This lactate peak is a marker of anaerobic glycolysis and suggests acute metabolic stress of cells in the CA1 region.

A number of studies have examined whether TGA is associated with regional changes in cerebral perfusion or metabolism using single photo emission computed tomography (SPECT) or positron emission tomography (PET). These have generally been carried out in single cases or small case series. The results (reviewed in Bartsch and Deuschl (2010)) have been mixed, with some showing changes specific to the medial temporal lobes but others revealing more widespread abnormalities, including in the thalamus, basal ganglia, cerebellum and frontal cortex. This variability is probably attributable to variations in study design, including the imaging protocol, resolution and timing relative to the amnesic episode. In two TGA patients, functional MRI during an episodic

memory task has revealed reduced activity in the medial temporal lobe bilaterally (LaBar *et al.*, 2002, Westmacott *et al.*, 2008).

The differential diagnosis of TGA

The main differential diagnosis of TGA is TEA, which is discussed in more detail below. The features that distinguish these two conditions are summarised in table 1. Other potential causes of transient memory loss include transient ischaemic attack and stroke, migraine, drugs, head injury and psychogenic amnesia. In such cases, the memory dysfunction usually has a different profile to that of TGA and is associated with other features that make the diagnosis straightforward. Some of these are discussed in the following section.

Pathophysiology

The pathophysiology of TGA remains a mystery. As mentioned above, early theories invoked thromboembolic, migrainous or epileptic mechanisms. Additional ideas have been added to the mix in recent years. Nevertheless, most authors agree that dysfunction is likely to be centred on the medial temporal lobes (MTLs), a region known to be critical for memory processing (Squire *et al.*, 2004).

Thromboembolic disease

Permanent amnesia can result from stroke, for example, when involving the thalamus or medial temporal lobes structures bilaterally. In such cases, the amnesia is usually associated with additional neurological deficits such as a visual field defect or focal motor weakness. It has been suggested that TGA might represent a transient ischaemic attack (TIA) affecting these brain regions. A number of studies have, however, shown that patients with TGA have fewer vascular risk factors than control subjects with TIA and a more favourable prognosis in terms of mortality and cerebrovascular events (Hodges and Warlow, 1990, Quinette *et al.* , 2006). Moreover, there is no evidence of an increase in imaging markers of small-vessel disease (white matter

hyperintensities on T2-weighted MR imaging) or vascular risk factors in patients with TGA compared with healthy control subjects (Enzinger *et al.* , 2008). The available evidence therefore argues strongly against thromboembolic ischaemia being the cause of TGA.

Migraine

Several authors have proposed a causal link between migraine and TGA (Caplan, 1981). In some cases of transient amnesia, a migrainous cause seems highly likely.

A 63 year old engineer with a long history of migraine with aura had a tennis fixture with a friend one evening. Upon arriving at the court, he noticed some dimming of his peripheral vision and felt that he was going to have a migraine. He therefore went back to his house to ring his friend and cancel the match. However, to his surprise he was unable to remember his friend's name, despite having known him for many years. When the friend arrived, it became apparent that the patient was amnesic for recent events, asked questions repetitively and seemed unable to take in new information. Apart from the amnesia, the patient was behaving entirely appropriately and there was no abnormality in his appearance. He did not seem overtly anxious and did not complain of any olfactory hallucinations. The amnesia resolved over about half an hour. By this time, the patient had developed a throbbing, unilateral headache associated with nausea. The headache gradually improved over the following 24 hours.

A past history of migraine has been reported to be present in up to 30% of patients with TGA (Hodges and Warlow, 1990), a significantly higher proportion than in controls. Furthermore, migrainous features, particularly headache and nausea, accompany about 20% of TGA attacks (Hodges, 1991). A study of 63 patients with TGA identified a history of migraine as a risk factor in patients under 56 years of age (Quinette *et al.* , 2006). Olesen and Jorgensen suggested that the underlying pathological mechanism behind both TGA and migraine might be the experimentally observed phenomenon of spreading depression (Olesen and Jorgensen, 1986). A range of stimuli, applied directly to the cortex,

may induce a wave of depolarisation that spreads at a rate of 3-5 mm/min and reduces cerebral blood flow for a period of about 1 hour. Spreading depression can be elicited in the hippocampus of experimental animals, in which it provokes a transient period of amnesia. According to the migraine hypothesis, emotional or physical stressors lead to the release of glutamate in the hippocampus triggering spreading depression and hippocampal dysfunction. Critics argue that the migraine hypothesis does not readily account for the typical age range of TGA or its low recurrence rate.

Psychological factors

The potential role of psychological factors in the pathogenesis of TGA was first suggested by Bender (Bender, 1960). It is widely recognised that certain forms of profound memory dysfunction are best explained in purely psychological terms.

A 43-year old construction worker was brought to hospital by colleagues. That morning, he had suffered a minor head injury when his fork-lift truck collided, at low speed, with an earth bank. Since then, he had a "complete loss of memory", with no recollection of any past events. He was unable to remember his own name and failed to recognise his colleagues or, when she arrived, his recently estranged wife. Despite this, there was no apparent difficulty in learning new information – he could recount in detail the events following his arrival at hospital. MRI of the brain was normal. It later emerged that, since an acrimonious separation from his wife, he had been showing signs of depression and drinking heavily. Over a two year follow up period, little improvement in memory was observed. The patient had suffered a period of concussion following a motorcycle accident in his 20's.

This picture is clearly distinct from TGA. The onset of psychogenic amnesia typically follows a stressful experience, such as a marital or financial crisis, and there is often a background of depression or alcohol abuse. It is thought that psychogenic amnesia is commonly associated with a history of 'organic' transient amnesia (Kritchevsky *et al.* , 2004). Knowledge of personal identity is often impaired: this is not a feature of organic amnesia. There may be a period of wandering, 'psychogenic fugue' that typically lasts for a few hours or days. There

is usually a relative preservation of anterograde memory, so that patients are able to 'relearn' about themselves, although they may complain that such memories lack the experiential aspect (autonoetic consciousness) that defines true episodic memory. Recovery is frequently protracted and incomplete.

Although TGA differs from psychogenic amnesia in many respects, psychological factors are often evident in the history. It has been reported that TGA patients are more likely to have phobic personality traits (Inzitari *et al.* , 1997, Quinette *et al.* , 2006) and a past history and family history of psychiatric disease (Pantoni *et al.* , 2005) than normal control subjects and patients with transient ischaemic attacks. Furthermore, as mentioned above, the onset of TGA is often preceded by an emotionally stressful event, such as a heated argument or the receipt of bad news. One proposed mechanism is that hyperventilation in response to a stressful situation leads to a reduction of cerebral blood flow in medial temporal regions and consequent transient amnesia (Pantoni *et al.* , 2000). Others have suggested that the hippocampal dysfunction results from excessive glutamate release and consequent calcium influx in response to psychological stress (Bartsch and Deuschl, 2010).

Jugular valve insufficiency

Given the relatively high frequency of TGA precipitants such as physical exercise, immersion in cold water, sexual intercourse and pain, Lewis (Lewis, 1998) proposed that high venous pressure and increased venous return towards the superior vena cava induced by Valsalva-like activities might lead to ischaemia in memory relevant structures – the diencephalon and medial temporal lobes. Lewis suggested that his hypothesis be tested by examining the competence of jugular venous valves during a Valsalva manoeuvre in patients with TGA. A number of subsequent studies have confirmed, using duplex ultrasonography, bubble-contrast ultrasonography or time-of-flight MRI, that the rate of jugular valve insufficiency is considerably higher in patients (~75%) than healthy controls (~35%) (Sander *et al.* , 2000). However, the significance of these findings remains controversial. Again, the venous congestion hypothesis does not explain the relatively low recurrence rate of TGA nor the fact that it

predominantly occurs in older people. Moreover, one might expect that venous congestion and ischaemia would result in a wider range of symptoms than isolated memory dysfunction.

A final common pathway?

The profusion of reported 'causes' of TGA implies that transient dysfunction of the medial temporal lobes may be a 'final common pathway' with numerous potential triggers. Some recent theories have aimed at explaining what this pathway might be. Sander and Sander (Sander and Sander, 2005), for example, have proposed that TGA results from focal hippocampal hypoxia-ischaemia caused by venous congestion in cases associated with jugular venous valve insufficiency and by vasoconstriction resulting from hyperventilation in cases associated with emotional stress. The CA1 region of the hippocampus is thought to be particularly susceptible to these processes because of its location at a vascular watershed. In contrast, Bartsch and Deuschl (Bartsch and Deuschl, 2010) reject the notion of vasoconstriction, proposing instead that stress-induced release of excitotoxic glutamate leads to cytotoxic oedema (detectable as DWI lesions) and transient dysfunction in the hippocampus. As yet, there is little hard evidence in support of either of these theories.

Clinical management

The diagnosis of TGA is predominantly a clinical one. A typical case requires little further investigation. The patient can be reassured that there are no long-term sequelae of the episode and the risk of recurrence is low. In the United Kingdom, there are no implications for driving with a car or motorcycle licence. Unusual features should prompt neuroimaging, preferably with MRI, to investigate alternative causes of transient amnesia. Where the amnesic attacks are recurrent, EEG may be helpful in identifying cases of TEA, although the sensitivity of this test is low (see below). Associated focal neurological features raise the possibility of an explanation in cerebrovascular disease: screening for risk factors is then appropriate.

Transient epileptic amnesia

It has been known for over a century that episodes of isolated memory impairment may be the sole or main manifestation of epileptic seizures. Perhaps the earliest description of epilepsy-related transient amnesia is to be found in a paper by Gowers' contemporary at Queen Square, John Hughlings-Jackson (Hughlings-Jackson, 1888). Hughlings-Jackson reported the case of Dr Z, a physician with focal epilepsy who, whilst at work, experienced the onset of his typical epileptic aura. He subsequently examined, diagnosed and treated a child with pneumonia, yet later had no recollection of the consultation. Some years later, Z's brain came to autopsy, and a single, circumscribed lesion in the left uncus was discovered (Hughlings-Jackson and Colman, 1898). Over subsequent decades, a steady stream of case reports and short series of patients with epileptic amnesia has appeared in the literature (reviewed in Butler and Zeman (2008)).

As mentioned above, some of these were initially classified as TGA. Hodges and Warlow's diagnostic criteria for TGA strive to exclude cases of epilepsy (see Box 1, criteria 5 and 7). Nevertheless, even in these authors' own, carefully screened series of 114 TGA cases (Hodges and Warlow, 1990), a small proportion (7%) went on to develop clear-cut seizures.

The term 'transient epileptic amnesia' was introduced by Kapur (Kapur, 1990), who highlighted that amnesic attacks caused by epilepsy can be similar to those occurring in TGA, but are usually distinguished by features including brevity and recurrence. Zeman and colleagues (Zeman *et al.*, 1998) proposed diagnostic criteria for TEA that have become widely used and are shown in Box 2. We have recently reviewed the clinical features of 94 published cases meeting these diagnostic criteria, including our own series of 50 patients from the United Kingdom (Butler and Zeman, 2008).

Epidemiology

The prevalence of TEA is unknown. Like TGA, the amnesic attacks typically begin in late middle age, with a mean age of onset of 57 years. Two thirds of patients are male.

Clinical features of the amnesic episode

The typical features of TEA are illustrated by the following case.

A 58-year old carpet fitter experienced 28 episodes of transient amnesia over 18 months. All occurred upon waking in the night and lasted about 20 minutes. He repetitively questioned his wife, but was responsive and coherent throughout. During one attack he was unable to recall the death of his brother a few days earlier. Routine EEG and MRI were normal. Lamotrigine abolished the attacks but they briefly returned, with associated olfactory hallucinations, during a period of non-compliance, and ceased again when he restarted the medication. At interview, he described rapid forgetting of recently acquired memories, patchy loss of salient autobiographical memories from the past 30 years, such as his wife's abdominal surgery and the wedding of his son, and significant new difficulties navigating around his local area.

The episodes of amnesia are generally briefer than those of TGA, lasting a median of 30 to 60 minutes, although longer episodes are not uncommon. As with most forms of epilepsy, the frequency of attacks is highly variable but, on average, they occur about once per month, a pattern very different from TGA. A third helpful clue to the diagnosis is that episodes of TEA characteristically occur upon waking, with around 70% of patients experiencing at least one attack in this context. During the amnesic episode, patients usually have difficulty laying down new memories (anterograde amnesia) and retrieving memories for past events (retrograde amnesia). In contrast to TGA, the anterograde component is often partial: 44% of patients later say they can “remember not having been able to remember”. Patients may repetitively ask questions during the attack, but this feature is less consistently present than in TGA.

Whilst amnesia is the predominant feature of TEA attacks, careful enquiry can, in some instances, reveal other signs suggestive of epilepsy. The most common of these is olfactory or gustatory hallucinosis, experienced by up to 50% of patients with TEA. Subtle oral automatisms (lip smacking or chewing) or brief periods of unresponsiveness may also accompany some attacks. A few patients develop more clear-cut 'complex partial seizures', but generalised tonic-clonic convulsions are rare.

The amnesic attacks of TEA typically respond very well to low dose monotherapy with an antiepileptic drug. However, treatment is often delayed as patients may be misdiagnosed as having TGA, 'psychogenic attacks' or dementia (Butler *et al.* , 2007).

Neuropsychology

To date, there has been no systematic study of the neuropsychological profile during TEA attacks. In contrast to TGA, however, TEA is associated with marked *persistent* – i.e. interictal – cognitive impairment. Despite effective treatment of the amnesic episodes, 81% of patients with TEA complain of significant ongoing memory difficulties (Butler *et al.* , 2007). The problems they describe are unusual: 70% report loss of memories for salient, personally experienced events from the remote past (autobiographical amnesia); 44% describe the excessively rapid fading of newly acquired memories over a period of days to weeks (accelerated long-term forgetting (ALF)); 36% report new difficulties with spatial navigation, even around previously familiar environments (topographical amnesia). Performance on standard neuropsychological instruments, which typically test retention of newly learned material over a delay of up to 30 minutes, is often normal. However, specifically designed memory tests have demonstrated that patients with TEA have extensive deficits of autobiographical memory (Butler *et al.* , 2007, Milton *et al.* , 2010) and an accelerated rate of forgetting over the days that follow learning (Butler *et al.* , 2007, Muhlert *et al.* , 2010) (see figure 2). The cause of these atypical forms of memory deficit is unknown. Possibilities include subtle structural damage to the brain or physiological disruption of memory circuits by seizure-related activity.

Investigations

Routine interictal EEG recording reveals epileptiform abnormalities in only about one third of cases of TEA, although sensitivity may be significantly enhanced by sleep-deprivation. Therefore, whilst an EEG may be helpful in the evaluation of a patient with transient amnesia, especially when there have been multiple episodes, a normal result should not be taken to rule out TEA. When identified, epileptiform discharges typically localise to the temporal regions (Butler *et al.* , 2007). MRI of the brain is usually clinically unremarkable between amnesic attacks. However, volumetric analysis has revealed subtle atrophy bilaterally in the hippocampus of patients with TEA (Butler *et al.* , 2009). In a few cases, brain imaging in the ictal or peri-ictal period has revealed focal changes in the hippocampus (see figure 3), supporting the hypothesis that the amnesic attacks of TEA are caused by focal MTL seizure activity.

Clinical management

Current evidence suggests that TEA attacks respond well to anticonvulsant medication, and often resolve completely with monotherapy (Butler *et al.* , 2007). It is unclear, however, whether persistent memory impairments such as accelerated long-term forgetting, autobiographical amnesia or topographical amnesia also respond to treatment. One case report of TEA suggests that there may be some memory improvement with anticonvulsant medication (Midorikawa and Kawamura, 2007). Nevertheless, persistent memory problems undoubtedly remain problematic for some patients even once the amnesic attacks have ceased (Butler *et al.* , 2007). In the United Kingdom, the diagnosis of TEA prevents patients from driving until they have been free of attacks for one year.

Conclusion

A lot has been learned about transient amnesic syndromes since Gowers' time, when such cases were probably regarded as a manifestation of 'hysteria'. TGA is

a highly consistent neurological syndrome characterised by a dense, focal and self-limiting disruption of declarative memory function. It is thought to reflect transient dysfunction of the medial temporal lobes, but the cause of this dysfunction remains unknown. Epilepsy is unlikely to be implicated in the majority of cases. Nevertheless, recent work has highlighted that temporal lobe seizures can lead to a very similar and sometimes indistinguishable clinical episode – the syndrome of TEA. Thus, sixty years after first being described, TGA remains steadfastly in the borderland of epilepsy and continues to resist claims to sovereignty from neighbouring territories.

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Box 1: Diagnostic criteria for Transient Global Amnesia (Hodges and Warlow, 1990)

1. Attacks must be witnessed and information available from a capable observer who was present for most of the attack
2. There must be a clear-cut anterograde amnesia during the attack
3. Clouding of consciousness and loss of personal identity must be absent, and the cognitive deficit must be limited to amnesia (that is, no aphasia, apraxia, etc)
4. There should be no accompanying focal neurological symptoms during the attack and no significant neurological signs afterwards
5. Epileptic features must be absent
6. Attacks must resolve within 24 hours
7. Patients with recent head injury or active epilepsy (that is, remaining on medication or one seizure in the past two years) are excluded

Box 2: Diagnostic criteria for Transient Epileptic Amnesia (Butler *et al.*, 2007)

1. a history of recurrent witnessed episodes of transient amnesia
2. cognitive functions other than memory judged to be intact during typical episodes by a reliable witness
3. evidence for a diagnosis of epilepsy based on one or more of the following:
 - a. epileptiform abnormalities on electroencephalography
 - b. the concurrent onset of other clinical features of epilepsy (e.g. lip-smacking, olfactory hallucinations)
 - c. a clear-cut response to anticonvulsant therapy

Figure legends

Figure 1: Magnetic resonance imaging in transient global amnesia (Bartsch *et al.* , 2006).

(a) Hippocampal subfields; (b), (c) and (d) Typical lesions seen in the hippocampus within 48 hours after onset on axial and coronal diffusion-weighted and T2 weighted sequences respectively. Note in this case the bilateral T₂ lesions in the CA-1 sector of the cornu ammonis (red arrow) extending over 4–5 mm (slice thickness 2 mm) which are clearly separated from the cavity of the pre-existing vestigial hippocampal sulcus (green arrow) located in deeper subcortical layers in the vicinity of the gyrus dentatus (reproduced with permission of Oxford University Press).

Figure 2: Accelerated Long-term Forgetting in transient epileptic amnesia (Butler *et al.* , 2007).

24 patients with transient epileptic amnesia and 24 normal controls learnt a list of 15 words. Despite normal learning and initial recall, patients showed accelerated forgetting over 3 weeks. Patients who complained of ALF (ALF+) showed much greater forgetting than patients who did not (ALF-) (reproduced with permission from John Wiley and Sons Inc).

Figure 3: Neuroimaging during a prolonged episode of transient epileptic amnesia (Butler and Zeman, 2008).

(a) FLAIR MRI scanning during a prolonged episode of transient epileptic amnesia revealed hyperintensity in the left hippocampus. (b) FDG-PET scanning

during the same episode showed hypermetabolism localized to the left anterior hippocampus. (c) This region had returned to normal one month later.