Case Report

Recurrent Transient Global Amnesia: Pathogenic Insights From Chronobiology?

Andrew J. Larner *

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Recurrent Transient Global Amnesia: Pathogenic Insights from Chronobiology?

Andrew J. Larner

Consultant Neurologist, Cognitive Function Clinic, Walton Centre for Neurology and Neurosurgery, Liverpool L9 7LJ, United Kingdom; andrew.larner2@nhs.net

Abstract: The pathogenesis of transient global amnesia (TGA), a dramatic but self-limiting episode of anterograde amnesia with a variable duration of retrograde amnesia, remains unknown. Although most episodes are single, TGA has a finite recurrence rate. Studies of case series and large patient cohorts have typically been used to investigate possible precipitating and predisposing factors for TGA. Study of recurrent TGA episodes in single cases might provide another way to address pathogenetic factors. A patient with recurrent TGA is presented to illustrate such considerations with respect to possible chronobiological factors in TGA pathogenesis.

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Introduction

The acute onset of amnesia has a potentially broad differential diagnosis,[1] but one of the most common causes of acute isolated amnesia with preserved level of consciousness and other cognitive functions (attention, language, perception) is transient global amnesia (TGA). This dramatic syndrome is characterised by a temporary, self-limiting (< 24 hours) episode of anterograde amnesia with a variable duration of retrograde amnesia.[2]

The pathogenesis of TGA is currently unknown. Standard suggestions include some type of cerebrovascular (arterial or venous), epileptic or migrainous event. The neurobiological phenomenon of spreading depolarisation (previously known as cortical spreading depression) may provide a possible unifying mechanism.

The collection of case series or larger cohorts of TGA patients has permitted the identification of certain predisposing factors (e.g. personal history of migraine) and precipitating factors (e.g. exercise, emotional upheaval, water exposure) for TGA.[3]

Such cohort studies have also addressed the chronobiology of TGA. Whilst some authors have concluded that seasonal factors might contribute to TGA pathogenesis, with peaks of incidence occurring in winter and in spring,[4] more recent data from two large TGA patient cohorts (n = 404 and 261 respectively) and found no variation of occurrence by day of the week, month, or season of the year, in contrast to a robust circadian rhythm of incidence (mid-morning, late afternoon).[5]

Although most instances of TGA are single or unique, recurrence is well described, Although the possible differential diagnosis of transient epileptic amnesia, TEA, should always be considered in patients with recurrent amnesic events,[6] there is evidence of an annual recurrence rate of TGA of around 3-6%. The purpose of this communication is to suggest that analysis of single patient cases with recurrent TGA episodes may provide another way, distinct from large patient cohorts consisting of mostly single episode TGA cases, to look at predisposing and precipitating factors, in a manner perhaps akin to the use of detailed single case studies in neuropsychology to tease out understanding of cognitive structure. As an illustration of the possible utility of this approach to analyse chronobiological factors, a patient with three TGA episodes is presented.

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The patient suffered three episodes of TGA over a period of 6.5 years during her seventh decade (mid to late sixties). She was generally in good health; her only regular medications were for hypertension, hypercholesterolaemia and thyroid replacement. She had a past history of migraine, no longer active, but no history of mood disorder. Other family members had migraine (sibling, niece) but there was no family history of TGA.[7]

The first amnesic episode (July 2016) occurred one morning when, after a shower, she appeared distressed and was repeatedly asking the same questions in a circular fashion. Her husband noted that she knew who she was but was mentally agitated and sometimes tearful. Fearing a stroke, he took her to the local hospital where acute CT brain imaging was normal. The event resolved after around 6 hours with no evident sequela. No further medical consultation or investigation was pursued at this time.

The second episode occurred around 18 months later (January 2018) whilst on holiday in the Southern hemisphere with other family members. After returning one evening from a day relaxing on the beach, she had a shower and was then observed by her husband to be asking repeated, circular questions, although on this occasion this lasted only for about 1 hour. During this period, it was evident that she had forgotten who was on holiday with them, indicating a period of retrograde amnesia. No medical assistance was sought acutely, but on return to the UK she saw a neurologist who undertook MR brain imaging which was normal. Subsequent brief cognitive screening was normal (Mini-Addenbrooke's Cognitive Examination score 29/30).

The third episode occurred 5 years later (January 2023). Pursuing household chores one morning, she became repetitive and distressed, and had forgotten a message she had previously sent to a relative a few days earlier. Her husband recognised the episode as essentially identical to the previous ones, although on this occasion it only lasted about 30 minutes.

Discussion

All three episodes reported by this patient fulfilled the widely used clinical diagnostic criteria for TGA.[8] Acute MR brain imaging, which might have shown typical changes in the hippocampal CA1 region supportive of the clinical diagnosis,[9] was not performed. The first two episodes followed showers, recognised to be a sufficient but not a necessary precipitating factor (water exposure) for TGA. There was nothing in the history to suggest TEA, an important differential diagnosis of recurrent episodes of acute amnesia, in which there are typically repeated brief (< 1 hour) attacks, particularly on awakening, sometimes associated with automatisms.[6] As quantitative EEG was not undertaken, the recently described EPIlepsy AMNEsia (EPIAMNE) score to differentiate TGA and TEA could not be applied.[10]

Considering the chronobiological features in this patient's three TGA episodes, as regards diurnal variation one event occurred in the morning and two in the evening. As regards seasonal variation, two events occurred in January, one in July, but since one of the January events occurred in the Southern hemisphere two events occurred in summer months and only one in the winter. Hence, no consistent pattern emerges regarding the chronobiology of TGA episodes in this patient. The variation in occurrence of recurrent TGA episodes by time of day, month, or season of the year, suggests chronobiological factors are unlikely to have been pertinent to pathogenesis in this patient.

A recent systematic review examining factors associated with recurrent TGA found suggestive evidence in favour of a personal or family history of migraine (as in this patient and other family members) and a personal history of depression, but chronobiological factors were not specifically examined in this review.[11]

Using the suggested methodology of serial examination of single recurrent TGA cases, as opposed to the more usual cross-sectional examination of multiple single event cases, allows each patient to act as their own control for potentially confounding factors such as genetic make-up and family history. Hence this is a methodology that might be used to examine predisposing and precipitating events in TGA, supposing that single event and recurrent TGA are coterminous disorders (only tentative evidence to contradict this supposition is available).

Clearly further individual case studies of recurrent TGA, ideally those with multiple episodes, should be investigated to add to the evidence base regarding any possible pathogenetic role of chronobiological factors in TGA.

Informed Consent Statement: Written informed consent was obtained from the patient for publication of this case report.

Data Availability Statement: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest: The author declares no conflict of interest relevant to this paper.

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