Factors determining recurrence in transient global amnesia

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Abstract

Aetiology of transient global amnesia (TGA) remains uncertain, though many have been proposed, including ischaemic, migrainous or epileptic pathologies. We attempted to determine risk factors for TGA, as well as prognostic factors that may cause recurrence. We evaluated clinical history, family history and magnetic resonance diffusion-weighted imaging (DWI) studies of 93 prospective patients with TGA. Patients were followed up regarding recurrence and prognostic factors. Fifteen of 93 (16%) patients experienced a recurrence of TGA. Among precipitating events, physical activities inducing Valsalva-like manoeuvres were most common, followed by emotional stress. Eighty-four patients had possible comorbidities or risk factor for TGA, though no single risk factor was ubiquitous. Risk factors associated with recurrence were head injury (isolated vs. recurrent, 16.7% vs. 53.5%, p < 0.01), depression (isolated vs. recurrent, 15.4% vs 46.7%, p = 0.01) and family history of dementia (isolated vs. recurrent, 20.5% vs 46.7%, p = 0.03). Of 15 patients with confirmed recurrent TGA, two developed dementia and four subjective memory impairment. DWI lesions were observed in 24 patients and located anywhere within the hippocampus. DWI lesions were not significantly associated with outcomes (recurrence, subjective memory impairment, dementia). Findings suggest TGA is a heterogeneous syndrome. Among those with recurrence, depression, previous head injury and family history of dementia may be predictive factors. Encouraging primary prevention of head injury, managing depression and assisting in development of adequate coping mechanisms may decrease incidence. Education of healthcare works will also increase diagnostic rates, allowing for improved education and comfort for patients and families.

Introduction

Transient global amnesia (TGA) presents as sudden onset anterograde amnesia, with some
features of retrograde amnesia, without residual cognitive impairment, of duration < 24 hours. Typically, it occurs in individuals aged 50 to 80 years, with decreased incidence in younger and older populations.[1,2] Meta-analysis has found no predominance for either gender.[1] The estimated minimum annual incidence of TGA is 3.4 per 100,000, though this is likely to be much higher as some people will not present to the hospital and others will be misdiagnosed.[3] While TGA occurs as a single event for many, estimates of recurrence have ranged from 2.9% to 26.3%, but some studies were retrospective.[4-8] Imaging investigations are used to support the clinical diagnosis of TGA. DWI on MRI provides specific, consistent findings of 1-5 mm focal lesion in the hippocampal CA-1 sector, which resolve 7-10 days after onset of TGA, with no long-term structural changes. [1,9,10] It is hypothesized that, as these neurons are in locations vital for memory consolidation, small lesions may significantly impair memory function,[10] though any effects on prognosis are unknown. For instance, memory and executive function impairment may objectively last up to five days post-TGA onset, despite patients subjectively reporting normal memory.[9,11] Other patients might develop long-lasting memory problems, especially those with recurrence.[12,13] Multiple mechanisms have been proposed for the aetiology of TGA. One hypothesis is that retrograde venous flow leads to venous congestion, possibly due to increased thoracic pressure or jugular valve incompetence, which in turn causes a transient ischemia due to hypoperfusion.[1,3,14-18] Support for this comes from the observation that many TGA cases are precipitated by Valsalva-like activities, particularly physical or emotional stressors, which would temporarily cause thoracic-pressure elevation.[1,3,14-16] Ischaemia from thromboembolism constitutes a contrasting hypothesis on pathogenesis. [13,19] Some studies have found TGA patients to have a higher vascular risk factors and greater frequency of carotid atherosclerosis, suggesting a Atherosclerotic embolic event.
as a cause.[4,20] One final hypothesis is that TGA is a type of migrainous aura, occurring due to cortical spreading depression, leading to cellular metabolic stress in vulnerable CA-1 sector neurons.[9,18,21-24] Genetics may also contribute to susceptibility, based on observations from limited case studies.[15,25-27]

Risk factors that might predispose to TGA recurrence are speculative. In those with recurrence, the presence of multiple risk factors may increase susceptibility. These include continued physical and emotional stressors, arterial hypertension and jugular vein incompetence.[1,2,4,6]

To date, TGA research has focused largely on aetiology and pathophysiology, yet our understanding remains incomplete. Few studies have focused on management, prognosis or clinical improvements that can be made to assist healthcare staff in identifying TGA patients more accurately. By identifying patients with recurrence of TGA and comparing them with patients who only experienced a single episode, this study aimed to establish possible risk factors for TGA and its recurrence, so that these patients can recognized and educated on first presentation, with the goal of improving prognostic outcomes and minimizing recurrence.

Materials And Methods

Subjects

Between 2004 and mid-2016, 107 patients presenting with acute memory dysfunction to Joondalup Health Campus Emergency Department (ED) or a neurology outpatient clinic were prospectively screened and recruited into the study. The supervising neurologist was responsible for making the clinical diagnosis, based on previously published definitions of TGA.[2] Ethics approval was obtained from the Human Research Ethics Committee at Joondalup Health Campus, endorsed by Ramsay Corporate Services JHC-HREC No. 2011/1018. All methods were performed in accordance with the relevant guidelines and
regulations of the JHC-HREC.

**Initial assessment**

All patients provided written informed consent to participate in this research. They were interviewed, and the following information was collected: demographic data; details of the episode (duration, symptoms, prior activity); past medical history; family history; and smoking history. A series of investigations were performed after each episode, including MRI with DWI. Consent was obtained from each participant to store results in a secure database. Additional information was obtained from the patients’ ED admission, in instances when they had presented to the hospital.

**Follow-up**

In July 2015, the follow-up period commenced. Patients were contacted by telephone to check if there had been any recurrence of an acute amnestic state, to collect any information not gathered from their files and to determine if they had experienced any deterioration in memory. Numbers achieved in follow-up are shown in Figure 1.

**Statistical analysis**

In comparing data groups, descriptive analyses, namely chi-square or Fisher’s exact test with hypergeometric distribution, were used to test the distribution of a factor. Statistical significance was determined at $p < 0.05$.

**Results**

**History of presentation**

**Total study population**

In a cohort of 102 patients presenting with a transient amnestic state, 93 had experienced one or more episodes of TGA. Mean age of TGA onset was 59.5 (SD 10.3, range 17-78) years, among 49 men and 44 women. In total, these 93 people experienced 117 episodes of clinically diagnosed TGA and 18 recurrent episodes of amnesia, not otherwise specified.
Mean duration of TGA was 6.0 (SD 7.8) hours.

In 85 (73%) of episodes, there was an identifiable precipitating event, including: stress (36%); exercise (18%); housework (17%); feeling unwell, often with associated with nausea or vomiting (16%); sexual intercourse (8%); hot shower (6%), coughing episode (5%); swimming in cold water (3%); and exposure to chemicals such as fresh paint (2%). Headaches were present either just prior to or during 21% of episodes.

Of the clinical features, repetitive questioning (88%) and disorientation to the day’s events (81%) were most commonly reported. Patients also displayed disorientation to place (54%), day (30%), time (28%), date (26%), and confusion (47%). Anxiety was less commonly reported (3%). No abnormal neurological signs were elicited during the episodes.

When compared as percentage prevalence values, a number of vascular and other risk factors were higher among the TGA cohort than the general population, as described by Australian Bureau of Statistic’s data.[30] These included hypertension, type 1 and 2 diabetes mellitus, dyslipidaemia, transient ischaemic attack, stroke, ischaemic heart disease, depression, anxiety and migraine (Fig. 2a).

In total, three patients were later diagnosed with dementia of the Alzheimer’s type, based on the clinical syndrome functional decline and neuropsychology, and 24 had subjective memory deficits, proven on neuropsychometric testing.

Recurrent episodes

Among the 15 patients with recurrent TGA, there were 39 episodes in total. The demographics of this group, and the duration of their TGA episodes, were similar to those with solitary TGA (Table 1). Stress (marital status, financial status, relationship, children, work, or a combination) was also the most common precipitating element among those with recurrence. Headache was less frequently noted, with less than a third frequency
compared to the isolated event group (isolated vs. recurrent, 27% vs 8%).

Regarding clinical features, repetitive questioning, disorientation to place and anxiety were more common in the recurrent group, though anxiety remained the least common episode characteristic.

A history of depression and previous head injury were significantly higher in the multiple-TGA group, compared to the single episode group (Fig. 2b). A family history of dementia had an increased association with recurrence of TGA (Table 2). No such associations were found for family history of cardiovascular disease or TGA.

Of the 15 with recurrent TGA, two were later diagnosed with dementia of the Alzheimer type and four reported subjective memory deficits – confirmed on neuropsychology.

**Investigations**

**Total study population**

MRI studies were performed 137 times, with patients receiving multiple investigations after an episode. 24 of 93 patients had DWI spots, 50% of whom had a positive smoking history (p=0.08) and 42% had hypertension (p=0.05). 25 of 26 positive DWIs were taken within one week of the episode (p<0.0001). In 21 scans, a single spot was seen; two spots in four scans; and three spots in two scans. Average size of spots was 3.5±1.6mm (mean ± standard deviation). All were in the hippocampus, though the specific location varied anywhere from the hippocampal head to tail; 12 were left-sided, 24 were right-sided. DWI spots had no greater frequency in patients who went on to develop recurrence, dementia or subjective memory problems (Table 3).

**Recurrent episodes**

One patient had recurrence of lesions on DWI with their second episode.

**Discussion**

**Risk factors**
Between recurrent and non-recurrent populations, age and gender did not differ significantly. Our findings for the events precipitating TGA were consistent with previous research.[1-4,14.25] Seventy-three per cent of TGA episodes were precipitated by an identifiable event, most commonly an emotional or physical stressor. Of the physical stressors, those that have previously been described as Valsalva-like manoeuvres, including coughing, vomiting, immersion in cold or hot water, and sexual intercourse did all occur in some patients. Of the emotional stressors, some occurred immediately prior to the episode, for instance, people watching a sporting grand final. Others were longer-term psychological stressors, present weeks or months prior to the episode, including home, family and workplace conflicts. With regards to these longer-term stressors, it has been suggested these increase susceptibility to TGA and its recurrence.[1,28] Among our recurrent patient, stress, as a precipitating factor, had a greater frequency but this finding was not statistically significant. With regards to possible risk factors, a history of depression was significantly increased among those with recurrence. Previous head injury was significantly increased in those with recurrence. Many cases were of mild head injuries, defined as losing consciousness for less than 30 minutes or feeling dazed without loss of consciousness, and in the absence of focal neurological deficits.[29] Sequelae of mild head injuries included migraine with or without aura. However, migraine itself was not found to be more prevalent among the recurrent group. Migraine, through cortical spreading depression, is a proposed mechanism for the pathogenesis of TGA, as it seems to occur at higher frequencies in TGA patients compared to age-matched controls.[3] TGA may occur during migraine.[15,21,24,27] While the design of our study did not include controls, 35.5% of our cohort had history of migraine, and headache was associated with 21% of episodes. This differs greatly from the 6% general population estimate for migraine.[30] Nevertheless, as history of migraine was
recorded in less than half of patients, it is unlikely an exclusive cause, even if it plays a role in the aetiology of TGA.

While other cardiovascular risk factors were present in the cohort, none were significantly associated with recurrence or a single episode. There was no control group in our study, but prevalence values from the Australian Bureau of Statistics’ for hypertension, type 1 and 2 diabetes mellitus, dyslipidaemia, transient ischaemic attack, stroke and ischaemic heart disease were all smaller than that found in our cohort, which suggests these are not risk factors for the development of TGA.[30] Earlier studies have found increased rates of these risk factors in TGA patients compared to controls,[5,31] others have not.[2,6] Recurrent patients have been observed to have increased incidence of atheroma and ischaemic heart disease, which may contribute to hippocampal vulnerability to an ischaemic insight.[4,20]

**Family history**

Incidence of TGA is low, so in cases where multiple family members are affected, it raises questions of whether there is a direct or indirect genetic component. Within our cohort, family history of TGA existed for five patients through a first degree relative, one patient through a cousin, and another patient through two first degree relatives and a cousin. This patient also had recurrent TGA; the other six had a single episode. The small sample size of patients with family history of TGA meant statistical analysis was not possible. Family history of dementia was found to be significantly associated with recurrence of TGA (Table 2). It is established that family history of dementia increases the risk of developing dementia among *APOE* ε4 carriers.[32] However, whether this or another genetic factor plays a role in TGA is yet to be determined.

**Recurrence**

Within our patient population, 26 of 93 (28%) had a second episode of amnesia, though in
only 15 of 93 (16%) was the documentation strong enough to conclusively support that the patient had two or more episodes of TGA within the study’s duration. The reason for this discrepancy is that, while patients and their family members could recall another episode of amnesia, few other characteristics were recorded in medical files and by the time they were re-interviewed, they had forgotten many of the details. TGA is a unique condition, in that the patient is rarely able to describe their symptoms, so it is important to take good notes on their cognitive deficits when they present to healthcare professionals. Otherwise a more precise figure for recurrence may never be reached.

**DWI investigations**

Another hypothesis for TGA pathogenesis relates to susceptibility of blood vessels around the CA-1 region of the hippocampus, based on observations of DWI lesions this area.[9,18] Our findings are not consistent with this hypothesis, with the 35 DWI spots observed located throughout the hippocampus, from head to tail.

All but one spot was detected within one week of TGA onset. We were not able to assess the minimum MRI latency for positive lesions, however infarctions on MRI within 24 hours may only have 82% sensitivity, creating a high frequency of false-negatives in this timeframe.[33-35] Repeat MRIs, when performed after one week, showed most lesions had disappeared, in keeping with previous findings. Sensitivity of DWI for acute infarctions after 24 hours ranges from 88-100%, and specificity is 86-100%.[36,37] False-positive causes of DWI lesions are rare, but include such non-ischaemic diagnoses as cerebral abscess, brain tumour, sudden onset isolated vertigo and loss of consciousness with seizure.[36,37]

Factors noted to increase incidence of positive DWIs include a history of smoking and systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 mmHg.[34] In our patient population, 50% and 42% of the patients with positive DWI had a history of smoking or
hypertension, respectively.

Nevertheless, among TGA patients with MRIs performed within 10 days from onset, 41% (25/61) had a visible, hyperintense lesion. False-negative DWIs may explain why some patients do not show areas of hyperintensity.

Posterior circulation infarctions are much likelier to give false-negative DWIs than an anterior circulation infarction.[35] Blood supply to the hippocampus is complicated as it is variable. In most the posterior cerebral artery (PCA), or a branch thereof, supplies the hippocampus. In some there are contributions from the anterior choroidal artery.[38] The anterior hippocampal artery, branching from the PCA, supplies the hippocampal head, whilst the middle and posterior hippocampal arteries supply the hippocampal body and tail, and have numerous anastomoses.[39] Therefore small infarctions in the body or tail of the hippocampus might not show DWI positivity because of these anastomoses.

It is also possible that, whatever the cause of TGA, it might not show a positive DWI.

Outcomes

Three patients from our TGA cohort later went on to develop dementia. One was a non-recurrent patient, who had an MRI performed outside of 10 days that was normal initially and later showed atrophy. The second patient had three episodes of TGA over 15 years, with normal MRIs, though all were performed outside of the 10-day window. The other patient had two episodes of TGA over 10 years, with hyperintense hippocampal lesions detected on DWI performed within one week, and atrophy appearing less than two months after the second episode.

Of the 24 patients with subjective memory impairment, only one showed signs of atrophy on imaging two months post-TGA. However, five other TGA patients, not reporting memory changes, had noticeable cortical atrophy on MRI, ranging in age from 59-78; two of the five had recurrent TGA and had scans performed 1 day to 2 months post-TGA.
Previous studies have suggested recurrence might be associated with longer-term changes to memory, ranging from verbal and non-verbal memory impairment to dementia.[12,13] We were unable to confirm this. Nevertheless, it is a concerning prospect if TGA is not benign, but rather a risk factor or early warning sign for dementia. It is also possible that, among the group of people who reported subjective memory impairment, anxiety from the experience of TGA may leave patients doubting their short-term memory capabilities.

In conclusion, our results suggest TGA is a heterogeneous syndrome, characterized by variable features in different patients. In our experience, depression and a history of previous head injury predicted recurrence. It is possible that encouraging primary prevention of head injury through education, managing depression and assisting patients in developing adequate coping mechanisms for stressors may decrease TGA and its recurrence.

Declarations

**Conflict of Interest**

On behalf of all authors, the corresponding author states that there is no conflict of interest.

**Author Contribution**

RT collected, collated and analysed the data, and drafted the manuscript.

PKP collected, collated and analysed the data; helped in drafting the manuscript and revised it.

**Declaration**

All supporting data is stored electronically and is password protected.

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Tables
Table 1. Patient demographics, history of presenting complaint and past medical history for patient with a
single episode of TGA compared to recurrent attacks.

|                                | Isolated episode | Recurrent episodes |
|--------------------------------|------------------|--------------------|
| Patient number                 | 78               | 15                 |
| Age of Onset (mean)            | 59.56            | 59.47              |
| Age of Onset (median)          | 61               | 62                 |
| Age of Onset (Std Dev)         | 10.83            | 7.34               |
| Minimum - Maximum Age          | 17 - 78          | 40 - 73            |
| Gender (M)                     | 42 53.85%        | 7 46.67%           |

| Episode characteristics       | No.  | %    | No.  | %    |
|--------------------------------|------|------|------|------|
| Length of episode (hours +/-  Std Dev) | 6.14 ± 8.66 | 5.64 ± 5.66 |
| Repetitive Question            | 66   | 84.62| 37   | 94.87|
| Disoriented date               | 24   | 30.77| 6    | 15.38|
| Disoriented day                | 26   | 33.33| 9    | 23.08|
| Disoriented time               | 27   | 34.62| 6    | 15.38|
| Disoriented place              | 41   | 52.56| 22   | 56.41|
| Disoriented day's events       | 70   | 89.74| 25   | 64.10|
| Confusion                      | 40   | 51.28| 15   | 38.46|
| Anxiety                        | 1    | 1.28 | 3    | 7.69 |
| Headache                       | 21   | 26.92| 3    | 7.69 |
| Feeling unwell                 | 13   | 16.67| 6    | 15.38|
| Stress                         | 24   | 30.77| 17   | 43.59|
| Swimming                       | 0    | 0    | 3    | 7.69 |
| Hot shower                     | 7    | 8.97 | 0    | 0    |
| Coughing fit                   | 2    | 2.56 | 3    | 7.69 |
| Sexual intercourse             | 8    | 10.26| 1    | 2.56 |
| Housework /gardening           | 15   | 19.23| 5    | 12.82|
| Gym / Exercise                 | 14   | 17.95| 5    | 12.82|
| Chemicals                      | 4    | 5.13 | 0    | 0    |
Table 2. Family history in patients with TGA

|                    | TGA once only | Multiple TGA | p value |
|--------------------|---------------|--------------|---------|
|                    | No.           | %            | No.     | %     |
| Family history     |               |              |         |       |
| TGA                |               |              |         |       |
| No                 | 72            | 92.3         | 14      | 93.3  |
| Yes                | 6             | 7.7          | 1       | 6.7   | p=0.41 |
| Family history     |               |              |         |       |
| dementia           |               |              |         |       |
| No                 | 62            | 79.5         | 8       | 53.3  |
| Yes                | 16            | 20.5         | 7       | 46.7  | p=0.03 |

The p value was calculated with hypergeometric distribution of Fisher’s exact test.

Table 3 MRI results within 15 days of symptom onset, compared with outcomes in TGA patients.

|                          | Normal MRI | Any DWI Spots | Small vessel ischaemic change |
|--------------------------|------------|---------------|------------------------------|
| Single Event (n = 42)    | 14 [33%]   | 19 [45%]      | 22 [52%]                     |
| Recurrent episodes (n = 15) | 5 [33%] | 5 [33%]      | 6 [40%]                      |
| Memory Problems (n = 16) | 6 [38%]   | 5 [31%]       | 3 [19%]                      |
| Dementia (n = 2)         | 1 [50%]    | 1 [50%]       | 1 [50%]                      |

White matter hyperintensities; compatible small vessel; ischaemic change

Figures
Patients presenting with acute amnestic events  
\[ n = 107 \]

- File not located  
  \[ n = 5 \]

- TGA diagnosis  
  \[ n = 93 \]
  - Non-TGA diagnoses  
    \[ n = 9 \]
    - Follow up consent withdrawn  
      \[ n = 2 \]
    - Died  
      \[ n = 5 \]
    - Follow up unsuccessful  
      \[ n = 13 \]

Follow up  
\[ n = 73 \]

Figure 1
Patient recruitment.
Figure 2

Frequencies (%) of comorbidities: (a) in patients compared to the general population (Australian Bureau of Statistics [30]); and (b) in patients with recurrent (n=15) versus single-episode transient global amnesia (n=78). p-values were calculated using the hypergeometric distribution of Fisher’s exact test.