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Differentiating Transient Global Amnesia From Hippocampal Infarction in the Presence of Bilateral Diffusion Restriction: A Case Report

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Abstract

Transient global amnesia (TGA) is a rare neurological syndrome described as a loss of memory that resolves within 24 hours. In this report, we present a 70-year-old man who presented to the emergency department after acute confusion, described as failure to recall familiar people and previous memories, with typical repetitive questioning. His episode lasted for four hours and completely resolved. Initial computed tomography (CT) of the head was unremarkable; however, magnetic resonance imaging (MRI) of the brain demonstrated two small foci of restricted diffusion bilaterally in the hippocampi. This was followed up later with further imaging that showed complete resolution of the lesion. This report highlights the diagnostic challenge of distinguishing TGA from hippocampal infarction when bilateral hippocampal diffusion restriction is present on imaging, and the importance of interpreting MRI findings alongside the clinical course, as both conditions can present with similar imaging findings, with the latter causing a longer duration of symptoms.

Categories: Neurology, Geriatrics, Internal Medicine
Keywords: anterograde amnesia, diffusion-weighted imaging, hippocampal infarction, hippocampus, transient global amnesia

Introduction

Transient global amnesia (TGA) is a neurological phenomenon characterised by sudden onset of anterograde and, less frequently, retrograde amnesia, accompanied by repetitive questioning, lasting up to 24 hours, with complete resolution. The estimated incidence of 5.2-10/100,000 is reported [1-3]. Aetiology and risk factors are not fully understood, with some proposed mechanisms such as venous congestion, migraine-related spreading depression and a stress-related response. Some studies have reported associations with older age, hypertension, hypercholesterolaemia and cardiac disease, although findings are inconsistent, and episodes are often preceded by emotional stress or physical exertion [4,5]. There is no confirmatory test for TGA, so the diagnosis is made on clinical grounds, most commonly using the criteria proposed by Hodges and Warlow [6]. These seven criteria specify that for TGA to be diagnosed: (1) the attack of anterograde amnesia must be witnessed by an observer, with (2) no involvement of altered consciousness or identity, with (3) cognitive impairment limited only to amnesia, and (4) lack of epileptic features. In addition, (5) episodes should resolve within 24 hours, (6) there are no accompanying focal neurological deficits, and (7) there is no recent head injury or active epilepsy [6]. Differentiating between TGA and hippocampal infarction is a crucial step in the management. While both conditions share similarities such as amnesia, symptoms of hippocampal infarction can persist beyond 24 hours and lead to lasting memory loss. Additionally, restricted diffusion, described as hyperintensity on diffusion-weighted imaging (DWI), can be seen in both; however, larger or more extensive involvement of other posterior circulation territories like the thalamus, occipital and medial temporal lobes can be found in hippocampal infarction [7,8]. The management of TGA is usually reassurance, in comparison to the necessary steps of secondary prevention and risk factor control. In this report, we discuss the case of a 70-year-old male who presented with sudden-onset anterograde amnesia and was later diagnosed with TGA. His MRI shared similar findings to those of hippocampal infarction, aiming to highlight the importance of accurate diagnosis and appropriate management.

Case Presentation

A 70-year-old man who self-presented to our emergency department following an episode of confusion, which was described as an inability to recognise familiar objects and people. Prior to this incident, he was reportedly well on waking, carrying on his regular activities, until his wife witnessed him staring into space for several minutes, during which he showed no automatisms. Afterwards, he was able to recognise his own identity and his family members. However, he could not recall where several household items had come from, including a blue folder placed in front of him and a balloon hanging for a recent special occasion. He was repetitively asking questions and was surprised when told about his son's recent marriage and current state of living, which he had known about previously. The amnesia was isolated, with no other cognitive or

neurological deficit. There were no sleep problems, head trauma history or substance abuse history prior to this incident. His amnesia was isolated, with no deficits in his cognition or further neurological deficits. He did not report any previous history of migraine, associated headaches, visual auras, nausea or vomiting. There was no history suggestive of seizure-like activity; no abnormal auditory, smell, or tactile sensations were noted; likewise, no symptoms such as numbness, weakness, vertigo, loss of balance, speech deficits, loss of consciousness, fever or shortness of breath were recalled. The deficit onset started at approximately 09:00 am, remained stable, and his memory gradually returned, with full recovery by approximately 4 hours. His first point of contact with the triage services in the hospital was at 14:21. During his initial presentation and assessment by the clinicians at 16:17, he was symptom-free and back to normal status.

His medical and surgical background included well-controlled hypertension and type 2 diabetes, managed by amlodipine 5 mg once daily, dapagliflozin 10 mg once daily and self-administration of Insulin. Additionally, it included severe glaucoma medicated at home with Brinzolamide/Brimonidine eye drops and Brimatoprost/Timolol eye drops, and was followed up regularly. No recent adjustments to any of his medications were noted.

The initial assessment was done when he was back to his normal baseline. His observations were stable, and he was found to be oriented to time, place and person. No apparent hallucinations, memory deficits or cranial nerve abnormalities were found. Motor examination demonstrated normal tone and full power bilaterally based on the Medical Research Council (MRC) scale [6] for muscle strength, and tendon reflexes elicited normal responses. No gait abnormalities were noted, and no evidence of neck stiffness or meningeal signs was found. The remaining cardiovascular, respiratory and abdominal examinations were uneventful.

Initial laboratory measurements were conducted to exclude organic pathologies. Full blood count, clotting studies and biochemistry were normal, with venous blood glucose of 13.6 mmol/L, reflecting a possible stress response in the background of diagnosed diabetes. He had a normal lactate level and negative urine dipstick. Thyroid function testing in the last six months was within acceptable limits. His electrocardiogram (ECG) showed sinus rhythm with no signs of arrhythmia.

He remained in the ED for a further 5 hours, during which he underwent a CT head that occurred 2 hours post-presentation and approximately 7 hours 28 minutes after onset. The scan found age-appropriate involutional cerebral changes, in addition to evidence of periventricular white matter sclerotic leukoencephalopathy. However, no evidence of ischaemic or bleeding changes was found to explain his sudden change in status (Figure *1*). A suspicion of transient ischaemic attack (TIA) was made, and the patient was referred for review by a stroke specialist through the TIA pathway. He was scheduled to undergo an urgent outpatient magnetic resonance imaging (MRI) brain within 48 hours, and was started on aspirin 300 mg once daily until further review. He was discharged home with appropriate advice and follow-up in the TIA clinic following his MRI.



A.1: Axial View. A.2: Coronal View

FIGURE 1: Initial CT head at the time of presentation, done within two hours of presentation

Imaging of A.1 Axial view and A.2 Coronal view revealing age-appropriate involutional brain changes, with white matter arteriosclerotic leukocephalopathy. No evidence of acute intracranial bleeding or early ischaemic changes noted.T, computed tomography

His MRI brain, done on the following day at around 31 hours post-onset, revealed 2 foci of restricted diffusion in the lateral aspects of the hippocampi bilaterally on DWI sequence (Figure *2*), which corresponded to low signal in the same affected areas on the apparent diffusion coefficient (ADC) map. Injury was localised to the hippocampi areas only, with no involvement of other posterior cerebral artery (PCA) territories. These findings were suggestive of possible ischaemic injury; however, the clinical context of symptom resolution makes TGA more probable. He also underwent a 72-hour Holter monitor 6 months prior to his episode, which was requested by his general practitioner for chronic palpitations. His report did not reveal evidence of atrial fibrillation. Approximately four weeks later, he underwent follow-up imaging with MRI, in addition to an MR angiogram of the neck and cerebral vessels in view of his vascular risk factors, which revealed resolution of the previously noted restricted diffusion foci (Figure *3*), with no evidence of narrowing of the carotid arteries or circle of Willis; the absence of stenosis lowers but does not remove the probability of an ischaemic mechanism. Infarction is made less likely by the short duration and full recovery in this case. Given the witnessed staring with reduced awareness at onset, a focal impaired-awareness seizure and transient epileptic amnesia were considered. TEA typically presents with recurrent, brief episodes, often on waking, and may be accompanied by other seizure features such as automatisms. In this patient, a single prolonged episode lasting four hours, with features of complete resolution, favoured TGA.

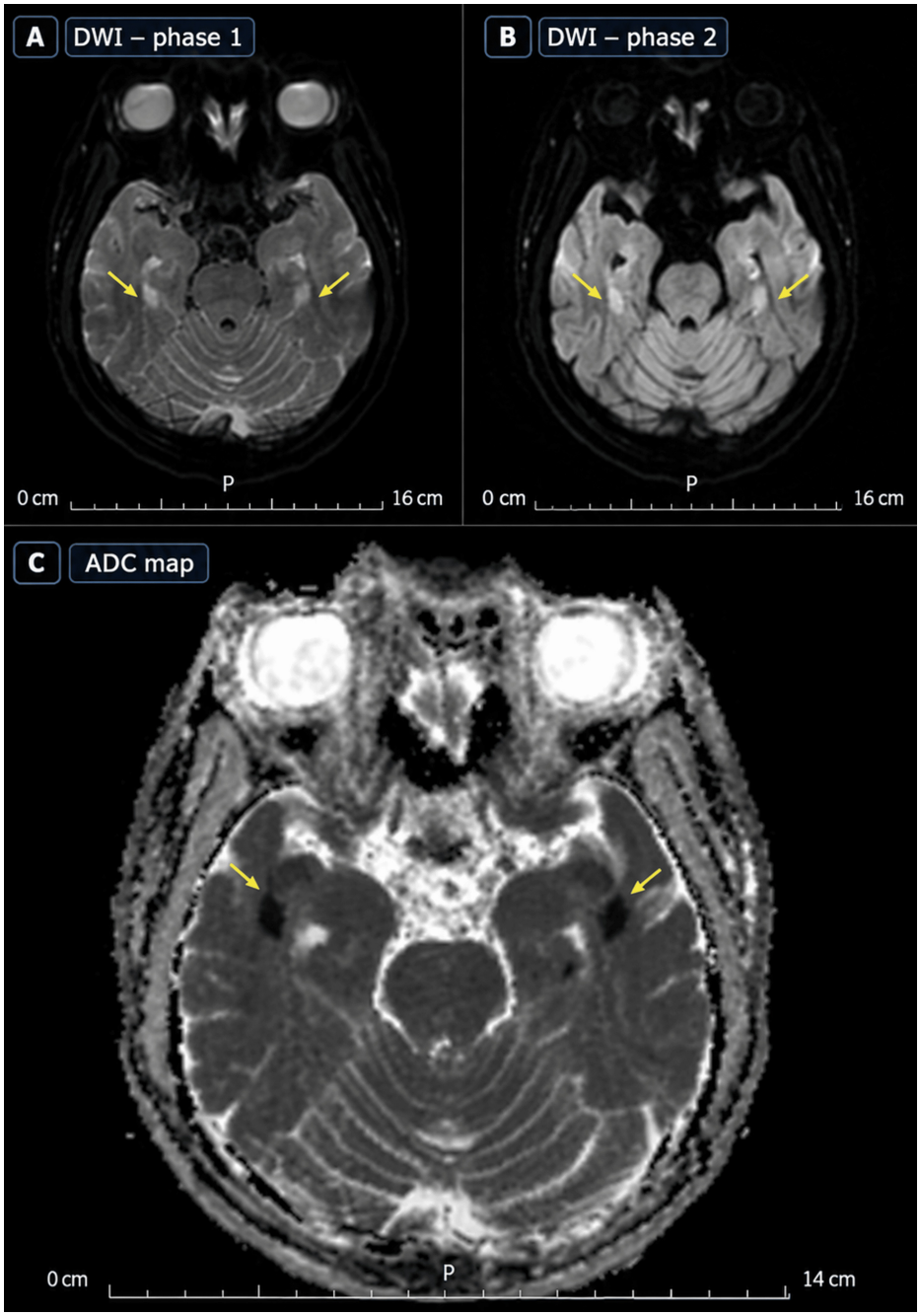


FIGURE 2: Initial MRI brain 31 hours after symptom onset showing bilateral hippocampal diffusion restriction

(A, B) Axial DWI at two levels shows two small foci of hyperintensity in the lateral aspects of the hippocampi (arrows). (C) The ADC map shows corresponding hypointensity (arrows), indicating restricted diffusion. The lesions are bilateral.

ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging



FIGURE 3: Follow-up imaging, including MRI and MRA, after four weeks to determine the extent of resolution

(A) The ADC sequence shows complete resolution of the previously seen hippocampal lesions bilaterally, with no residual signal abnormality or volume loss. (B) Axial and (C) frontal views of MRA of the circle of Willis and posterior circulation show normal appearances with no stenosis or occlusion of the posterior cerebral or basilar arteries.

ADC, apparent diffusion coefficient; MRA, magnetic resonance angiography

He was reviewed in the TIA clinic. The diagnosis of TGA in this patient is based on the combination of clinical and imaging features rather than any single finding. Clinically, the episode was witnessed, consisted of isolated anterograde amnesia with repetitive questioning and loss of recent memories, with preserved identity and no other cognitive or focal neurological deficits, and resolved completely after approximately four hours, thereby meeting the Hodges and Warlow criteria [6]. Radiologically, the lesions were small, punctate, with restricted diffusion appearing several hours after the onset and resolving completely on

follow-up imaging, without involvement of other posterior circulation territories. As no interval imaging was performed, the exact time to radiological resolution is unknown. Each of these features is characteristic of TGA but not specific to it. His medication, aspirin 75 mg once a day, was changed to clopidogrel 75 mg once a day, in line with national stroke guidance recommending clopidogrel over aspirin for long-term prevention against vascular events [9]. In addition, his lipid profile was reviewed, which was normal; however, the clinical decision to give atorvastatin 20 mg once a day was made after a thorough discussion with the patient in view of significant risk factors, comorbidities and the associated risk of hyperlipidemia with cerebrovascular accidents. Both medications were prescribed as lifelong vascular risk reduction, as hippocampal ischaemia could not be excluded at presentation, and not as treatment for TGA.

Discussion

TGA is a neurological syndrome characterised by the sudden onset of reversible and temporary disruption in the functions of the hippocampus. Epidemiological data estimated that TGA commonly affects those in the seventh decade of life, with a recent review estimating the range to be between 61 and 67.3 years [10].

Although the definitive aetiology behind TGA has not been identified yet, several risk factors are mentioned in the literature. Quientte et al. noted that 90% of the TGA episodes are caused by psychological or physical triggers. Cases have been recorded in which triggers such as emotional stress due to birth and death announcements and difficult workdays [11,12]. The pathophysiology of TGA remains a mystery, with several hypotheses being made. Suggestions include deficits involving arterial compromise, abnormal venous flow, migraine association and psychogenic factors. The existence of shared similarities between TGA and TIA led to assumptions that both conditions are caused by hypoxia. However, recent evidence argues against this, as TIA lasts less than 60 minutes, with the majority of TIAs lasting several minutes, while TGA lasts between 4 and 8 hours and a duration of less than 1 hour is not common [10,11,13]. Additionally, the absence of motor or speech weakness and further neurological signs fails to link the association between the two conditions. It has also been hypothesised that deficits in venous drainage, described as incompetence in the internal jugular vein valves, trigger retrograde cerebral venous congestion/hypertension [14]. This was disputed with a recent study showing low rates of retrograde venous flow in time-of-flight magnetic resonance angiography (MRA) to observe the abnormalities in jugular venous reflux within TGA patients and the control group [15]. Numerous studies suggest a link between migraine and the risk of developing TGA, due to the similar pathophysiological grounds. Migraines are characterised by glutamate-mediated transient depolarisation in neuronal and glial cells, leading to suppression of neuronal activity. This is similarly suggested in TGA, as the hippocampus is considered a vulnerable area for various stressors; stressful events can lead to the destabilisation of the CA1 sector of the hippocampus [16]. The fact that patients do not typically show symptoms suggestive of an acute migraine attack or the presence of aura argues against this link. In addition, the final mechanism, where catecholamines are released due to stress or physical effort like sexual activity and exposure to different temperatures (i.e., hot baths, cold showers), was noted in several cases [14]. This results in the temporary inhibition of memory formation in the hippocampus. Our patient had no history of migraine or aura, and his episode lasted about four hours with isolated amnesia and no focal deficit, which is longer than a typical TIA and less in keeping with an ischaemic mechanism. He experienced significant emotional stress beforehand (buying a new house and his son's marriage), making a stress-related mechanism the most plausible explanation, although the cause in an individual case cannot be established.

While the diagnosis of TGA is clinical, Hodges and Warlow established the criteria for diagnosing TGA in 1990, which is still followed to this day. It suggested several conditions, including (i) witnessed episodes by an observer, (ii) characterised by anterograde amnesia, (iii) there must be no clouding of consciousness or loss of identity, (iv) absence of focal neurological signs or symptoms before, during or after the attack, (v) absence of epileptic features, (vi) resolution of symptoms within 24 hours, and (vii) no recent head injury or underlying epilepsy [15]. Investigations for TGA include CT head to exclude initial abnormalities, which is typically normal in TGA cases [6]. Patients should undergo MRI brain, which will show a typical appearance of small punctate lesions (1 to 5 mm) in the lateral hippocampal regions in the subacute phase, approximately between 48 and 72 hours following TGA symptoms [8,14].

Figure *4* is an example of how lesions associated with TGA can appear; however, in this case, it occurred following a seizure associated with hippocampus injury [16]. Seizure-related amnesia is classically described as transient epileptic amnesia (TEA), a form of temporal lobe epilepsy. It typically presents with recurrent, brief episodes, usually lasting less than an hour, often on waking, sometimes with olfactory hallucinations or automatisms, and is supported by EEG abnormalities or a response to anticonvulsants [1,2]. TGA, in contrast, is usually a single episode lasting several hours [1]. Imaging does not reliably separate the two. Yokosaki et al. reported bilateral punctate CA1 hippocampal hyperintensities on DWI, the lesion typically associated with TGA, after epileptic seizures in a patient without any TGA-like episode [17], showing that these lesions are not specific to TGA and can follow seizure activity, although this is a single case. In our patient, the single prolonged episode with no recurrence and no automatisms favoured TGA. However, given the witnessed staring with reduced awareness and the absence of EEG, a seizure cannot be completely excluded. These MRI appearances can last for up to 7 to 10 days, therefore making a follow-up MRI almost mandatory. The differentiation between TGA and ischaemic events to the hippocampus area remains a challenge, as both can affect the same areas. However, ischaemic events have no typical characteristics, in

addition to their ability to involve large PCA territories, such as the occipital lobe, thalamus and corpus callosum [7,8]. Moreover, lesions related to TGA can appear late, often 12-72 hours following the onset, so an early MRI can be false negative in these cases [18]. This is perhaps related to the unknown mechanism of TGA. In comparison, ischaemic events are always visible on DWI sequences. In the long term, TGA does not leave residual evidence on the MRI, and the patient fully recovers, as in our patient. However, in ischaemic events, gliosis and volume loss will be apparent on T2 and fluid-attenuated inversion recovery (FLAIR) sequences corresponding with residual deficits in the patient, which was not the case. Vascular imaging can also contribute to accurate diagnosis sometimes, as MRA is normal is TGA, while it may show PCA or basilar stenosis or occlusion, although not always [12]. Given the risk factors that our patient possessed (positive family history of ischaemic events, diabetes and hypertension, MRA was performed for early detection of any underlying stenosis. The reason why distinguishing between the two is crucial lies in the importance of preventing further events. It is still ambiguous whether starting antiplatelet therapy may play a role in preventing the further recurrence of TGA, as the prognosis of TGA is benign and self-limiting, and the overall recurrence rate is estimated to be between 3% and 24%, with several studies denying the increased risk of future cerebrovascular events [18]. In our case, our patient was started on lifelong antiplatelet (aspirin, later changed to clopidogrel) as a secondary prevention method due to his pre-existing underlying risk factors of cerebrovascular illnesses. No specific treatment or driving restrictions are mandated for TGA patients, with outpatient follow-up as the mainstay of treatment if clinically indicated.

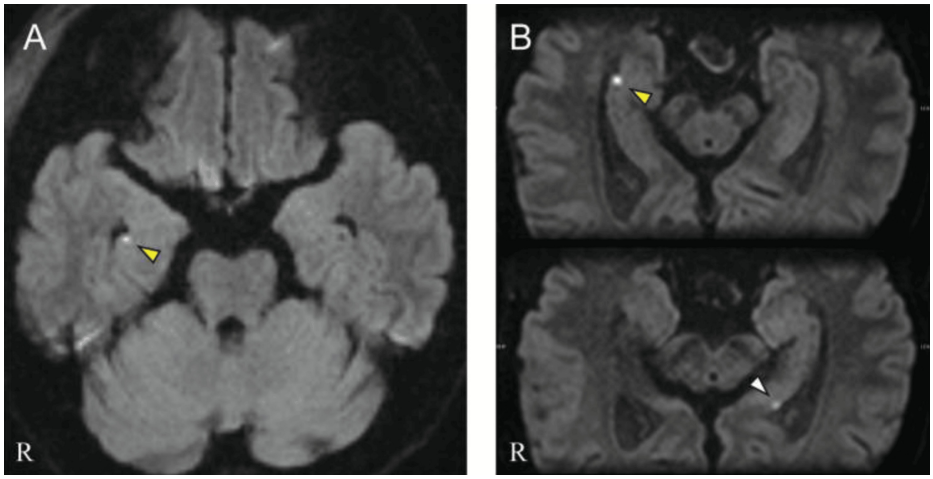


FIGURE 4: The appearance of punctate lesions on MRI

An appearance of punctate hippocampal diffusion abnormalities following epileptic seizures on the second day of hospitalisation of a reported case (A), in addition to the third day (B). Both lesions are located in the CA1 regions. This is similar to the appearance on TGA, illustrating that such lesions are not specific to TGA and that seizures and ischaemia should be considered in the differential.

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Conclusions

Bilateral hippocampal diffusion restriction in a patient with acute amnesia poses a diagnostic challenge, as similar lesions can occur in TGA, hippocampal infarction and after seizures. In this patient, the typical clinical course, complete recovery within approximately four hours and resolution of the lesions on follow-up favoured TGA. However, resolution of diffusion abnormalities and normal vascular imaging are supportive rather than definitive, and the absence of an EEG means epileptic causes could not be fully excluded.

This case highlights the importance of careful clinical assessment alongside radiological interpretation that considers lesion pattern, timing and follow-up findings. Accurate differentiation matters because management and secondary prevention differ, particularly in patients with vascular risk factors. This report has the inherent limitations of a single case. It cannot establish the incidence, prognosis, or optimal management of hippocampal diffusion restriction in TGA, and our observations may not be generalisable. An EEG was not performed because it was not available at our hospital and would have required arrangement at another hospital. An epileptic cause therefore cannot be excluded with certainty, and the absence of EEG is a limitation of this report. Larger series would be needed to clarify the clinical and imaging features that reliably distinguish TGA from hippocampal infarction.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Ruaa Ibrahim, Yaw Affum Duodu

Acquisition, analysis, or interpretation of data: Ruaa Ibrahim

Drafting of the manuscript: Ruaa Ibrahim

Critical review of the manuscript for important intellectual content: Ruaa Ibrahim, Yaw Affum Duodu

Supervision: Yaw Affum Duodu

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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