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A case of transient epileptic amnesia with radiological localization

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SUMMARY

Background A 54-year-old man presented to a cognitive disorders clinic having experienced recurrent episodes of transient amnesia over a number of years. The attacks often occurred on waking, did not affect other cognitive abilities such as perception, language or judgment, and typically lasted about half an hour. The attacks were sometimes associated with olfactory hallucinations. Between amnestic episodes, the patient noticed a gradual deterioration in his recall of remote events, despite normal performance on standard memory tests.

Investigations Physical examination, laboratory tests, EEG, MRI brain scan, PET imaging, and neuropsychological assessment.

Diagnosis Transient epileptic amnesia.

Management Anticonvulsant medication.

KEYWORDS epilepsy, memory, MRI, PET, transient epileptic amnesia

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Learning objectives

Upon completion of this activity, participants should be able to:

1 Describe diagnostic criteria for transient epileptic amnesia (TEA).
2 Distinguish clinical features of TEA from transient global amnesia and psychogenic amnesia.
3 Recognize the types of persistent amnesia seen in patients with TEA.
4 Identify the most likely anatomic seizure focus of patients with TEA.
5 Describe the most appropriate treatment for TEA.

Competing interests

The authors, the Journal Editor H Wood and the CME questions author D Lie declared no competing interests.

THE CASE

A 54-year-old, right-handed university Professor presented to a cognitive disorders clinic with a 4-year history of recurrent episodes of transient amnesia and a progressive decline in memory function. The patient had no other notable past medical or psychiatric history. He contacted the clinic after concluding from a search of the internet that he was likely to be experiencing transient epileptic amnesia (TEA).

At the age of 50 years, the patient had experienced an episode of transient amnesia that began abruptly as he emerged from the shower at 10.00 h one morning. He could not recall recent events. Alone in the house and curious as to why he should be showering so late, he went out to his car and felt that the bonnet

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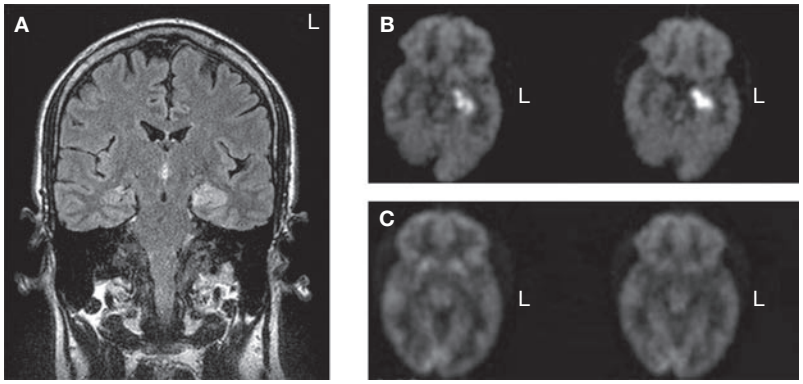

Figure 1 Brain scans from a patient with transient epileptic amnesia. (**A**) Fluid-attenuated inversion-recovery MRI scanning during a prolonged amnestic episode reveals hyperintensity in the left hippocampus. (**B**) 2-Fluoro-2-[^{18}F]-deoxy-D-glucose PET scanning during the same episode shows hypermetabolism localized to the left anterior hippocampus. (**C**) Metabolism in the left anterior hippocampus returned to normal 1 month later. Abbreviation: L, left.

was warm, implying that he had already been out. Over the next hour the patient's memories from earlier in the day gradually returned. He recalled that earlier that morning while out jogging with friends, he had briefly felt dizzy and had noticed a strong, unpleasant smell that was not detected by the other individuals. Later that day, he recounted the details of the episode to his doctor. Physical examination, a CT head scan and a neuropsychological assessment were unremarkable. The patient was given a diagnosis of transient global amnesia and was assured that recurrence was unlikely.

Over the 3 years that followed this initial episode, the patient experienced six further amnestic attacks. The attacks all occurred on waking and were characterized by retrograde amnesia for events of the past few days or weeks. In one journal entry, he noted: "Woke up at 3.30 am—had no idea where I was. After stumbling around to find a light switch, found that I was in a small room in the…hotel in Milan (Italy). Initially had no idea why I was here. Found documents in room with my itinerary…gradually began to recall that I was on a trip to attend meetings in Milan and Lugano." The patient's anterograde memory was relatively well preserved—he did not repetitively ask questions, and was subsequently able to remember and record in his journal many details of the attacks—and other cognitive capacities were not noticeably impaired. There were no observed automatisms or periods of unresponsiveness during attacks. Over a period of 30–60 min, his memories would gradually return, although the details of recent events sometimes remained hazy. The patient was assessed on several occasions by a neurologist and neuropsychologist; they reported that "no organic etiology" could be identified and that "depression and anxiety are likely to be contributing". A psychiatrist, however, found no evidence of a psychiatric disorder.

Three and a half years after his first attack, the patient experienced a more-prolonged amnestic episode that was followed by several days of what he described as "anxiety, mental confusion and quasi-hallucinations—like 'Groundhog Day'." He was admitted to hospital for investigations. Neurological examination was normal, and the patient scored 27 out of 30 on the Mini Mental State Examination, consistently failing to recall three words after a brief delay. Routine blood tests, chest X-ray, electrocardiography, and head CT with angiography were unremarkable. No cells or biochemical abnormalities were detected in a cerebrospinal fluid sample. MRI, EEG, and 2-fluoro-2-[^{18}F]-deoxy-D-glucose PET were performed during the symptomatic period. The EEG showed an increase in slow-wave activity over the left frontotemporal region but no overt epileptiform features. The fluid-attenuated inversion-recovery MRI scan revealed high signal in the left hippocampus (Figure 1A). Dramatic and circumscribed hypermetabolism in the left medial temporal lobe was evident on the PET scan (Figure 1B). The patient's condition improved gradually over his 5-day hospital stay. A seizure disorder was considered to be the most likely cause of his symptoms, and levetiracetam (1,500 mg twice daily) therapy was started. After 1 month, during which the patient had no intervening acute episodes, the PET abnormalities had resolved (Figure 1C). Extensive further investigations, including a blood test for antibodies against voltage-gated potassium channels, were normal.

EEG videotelemetry was performed while the patient was still receiving levetiracetam. Hyperventilation provoked a brief (<1 min) period during which the patient was unresponsive to questions or commands, and spikes on the EEG were observed over the left temporal region. The EEG rapidly normalized, but, on subsequent questioning, the patient proved to be unable to recognize the EEG technicians and gave the year as 1989. The anticonvulsant treatment was changed to lamotrigine (150 mg/day), and the

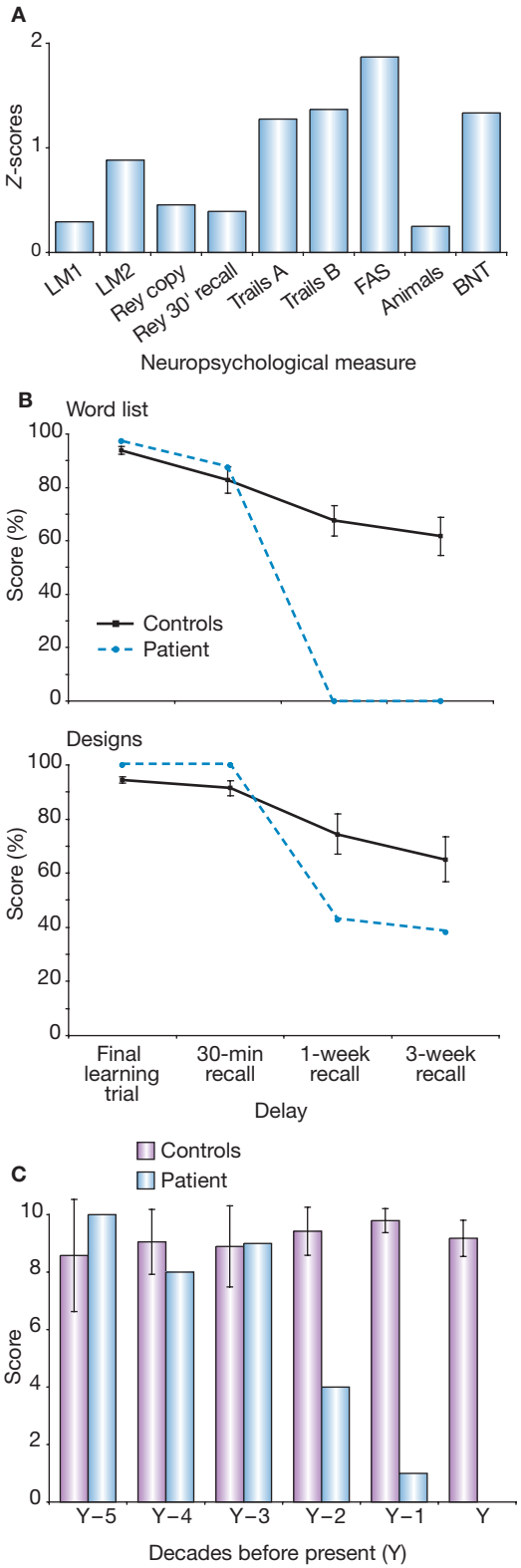

Figure 2 Neuropsychological assessment of a patient with transient epileptic amnesia. (**A**) The patient's performance on various standard neuropsychological tests is shown as *Z*-scores indicating the number of standard deviations from the mean score of a group of normal control individuals (mean age 67.7 years [SD ± 8.1]; mean IQ 120 [SD ± 14.4]).[1] Memory tests included logical memory from the Wechsler Memory Scale, 3rd edition (LM1 and LM2) and copy and delayed recall of the Rey Complex Figure (Rey copy and Rey 30' recall). Executive function tests included the Trail-Making Test (Trails A and Trails B), and Verbal Fluency for letters (FAS) and categories (Animals). The Boston Naming Test (BNT) was used to assess semantic memory. (**B**) The patient's long-term recall of a learned word list and of a set of designs was compared with performance of normal controls.[1] Despite normal learning and 30-min retention, the patient demonstrated accelerated forgetting over longer intervals; error bars indicate 2 SEs of the mean. (**C**) The Modified Autobiographical Memory Interview[1] was used to assess the patient's memory for events relating to two varying topics (e.g. 'holiday') for each decade of his life. For each topic, he was asked to produce one detailed episodic memory (e.g. "Can you recall any incident, even if small, that occurred during your holiday in San Diego?"), which was scored out of 5 for detail. His performance with regard to recall of events from the previous three decades was significantly impaired relative to controls. Y indicates the most-recent life decade; error bars indicate 2 SEs of the mean.

patient had no further acute episodes of memory loss or confusion.

Coincident with the onset of the amnestic episodes, the patient began to notice persistent memory problems. He found that some newly acquired memories faded irredeemably over a period of days or weeks. For example, he went out to the cinema and the next day related his disappointment at the film to his daughter. One week later, however, he was no longer able to recall anything of the evening's events. In his journal, he described his memories "evaporating—as if random chunks of my memory have been erased". Furthermore, he began to notice that his recollection of many remote, salient, personal events, such as family holidays and weddings from the past 30 years, had become "sketchy or completely absent".

The patient also noticed problems with his spatial memory. He complained that he was unable to navigate around previously familiar neighborhoods. For example, he retraced a favorite running route around local streets, but found that "hardly anything looked familiar". He frequently took wrong turns when driving alone.

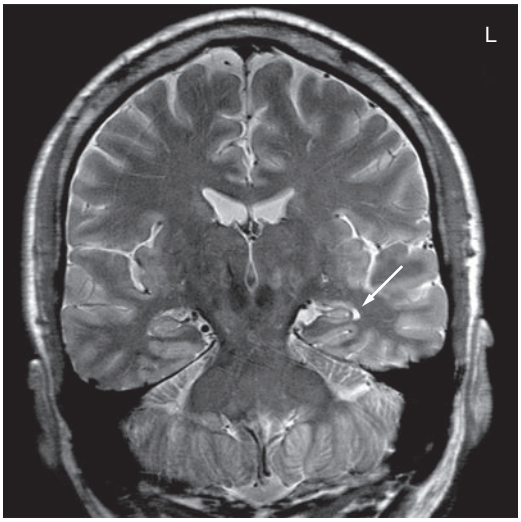

Figure 3 4-Tesla fast spin-echo MRI sequence from a patient with transient epileptic amnesia. The sequence was acquired at the time of detailed neuropsychological testing. The image shows focal atrophy of the left hippocampus (arrow). Abbreviation: L, left.

Box 1 Diagnostic criteria for transient epileptic amnesia.[1]

History of recurrent witnessed episodes of transient amnesia

Cognitive functions other than memory judged by a reliable witness to be intact during typical episodes

Evidence for a diagnosis of epilepsy made on the basis of one or more of the following features:

- Epileptiform abnormalities on EEG
- Concurrent onset of other clinical features of epilepsy (e.g. lip smacking, olfactory hallucinations)
- Clear-cut response to anticonvulsant therapy

Despite his memory problems, the patient continued with teaching and research responsibilities, although he commented that: "My productivity is certainly affected by this, inasmuch as I also have trouble remembering the contents of any papers I've read lately—or even papers that I have written!"

The patient presented to a cognitive disorders clinic 6 months after his last amnesic episode, and underwent neuropsychological assessment. His IQ was found to be 136, which is in the 'very superior' range. His performance on a variety of standard neuropsychological tests revealed well-preserved anterograde memory for both verbal and nonverbal material over a 30-min delay, as well as normal language and executive function (Figure 2A).

To investigate the complaint of "evaporating" memories, the patient's long-term memory was tested over a period of 3 weeks using a 15-word list and a set of 7 simple designs. The material was learned over repeated presentations until the patient attained 90% recall accuracy. Free recall was then tested after 30 min, 1 week and 3 weeks. The results are shown alongside those of a group of healthy controls in Figure 2B. After 30 min, the patient's recall was intact. After extended delays, however, he recalled nothing of the word list, and had even forgotten that it had been administered. His recall of the designs was also significantly impaired.

A semi-structured interview was used to assess the patient's memory for autobiographical events. Figure 2C shows that, in comparison with the control group, the patient had marked impairment of autobiographical memory, such that he had difficulty remembering events from the previous three decades but not from before this period.

The patient underwent brain MRI at 4-Tesla field strength. The image, shown in Figure 3, revealed atrophy restricted to the left hippocampal region.

DISCUSSION OF DIAGNOSIS

This case illustrates many of the characteristic features of the recently described syndrome of TEA,[1,2] and provides the first radiological evidence of a hippocampal seizure focus in this disorder.

It has been recognized for over 100 years that episodes of transient, isolated amnesia can be caused by epilepsy.[3] More recently, it has been shown that such episodes are frequently associated with persistent memory deficits.[1,4] We recently described the clinical characteristics of TEA by studying a series of 50 patients who met the diagnostic criteria outlined in Box 1.[1] The mean age of onset of TEA is 62 years, with very few patients presenting below 45 years of age. Amnestic attacks frequently occur on waking and typically last 30–60 min, although much longer episodes have been reported.[5] Anterograde memory can be relatively preserved, so that patients report being "able to remember not having been able to remember". A reliable witness account is crucial in making the diagnosis. A cardinal feature of TEA is recurrence, the frequency of which varies considerably

Table 1 Distinguishing clinical features of the transient amnesic syndromes.

Feature	Transient epileptic amnesia	Transient global amnesia	Psychogenic amnesia
Typical age of onset	50–70 years	50–70 years	Any age
Past medical history	None	Migraine	'Organic' transient amnesia; substance abuse; psychiatric illness
Precipitants	Waking	Cold water; physical exertion; psychological stress	Minor head injury; stress; depression
Ictal memory profile	Anterograde and retrograde amnesia showing within-patient variation; patient might later partially recall attack); retrograde procedural memory intact	Profound anterograde amnesia including repetitive questioning; variable retrograde amnesia; intact nondeclarative memory	Highly variable: often profound retrograde amnesia with loss of personal identity; relatively preserved anterograde memory; variable procedural memory
Duration of amnestic episode	Usually <1 h but can last much longer (days)	Typically 4–10 h	Days or months
Recurrence	Mean frequency 13 attacks per year	Rare	Rare
Postictal and interictal memory	Accelerated forgetting; remote autobiographical memory loss; topographical amnesia	Grossly intact, but subtle deficits might persist for several months	Variable: patient might be able to 'relearn' the past
Other features	Olfactory hallucinations; oroalimentary automatisms; brief loss of responsiveness	Headache and/or nausea	Focal 'neurological' symptoms or signs, such as hemiparesis

between individuals. Olfactory hallucinations are experienced by about 40% of patients. There is evidence that amnesia in TEA can be either ictal or postictal.[1] The interictal EEG is often normal, but epileptiform features are seen in approximately a third of cases, especially in patients who have experienced sleep deprivation. The EEG should be interpreted with care in elderly patients, as unusual features are not necessarily pathological in such individuals.

Persistent memory impairment is reported by about 75% of patients with TEA, with three distinct types of memory difficulty being identified: accelerated forgetting, over days to weeks, of newly acquired information; dense but patchy loss of memories for salient autobiographical events often extending back over several decades; and topographical amnesia. These impairments cause appreciable problems in day-to-day life, but remain undetected by standard neuropsychological tests, which typically assess learning and memory of new material over intervals of up to 1 h.

There is often a delay in the diagnosis of TEA[1]—it is commonly mistaken for transient global amnesia or 'psychogenic amnesia', as illustrated by the present case. The distinctive features of these conditions are illustrated in Table 1. Other reported causes of transient amnesia include transient ischemia, closed head injury, migraine, and medications including anticholinergic drugs and benzodiazepines.[6]

The nature of the amnesia during attacks, the frequent occurrence of olfactory hallucinosis, and the location of interictal epileptiform discharges on EEG suggest that in TEA the seizure focus lies in the medial temporal lobes—brain regions intimately involved with declarative memory.[7] The present case, in which the peri-ictal PET scan showed focal hypermetabolism in the left hippocampus with associated high signal on structural MRI, supports this hypothesis.[8]

As with the majority of TEA cases,[1] the present patient's previous structural MRI scans were normal. Over time, however, and possibly as a consequence of a prolonged period of nonconvulsive status epilepticus, atrophy became apparent in the left hippocampus. It is not clear whether the patient's persistent memory deficits were related to this structural damage or to ongoing subclinical seizure activity.

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Competing interests
The authors declared no competing interests.

TREATMENT AND MANAGEMENT

In common with patients who have other forms of late-onset epilepsy, individuals with TEA usually respond well to a low dose of anticonvulsant medication. In our recent study,[1] 96% of patients became seizure-free on anticonvulsant monotherapy. When attacks are very infrequent, treatment responsiveness is difficult to assess; therefore, it is important to obtain a secure diagnosis to avoid unnecessary use of medication. As the present case demonstrates, interictal memory problems might persist despite anticonvulsant treatment. The long-term prognosis of TEA is not yet well characterized. However, the few cases that have been followed for a number of years indicate that once seizures are controlled, cognitive function does not progressively deteriorate.

CONCLUSIONS

This case illustrates many of the typical features of TEA and provides the first radiological evidence that the syndrome can result from seizure activity in the hippocampus. When confronted with a case of recurrent transient amnesia, physicians should look out for features indicative of epilepsy, such as olfactory hallucinations, automatisms, periods of unresponsiveness, or ongoing memory difficulties. Early treatment with anticonvulsants is usually effective in stopping the amnestic attacks that occur in TEA, although interictal memory impairment might persist.

References

1 Butler CR *et al.* (2007) The syndrome of transient epileptic amnesia. *Ann Neurol* **61:** 587–598
2 Zeman AZ *et al.* (1998) Transient epileptic amnesia: a description of the clinical and neuropsychological features in 10 cases and a review of the literature. *J Neurol Neurosurg Psychiatry* **64:** 435–443
3 Hughlings-Jackson J (1888) On a particular variety of epilepsy (intellectual aura), one case with symptoms of organic brain disease. *Brain* **11:** 179–207
4 Manes F *et al.* (2005) Autobiographical amnesia and accelerated forgetting in transient epileptic amnesia. *J Neurol Neurosurg Psychiatry* **76:** 1387–1391
5 Vuilleumier P *et al.* (1996) Failure to recall (but not to remember): pure transient amnesia during nonconvulsive status epilepticus. *Neurology* **46:** 1036–1039
6 Hodges JR (1991) *Transient Amnesia*. London: WB Saunders
7 Squire LR *et al.* (2004) The medial temporal lobe. *Annu Rev Neurosci* **27:** 279–306
8 Newberg AB and Alavi A (2005) PET in seizure disorders. *Radiol Clin North Am* **43:** 79–92