Transient global amnesia

The syndrome of transient global amnesia is characterized by an abrupt and temporary disruption in anterograde memory. Patients commonly present to either GPs or general physicians who may be unfamiliar with this unusual diagnosis (Larner, 2007; Owen et al, 2007). This unfamiliarity may result in inappropriate investigation, management and lifestyle advice being given to patients. This article introduces this clinical diagnosis so that doctors in core training may more confidently recognize the presentation as well as recognize atypical features that might indicate alternative pathology. The importance of obtaining a detailed history is paramount, and steps should be taken to get a reliable witness account of events.

Clinical features

In their proposed diagnostic criteria for transient global amnesia, based on the Oxford TGA Study (Hodges, 1991), Hodges and Warlow (1990) identified a number of characteristic clinical features (*Table 1*). The most striking of these is the abrupt onset of prominent anterograde amnesia. Patients have an inability to encode new memories and as such are disoriented in time, with a tendency to ask repeatedly the same questions and repeat the same statements, often in the same order. Retrograde amnesia, loss of memory for events covering a variable period of time before the attack, can also occur but is a less prominent clinical feature. Other cognitive functions, such as attention and language, are spared and importantly there is no loss of self-awareness, no clouding of consciousness and no other focal neurological deficit. Non-focal symptoms such as headache, nausea and/or vomiting may occur, usually immediately after an attack. The duration of transient global amnesia can vary, but typically lasts between 1 and 8 hours. Symptoms should resolve within 24 hours and patients are left with an amnesic gap for the duration of the episode.

Preceding event 'triggers' have been reported in some patients with transient global amnesia, including emotional events, physical exertion (including sexual activity; Larner, 2011), and changes in body temperature (e.g. swimming in cold water: 'transient global amnesia at the seaside'). The significance of such triggers is uncertain but may be linked to the underlying pathophysiology of the condition. A prior history of similar episodes is unusual and would warrant reconsideration of the diagnosis.

Affected individuals are usually aged over 40 years (*Figure 1*), although there may be selection bias in hospital clinic-based series. Different large case series report either male (Hodges, 1991) or female (Quinette et al, 2006) predominance.

Table 1. Diagnostic criteria for definite transient global amnesia

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

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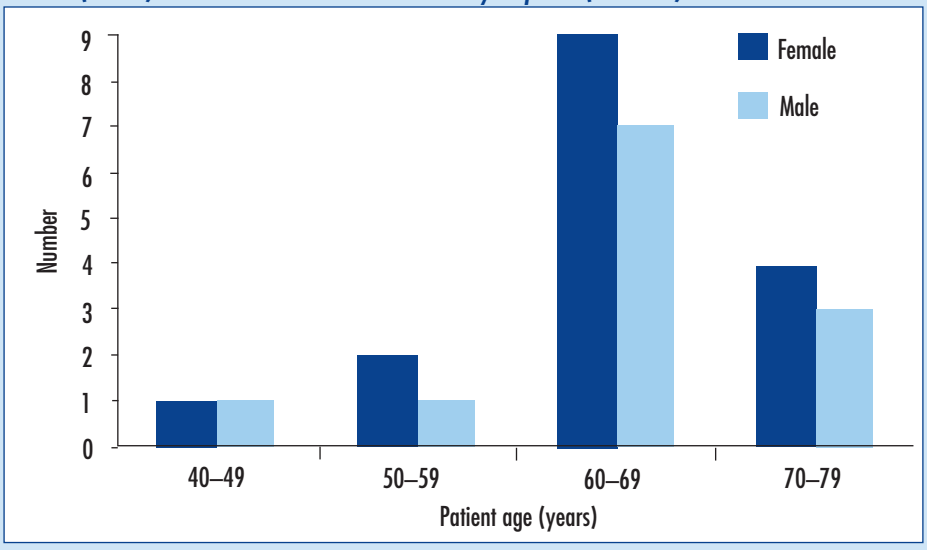
Pathogenesis

The aetiopathogenesis of transient global amnesia remains controversial. Several possible aetiologies have been suggested.

Because of the acute nature of transient global amnesia, transient ischaemia of memory eloquent brain areas has often been considered, perhaps secondary to venous congestion, but there are clear data to show that patients with transient global amnesia differ from those with transient ischaemic attacks in terms of vascular risk factors and prognosis for vascular events (Hodges, 1991). Nevertheless, sophisticated neuroimaging techniques undertaken acutely may show changes suggestive of transient hypoperfusion of memory eloquent brain structures such as the hippocampus and the medial temporal lobe (Sander and Sander, 2005).

Figure 1. Age and sex distribution of consecutive cases fulfilling diagnostic criteria for transient global amnesia (n = 28) seen in the authors' clinic over a 13-year period (2002–14).



Transient global amnesia has sometimes been conceptualized as a variant of migraine, with cortical spreading depression responsible for the clinical features (Owen et al, 2007). There may be clinical overlap with acute confusional migraine of childhood (Larner, 2013), and at the population level there is evidence that migraine may be associated with increased risk of transient global amnesia, particularly in women aged 40–60 years (Lin et al, 2014). Genetic factors may also play a predisposing role, although only occasional familial presentations of transient global amnesia have been reported (Davies and Larner, 2012).

Perhaps no one theory will be able to account for all aspects of transient global amnesia. As a syndrome, transient global amnesia may have more than one possible cause.

Differential diagnosis

There are a number of other conditions that can present with acute memory impairment. Knowledge of these conditions, and of which clinical features support or problematize a diagnosis of transient global amnesia, is therefore important (Ung and Larner, 2014). Three differential diagnoses are considered below: transient epileptic amnesia, transient ischaemic attack, and psychogenic amnesia (*Table 2*).

Patients presenting with transient epileptic amnesia may pose a significant differential diagnostic challenge (Hodges, 1991). In transient epileptic amnesia, symptoms arise secondary to epileptiform activity occuring in the medial temporal lobes (Butler, 2006). Both transient epileptic amnesia and transient global amnesia affect similar age groups and present with prominent anterograde amnesia, but in contrast to transient global amnesia patients with transient epileptic amnesia are more likely to present following multiple events. Furthermore, transient epileptic amnesia events are more likely to occur on waking and are typically much briefer than transient global amnesia, lasting several minutes (usually less than 1 hour) before resolving. Evidence supporting a diagnosis of transient epileptic amnesia includes epileptiform changes on electroencephalography (only seen in about one-third of cases), co-occurrence of other clinical features of epilepsy (automatisms, olfactory hallucinations), or a clear-cut response to antiepileptic drugs.

Transient ischaemic attacks are unlikely to present with isolated amnesia without other neurological deficit. Nevertheless, the diagnosis should be considered (as is often done unwittingly, because of the acute onset; Larner, 2007) in patients with risk factors for vascular disease because of concerns regarding future stroke risk. Thorough neurological examination is required to ensure there are no associated neurological deficits, including careful assessment of visual fields, which if abnormal would argue against a diagnosis of transient global amnesia.

Psychogenic amnesia may also be referred to as 'dissociative amnesia', 'hysterical amnesia', or transient psychological amnesia. It may be either situation-specific or global, such as the 'psychogenic fugue state'. In both transient global amnesia and psychogenic amnesia the episode may be preceded by a stressful or significant life event and investigations may be normal. However, distinguishing features of psychogenic amnesia include loss of autobiographical memory and personal identity (Pujol and Kopelman, 2003), exclusion criteria for transient global amnesia (*Table 1*). The repetitive questioning seen in transient global amnesia is also often absent, indeed patients may appear indifferent to the apparent severity of memory loss. Because of the loss of personal identity, these patients are sometimes the subjects of reports in the media ('Do you know this man?').

Other conditions which might present with acute impairments in cognition include herpes simplex encephalitis, hypoglycaemia, head injury, drug and alcohol withdrawal and other causes of delirium (toxic-metabolic encephalopathy). These conditions typically result in more global impairment in cognition, sometimes with clouding of consciousness, as opposed to the selective problems affecting memory in clear consciousness seen in transient global amnesia.

Investigations

Transient global amnesia is usually a clinical diagnosis and, since few patients are seen during an attack, dependent on the quality of the history obtained. If necessary, attempts to contact collateral sources should be made. In the authors' series (*Figure 1*), around a quarter of suspected cases of transient global amnesia (8/36) could not be confirmed because of the absence of an adequate witness account.

In uncomplicated cases fulfilling transient global amnesia diagnostic criteria, further investigation may not be necessary. Investigation is usually directed towards excluding other potential causes and it is therefore important to recognize when atypical features are present. A possible flow chart to illustrate decision processing in the management of suspected transient global amnesia is shown in *Figure 2*.

In the emergency department the relative ease of access to computed tomography means that this is often undertaken; typically it is normal. Occasional cases of brain tumour associated with transient global amnesia are reported, but this is either chance concurrence or in fact transient epileptic amnesia masquerading as transient global amnesia (Milburn-McNulty and Larner, 2015). Diffusion

Table 2. Comparison of typical features of transient global amnesia, transient epileptic amnesia, transient ischaemic attack and psychogenic amnesia

Clinical feature	Transient global amnesia	Transient epileptic amnesia	Transient ischaemic attack	Psychogenic amnesia
Anterograde amnesia during attack	Yes	Yes	Yes	No
Focal neurological deficits	No	No	Yes	No
Aura, automatisms	No	Yes	No	No
Symptom duration	<24 hours	Usually <1 hour	<24 hours	Variable
Recurrence rate	Low	High	Varied	Varied
Triggers	Emotional stress or physical exertion	Can occur on waking	No	Emotional stress
Responds to antiepileptic drugs	No	Yes	No	No
Electroencephalography abnormalities during attack	No	Yes	No	No

weighted magnetic resonance imaging may show changes in signal intensity in memory relevant structures such as the hippocampus and medial temporal lobe in the acute stage, but interval magnetic resonance imaging is normal or shows only incidental findings. Modalities such as functional magnetic resonance imaging may inform future understanding of the pathophysiology underlying the condition (Sander and Sander, 2005) but are not generally available in clinical situations.

If transient epileptic amnesia features in the differential diagnosis, principally because of multiple and/or brief amnesic episodes, either ictal or interictal electroencephalography may be performed. Normal or non-specific changes on interictal electroencephalography do not exclude the diagnosis; sleep-deprived electroencephalography may be required.

CSF analysis contributes nothing to the diagnosis of transient global amnesia, and hence lumbar puncture is not indicated in uncomplicated cases.

Treatment and prognosis

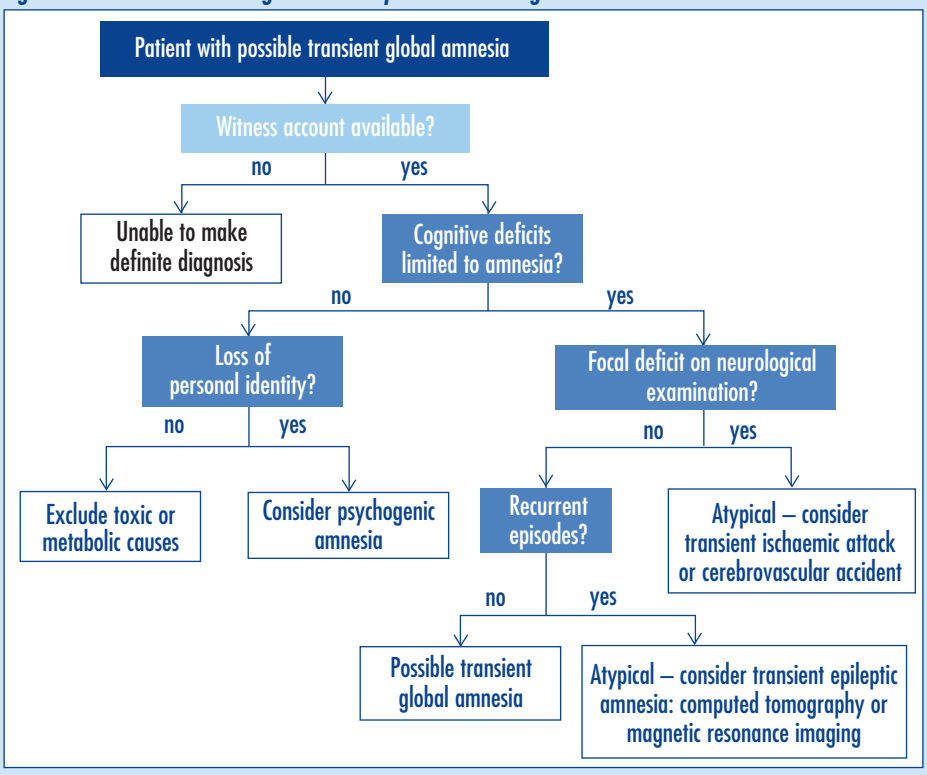
Once the diagnosis of transient global amnesia has been confirmed, there is no specific treatment other than patient explanation and reassurance. There is no increased risk of future stroke, epilepsy or other cognitive impairments. There is no need to inform the Driver and Vehicle Licensing Agency following a single episode (in the authors' experience, patients are sometimes erroneously told to stop driving).

The prognosis of transient global amnesia is good. Only a small minority of affected individuals (<5%) will go on to have recurrent events. If this occurs, the diagnosis should be reviewed, and the possibility of transient epileptic amnesia considered.

Conclusions

Patients with transient global amnesia present with an abrupt onset of anterograde amnesia; the typical phenotype is easily recognized and generally does not require investigation. However, an awareness of atypical features is important as this may suggest an alternative diagnosis. Differential diagnosis includes transient epileptic amnesia and transient ischaemic attack. Several theories to explain the pathophysiology of transient global amnesia have emerged. Regardless of aetiology a key brain region appears to be the medial temporal lobes, an area involved in formation and retrieval of episodic memory. No specific treatment is required for transient global amnesia and overall patients have a good prognosis. BJHM

Figure 2. Flow chart for management of suspected transient global amnesia.



Conflict of interest: none.

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KEY POINTS

- Transient global amnesia is an easily recognized clinical syndrome of anterograde memory impairment occurring in clear consciousness.
- The aetiology of transient global amnesia remains uncertain, but this uncertainty has no impact on diagnosis or management.
- The differential diagnosis of transient global amnesia includes transient epileptic amnesia, transient ischaemic attack, and psychogenic amnesia.
- Few investigations are required in typical transient global amnesia.
- Prognosis is excellent, and in the UK there is no driving restriction.