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Transient global amnesia

CLINICAL REVIEW

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Transient global amnesia is an acute, temporary failure of the ability to form new memories. The underlying mechanism is not fully understood but is thought to involve dysfunction of the hippocampus, particularly *Cornu Ammonis* 1 (CA1). Traditionally, the condition has been regarded as rare, isolated and fully reversible; however, but recent data suggest a more complex symptom profile. The diagnosis is still based on criteria from 1990, established before high-field MRI was widely available. Although the

diagnosis is clinical, MRI can provide important clarification for both differential diagnosis and therapeutic decision-making. This clinical review discusses the functional neuroanatomy of the memory system, possible pathophysiological mechanisms and diagnostic aspects of transient global amnesia.

Transient global amnesia is a neurological syndrome that is characterised by a sudden onset of memory loss. Patients lose the ability to form new memories (anterograde amnesia) and experience memory loss for past events (retrograde amnesia), the degree and duration of which vary. Memory functions usually return to normal within 24 hours (1). There is typically full recovery of cognitive function, but hippocampus-related processes such as spatial orientation may remain affected for months (2, 3). The condition has an annual incidence of 3–8 per 100,000 population and most frequently affects individuals aged 50–70 years and rarely those under the age of 40 years (1). It is often associated with migraine in patients younger than 56 years.

Although the condition was previously considered to be an isolated episode, one in eight patients experiences recurrence, particularly in cases involving migraine, depression, or episodes triggered by sexual activity (4). Transient global amnesia is associated with psychiatric disorders, phobic personality traits, as well as psychological or emotional instability, and can be triggered by emotional or physical stress, such as cold-water immersion or Valsalva-like manoeuvres (1, 5). Recent data suggest chronic hippocampal damage (6), as well as an increased risk of epilepsy and dementia (7). The aetiology of transient global amnesia remains unclear.

This clinical review is based on a discretionary selection of literature and the authors' own experience. We look at the functional neuroanatomy of the memory system, possible pathophysiological mechanisms and clinically relevant aspects of diagnostic evaluation, including the role of MRI scans.

Medial temporal lobe

Episodic memory, the ability to remember 'what', 'where' and 'when' we experienced events in life, is associated with the medial temporal lobe, and particularly the hippocampal formation. This structure consists of the dentate gyrus, the cornu ammonis fields and the subiculum. The structure receives processed information from the entorhinal cortex, which in turn integrates information from various areas of the brain. The complex functional architecture of this network plays a key role in memory formation and retrieval of information (Figure 1) (8).

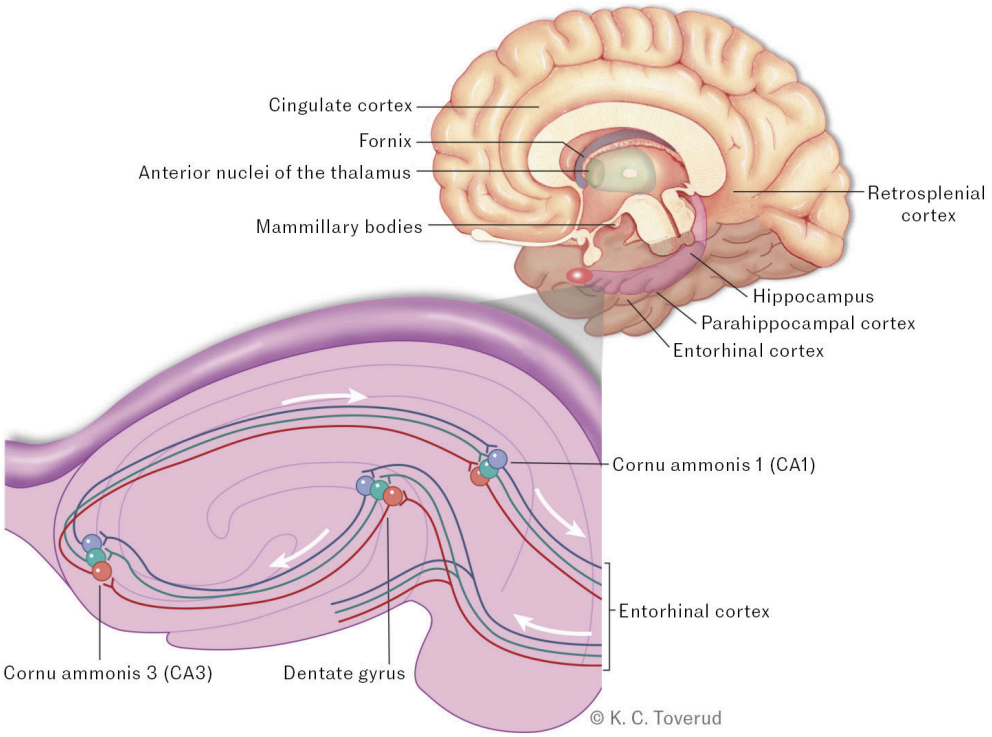

Figure 1 Functional anatomy of the memory system. Episodic memory, the ability to remember what, where and when we have experienced something, is associated with the medial temporal lobe, particularly the hippocampal formation. This consists of the dentate gyrus, the cornu ammonis fields (CA3 and CA1; CA2 has been omitted for simplicity) and the subiculum. These structures receive processed multisensory information from the entorhinal cortex, which integrates signals from multiple cortical areas. Information is transmitted through the fornix to the mammillary bodies, further to the anterior thalamic nuclei, and via the cingulate cortex to the retrosplenial and parahippocampal cortices, before projecting back to the entorhinal cortex. Together, these structures form Papez's circle, central to the encoding, consolidation and retrieval of episodic memories.

The role of the hippocampus in episodic memory was demonstrated by the renowned case study of epileptic patient H.M. (Henry Molaison). Following bilateral resection of the medial temporal lobe, he lost the ability to form new episodic memories, while his procedural memory, such as mirror drawing, remained intact (9). A related phenomenon is seen in transient global amnesia.

Research by May-Britt and Edvard Moser, in collaboration with John O'Keefe, has expanded our understanding of the role of the medial temporal lobe in episodic memory and spatial orientation. The discoveries of place cells in the CA1 region of the hippocampus and grid cells in the entorhinal cortex have revealed neural mechanisms for spatial and episodic memory (10–12). This research, awarded the Nobel Prize in 2014, has expanded our knowledge of the neural circuits that control memory, with significance for cases such as H.M. and patients with transient global amnesia.

Pathophysiology

The CA1 field is particularly susceptible to metabolic, hypoxic and cytotoxic stress, a vulnerability observed in conditions such as hypoxia-ischemia, temporal lobe epilepsy and Alzheimer's disease (1,13–15). Lesions are thought to affect this area in patients with transient global amnesia, which may explain the temporary loss of the ability to form new memories, while older memories remain largely intact. The leading pathophysiological hypotheses include epileptic, vascular and migraine-related mechanisms, including cortical spreading depression. There is no neurophysiological support for an epileptic cause (16). Nor have typical vascular risk factors, as seen in transient ischaemic attack, been identified, and the diffusion changes differ from those observed in migraine with aura (1).

Diagnostic strategy

The diagnosis of the condition remains clinical, based on the criteria established by Hodges and Warlow in 1990, which are in turn adapted from the previous classification proposed by Caplan (Box 1) (17, 18). A case history should identify risk factors for cerebrovascular disease, both in the patient and their close family, and assess relevant differential diagnoses. Migraine and depression may support the diagnosis of transient global amnesia (Box 1). It is essential to investigate the beginning of the symptoms, their duration and any triggering factors. Repeat or frequent episodes should always prompt further investigation. Patients often have both anterograde and retrograde amnesia, including memory loss surrounding the episode and memories dating back several decades (19). Information gathered by taking a collateral history is important, and witnesses should describe behaviour without leading questions (for example, avoid asking whether the patient has repeated the same questions multiple times before the witnesses have described the episode). Symptoms such as paresis, seizures or decreased consciousness are not consistent with transient global amnesia.

Box 1 Diagnostic criteria by Hodges and Warlow (17)

Diagnostic criteria:

- Anterograde amnesia observed by a reliable observer present during most of the episode
- Cognitive impairment is limited to amnesia, with no loss of personal identity or alteration of consciousness
- No accompanying focal neurological deficits
- Absence of epileptic features
- Resolution of symptoms within 24 hours
- Recent head injury or active epilepsy are exclusion criteria

Clinical findings that support the diagnosis:

- The patient asks repetitive questions related to orientation
- Experience of physical exertion or mental/emotional stress prior to the episode
- Mild vegetative symptoms such as headache, dizziness or nausea may occur
- A history of migraine or depression
- Altered episodic spatial orientation abilities

The main differential diagnoses include transient epileptic amnesia, transient ischaemic attack, migraine with aura, dissociative amnesia, and Wernicke's encephalopathy. *Transient epileptic amnesia* usually lasts less than an hour, is recurrent and often occurs in the morning. The diagnosis is supported by EEG findings or response to anticonvulsant treatment. *Transient ischaemic attack* can cause isolated amnesia, but is generally accompanied by focal deficits involving the posterior circulation (visual field defects, dysarthria, ataxia). MRI may detect ischaemic lesions, but not in all cases. *Migraine with aura* can cause temporary cognitive symptoms, but it usually occurs together with visual disturbances and headache. In *dissociative (psychogenic) amnesia,* the patient has intact learning abilities and selective retrograde amnesia without neurological deficits. *Wernicke's encephalopathy* occurs with alcohol abuse or malnutrition and is characterised by ataxia and ophthalmoplegia (20).

Therefore, clinical assessment, observation and targeted supplementary investigations, in particular MRI and, if applicable, EEG, are essential to distinguish between the conditions and ensure the correct treatment. Blood samples should be taken to rule out hypoglycaemia, infection or metabolic disturbances. The patient should be observed for the duration of the episode of amnesia since resolution of symptoms within 24 hours is one of the criteria required for the diagnosis of transient global amnesia. There is currently no treatment for transient global amnesia (20).

Relevance of MRI scan

Although transient global amnesia is still regarded as a clinical diagnosis, MRI can help support the diagnosis and rule out important differential diagnoses, particularly in cases with atypical symptoms. Ischaemic injury in strategic locations, for example, in the thalamus, fornix or temporal lobe, can present with clinical symptoms that mimic transient global amnesia, but requires rapid treatment (21–25). In addition, recent data have demonstrated that almost one in five patients with presumed transient global amnesia are subsequently reclassified as having transient epileptic amnesia after thorough evaluation with EEG and follow-up (26). In contrast to transient global amnesia, which can be associated with characteristic lesions in the hippocampus, MRI findings are generally normal in transient epileptic amnesia (26), but the condition

requires specific treatment with anticonvulsant medication. Therefore, an appropriate MRI protocol performed within the correct timeframe has important implications for the differential diagnosis and treatment strategy.

In patients with transient global amnesia, small punctate lesions (1–8 mm) can often be detected in the hippocampus on diffusion-weighted and T2-weighted MRI sequences (1, 27). They are presumed to be located in the CA1 region of the hippocampus, although extra-hippocampal lesions have been reported in rare cases (28). These lesions are best detected on diffusion-weighted sequences after 12–24 hours and on T2-weighted sequences after 24–72 hours, after which they gradually resolve over 7–10 days (1). Standard MRI scans with field strengths of 1.5–3 Tesla have traditionally been used in cases of suspected transient global amnesia, and recent data demonstrate that even higher field strengths (7 Tesla) can double the detection rate (29). Although 7-Tesla MRI technology is currently only available at a few research and specialist units, the highest possible magnetic field (Figure 2), using thin slices in the coronal plane without slice gaps, perpendicular to the long axis of the hippocampus, is recommended for the best possible visualisation of the anatomy of the hippocampus, as well as the use of high b-values (> 2000) for maximum sensitivity (1). Comparison of diffusion-weighted and T2-weighted sequences in the same section plane provides a good anatomic overview and visualisation of lesions. False negative findings are usually due to unsuitable MRI protocols or imaging performed too early, since the condition is initially investigated as a possible cerebrovascular event.

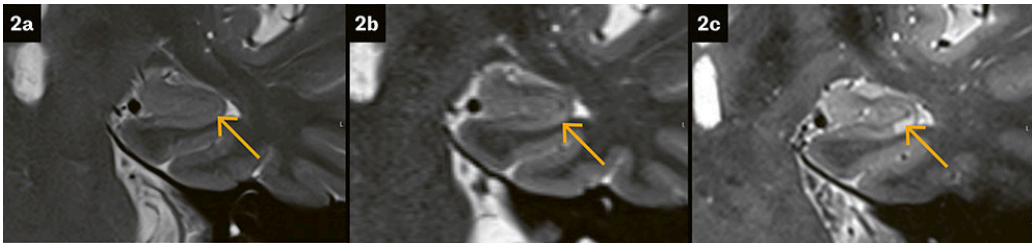

Figure 2 Hyperintense punctate lesion in the left hippocampus in transient global amnesia (arrow). T2-weighted sequences in the coronal plane, taken with the following MRI field strengths: 1.5 T (a), 3 T (b) and 7 T (c). Higher field strengths improve conspicuity of the lesion (1.5 T: not visible, 3 T: barely visible, 7 T: clearly visible).

Transient global amnesia is an acute, temporary and benign condition, but with a more complex symptom profile than previously thought. Improving understanding of its underlying mechanisms will require integrated clinical and experimental studies.

The article has been peer-reviewed.

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