Incidence of transient global amnesia in patients hospitalized at the Department of Neurology, UHC Split, in the period from January 1, 2015, to December 31, 2019

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Abstract:

Introduction: The aim of this study was to present the incidence and recurrence of transient global amnesia (TGA) as well as identify potential etiological factors. Materials and Methods: This retrospective study involved 139 patients diagnosed with TGA between January 1, 2015 and December 31, 2019, at the Department of Neurology, University Hospital Center Split. After reviewing protocols and medical history archives, we collected the following patient data: basic demographic characteristics (age and sex), duration of amnesia, circumstances of onset of amnesia, accompanying symptoms, and comorbidities. For statistical analysis, we utilized descriptive statistical methods, the Chi-square ($\chi 2$) test, and the t-test. Results: In total, 39.6% of patients were male, and 60.4% were female. The median age at TGA diagnosis was 65 years. The average annual incidence rate of TGA during the observed period was 6.12/100,000 persons. TGA occurrence was significantly higher in the morning. The median duration of amnesia was 1 hour. The most common symptoms associated with the memory disorder were headache, nausea, and vertigo. In 9.4% of patients, TGA occurred after Valsalva maneuver-associated activities. Depression or anxiety was present in 5.8%, and migraine in 5.04% of patients. The recurrence rate of TGA was 8.6%. Conclusions: The etiology of episodic short-term memory dysfunction may be multifactorial and requires further investigation for clarification.

Keywords: epidemiology, incidence, neurology, transient global amnesia, Croatia

Sažetak

Incidencija privremene amnezije u bolesnika hospitaliziranih u KBC Split od siječnja do prosinca 2019. godine

Uvod: Cilj ovog istraživanja bio je prikazati učestalost i recidiv prolazne globalne amnezije (TGA) te identificirati potencijalne etiološke čimbenike.

Materijali i metode: Ova retrospektivna studija uključila je 139 bolesnika s dijagnozom TGA između 1. siječnja 2015. i 31. prosinca 2019. na Klinici za neurologiju KBC-a Split. Pregledom protokola i arhive povijesti bolesti prikupili smo sljedeće podatke o bolesnicima: osnovne demografske karakteristike (dob i spol), trajanje amnezije, okolnosti nastanka amnezije, popratne simptome i komorbiditete. Za statističku analizu koristili smo deskriptivne statističke metode, Hi-kvadrat ($\chi 2$) test i t-test.

Rezultati: Ukupno je 39,6% pacijenata bilo muškaraca, a 60,4% žena. Prosječna dob pri postavljanju dijagnoze TGA bila je 65 godina. Prosječna godišnja stopa incidencije TGA u promatranom razdoblju bila je 6,12/100.000 osoba. Pojava TGA bila je značajno veća ujutro. Medijan trajanja amnezije bio je

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1 sat. Najčešći simptomi povezani s poremećajem pamćenja bili su glavobolja, mučnina i vrtoglavica. U 9,4% bolesnika TGA se pojavio nakon aktivnosti povezanih s Valsalvinim manevrom. Depresija ili anksioznost bila je prisutna u 5,8%, a migrena u 5,04% bolesnika. Stopa recidiva TGA bila je 8,6%.
Zaključci: Etiologija epizodne disfunkcije kratkotrajnog pamćenja može biti multifaktorska i zahtijeva daljnje istraživanje radi pojašnjenja.

Ključne riječi: epidemiologija, incidencija, neurologija, prolazna globalna amnezija, Hrvatska

Introduction

Transient Global Amnesia (TGA) is a clinical syndrome of unknown cause characterized by the sudden onset of anterograde amnesia, sometimes with retrograde memory loss. The duration of the episode is under 24 hours, with other cognitive functions, as well as neurological tests, remaining normal. The memory disorder resolves spontaneously, with no long-term consequences, and is not associated with other neurological disorders (1). First described over fifty years ago, TGA remains one of the most puzzling syndromes in clinical neurology. Several causative factors have been proposed, such as local ischemia, venous insufficiency, epileptic events, and psychological or physical stress, but the mechanism of TGA onset is still unknown (2). Current data suggest that short-term memory is formed in the hippocampal and entorhinal cortex network and potentially stored as long-term memory in the neocortex (3). Special attention has been given to the *cornu ammonis* (CA1) field of the hippocampus, presumed to play a central role in the pathophysiology of TGA due to its exceptional sensitivity to cellular stress (4,5). Recent diffusion-weighted magnetic resonance imaging (DWI or DW-MRI) studies have identified imaging changes strongly associated with TGA. These hyperintense punctiform lesions in the hippocampal CA1 region are typically unilateral and small (1-3 mm) (4,5-7). TGA syndrome is clinically diagnosed using the criteria created by Hodges and Warlow in 1990 (Table 1) (8). The most prominent clinical feature is the sudden onset of anterograde amnesia. During an episode, patients are disoriented in time and tend to ask repetitive questions. Vegetative symptoms are often associated with the disorder, most commonly headache, nausea, and vomiting (8). Several disorders pose a common differential diagnosis challenge: transient epileptic amnesia, transient ischemic attack, and psychogenic amnesia. Patients normally first seek help from their primary care physicians, who may often be unfamiliar with this rare syndrome, resulting in ill-suited tests and advice. All physicians, including family doctors and non-neurology specialists, should learn about TGA diagnosis to be able to recognize TGA with greater confidence in their everyday practice (9).

Materials and methods

This retrospective descriptive incidence study involved patients with clinical features of TGA admitted to University Hospital Center Split from the beginning of 2015 to the end of 2019. Inclusion criteria were treatment at University Hospital Center Split during the specified timeframe and clear clinical features of TGA. Exclusion criteria were incomplete medical records and incomplete diagnostic processing. Information on basic demographic characteristics (age and sex), duration of amnesia, circumstances of TGA onset, accompanying symptoms, and comorbidities was collected by reviewing protocols and patient history archives. The research was approved by the Ethics Committee of the Clinical Hospital Centre Split and was conducted in accordance with all ethical principles of the seventh revision of the Helsinki Declaration from 2013.

Statistical analysis

The collected data were entered into and analyzed using a Microsoft Excel spreadsheet. Numeric variables were presented as median values and interquartile ranges (IQR). Nominal and ordinal variables were presented as frequencies with a 95% confidence interval, as well as percentages. The $\chi 2$-test was used to analyze TGA incidence by sex and time of day, with a significance criterion set at P-value < 0.05.

Table 1. Diagnostic criteria for transient global amnesia

• Attacks must be witnessed and information available from a capable observer who was present for most of the attack.
• There must be clear-cut anterograde amnesia during the attack.
• Clouding of consciousness and loss of personal identity must be absent, and the cognitive impairment limited to amnesia.
• There should be no accompanying focal neurological symptoms during the attack and no significant neurological signs afterward.
• Epileptic features must be absent.
• Attacks must resolve within 24 hours.
• Patients with recent head injury or active epilepsy (that is, remaining on medication or one seizure in the past two years) are excluded.

Results

In total, 139 patients admitted to University Hospital Center Split were diagnosed with TGA between January 1, 2015, and December 31, 2019. Among them, 55 (39.57%) were male, and 84 (60.43%) were female. The higher proportion of women was statistically significant (χ2-test; P = 0.014). The median age at TGA diagnosis was 65 years (Q1–Q3: 59.5–70; min–max: 41–90). The average annual hospitalization rate for TGA between 2015 and 2019 was 27 patients per year (Figure 1).

The peak incidence of TGA was in 2019 (7.92 per 100,000 people), while 2015 had the lowest incidence (3.30 per 100,000 people). The average annual incidence of TGA during the observed period was 6.12 per 100,000 people (95% CI [4.56–7.68]), or 4.97/100,000 (95% CI [3.60–6.34]) for males and 7.19/100,000 (95% CI [4.60–9.78]) for females.

Among the 98 patients with known onset times, amnesia occurred in the morning for 60 (61.22%) patients, in the afternoon for 22 (22.45%), and in the evening for 16 (16.33%) patients (n = 98). Morning onset was significantly more common (χ2-test; P = 0,000). The episodes ranged from 10 minutes to 10 hours (n = 52), with a median duration of 1 hour (Q1–Q3: 0.5–3; min–max: 0.17–10). Retrograde amnesia occurred in 33 patients (23.74%), most frequently with memory loss from the beginning of the previous day. The shortest extent was a few hours before TGA onset, with isolated cases covering the period from one month to about ten years.

Headache was the most common associated symptom (17.27%), followed by nausea (10.07%), vertigo (3.6%), and vomiting (2.16%). Other symptoms occurred only in single cases.

Imaging (MR/CT of the brain) was performed on 126 patients, all with normal findings. EEG was recorded in 88 patients, with 62 (70.45%) having normal results, and the remaining 26 (29.55%) showing nonspecific changes. Angiosonography of the internal carotid arteries was conducted on 114 patients, with only three showing significant changes. Vertebral artery flow data were available for 112 patients, with significant pathology found in only five.

A risk factor analysis of our patients (Figure 2) showed that cardiovascular risk factors were the most prevalent. Seven patients (5.04%) had a history of migraines, four of whom experienced a migraine episode linked with TGA onset. Additionally, 6 (4.32%) patients had other primary headaches in their medical history, with none experiencing a headache at TGA onset. One patient had a history of ice pick headaches and two experienced post-traumatic headaches. Twenty-four patients (17.27%) experienced headaches coinciding with TGA onset, with 18 (12.95%) not having a history of headaches before the episode. Depression or anxiety disorders were reported in 8 (5.76%) patients. Together with 5 (3.60%) patients who experienced emotionally charged situations before memory loss, a total of 13 (9.35%) patients may have had psychogenic TGA.

Various events preceded TGA onset (Figure 3). Coughing, vomiting, defecation, and physical exertion are all activities that simulate the Valsalva maneuver. One patient held their head in a retroflexed position for an extended period during physical activity, while another did so in an anteflexed position. Although we identified emotional stress primarily as a psychogenic etiological factor, its potential pathophysiological mechanism is twofold.

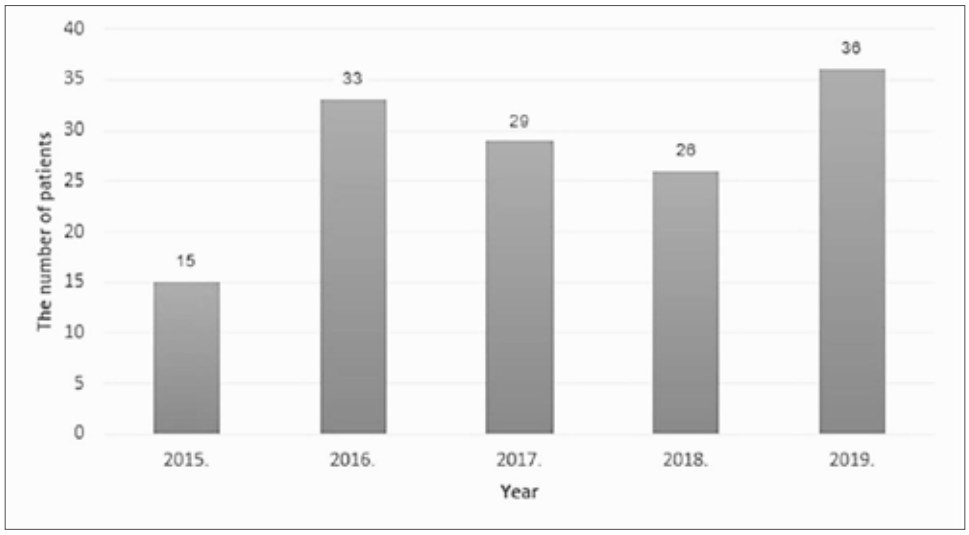

Figure 1. The number of TGA patients treated at the Department of Neurology, University Hospital Centre Split, between January 1, 2015 and December 31, 2019.

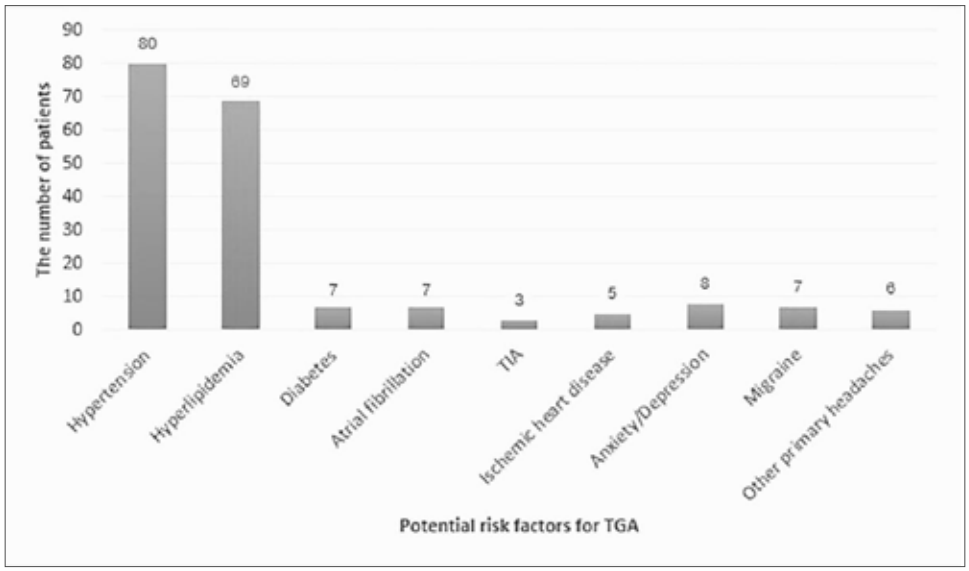

Figure 2. Potential risk factors for TGA in patients treated at the Department of Neurology, University Hospital Centre Split, between January 1, 2015 and December 31, 2019.

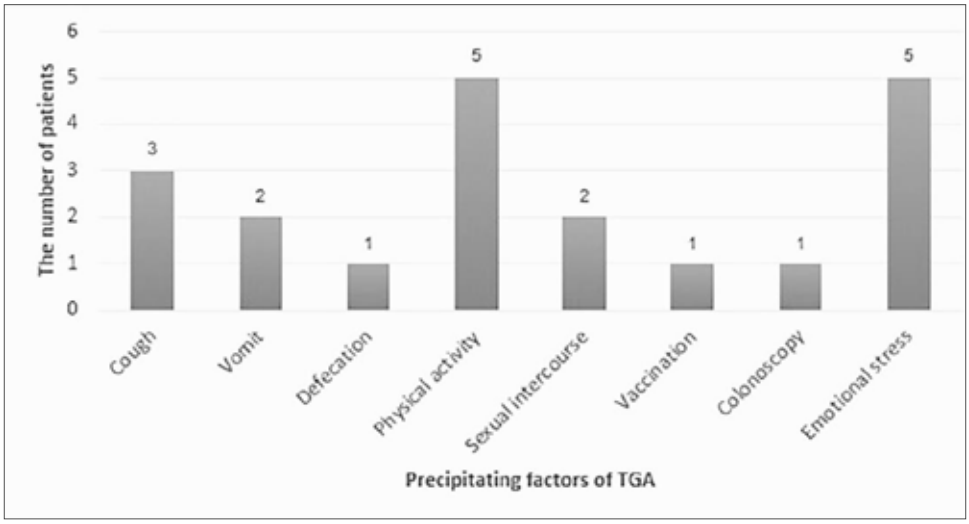

Figure 3. Precipitating factors of TGA in patients treated at the Department of Neurology, University Hospital Centre Split, between January 1, 2015 and December 31, 2019.

Specifically, it is conceivable that emotionally charged events precipitate bodily responses akin to those in the Valsalva maneuver. Of the total patient pool, 12 (8.63%) experienced a recurrent TGA episode, with intervals ranging from one day in one (8.33%) patient to about ten years between episodes in three (25%) patients (n = 12). The median of recurrence was 3 years (Q1–Q3: 1.75–7; min–max: 0.03–10).

Discussion

TGA incidence at University Hospital Centre Split is comparable to figures reported in other studies (3.4 to 10.4/100,000) (10,11). In a study conducted in the province of Belluno in Italy, the incidence by sex was 9.35/100,000 for males and 11.37/100,000 for females (12). The predominance of female patients was even more pronounced in the Finnish city of Turku (16/100,000 compared to 3/100,000 in males); however, a study from Merano found a slightly higher incidence in males (13,14). In our study, women were more likely to experience TGA. This is consistent with the literature, where the ratios of female patients with this diagnosis range between 54 and 67% (15). Data from other studies indicate that TGA most commonly occurs in the seventh decade of life, with the mean age of onset ranging from 61 to 67.3 years, which aligns with our findings (10, 16, 17). In a study by Quinette et al., 96% of TGA patients were between 51 and 80 years old (18). Similarly, 94.3% of patients from Split-Dalmatia County fell within this age bracket. Some epidemiological studies found no cases of TGA in people under 55 (10).

In the study by Quinette et al., TGA also most commonly occurred in the morning and least commonly in the evening. The average duration of a TGA episode was four to eight hours, with 97% of episodes lasting over one hour (18). Other sources reported average durations between one and eight hours (19).

In their 1990 study, Hodges and Warlow identified the most common accompanying symptoms of TGA as headache, nausea, and vomiting, each with a frequency of 10%, while Quinette et al. added dizziness, paresthesia, and chest pain (8, 18). This was also observed in our patients. However, Quinette et al. also listed chills or hot flashes, fear of dying, cold extremities, emotionalism, trembling, and sweating, which we did not observe in our study.

In a Minnesota study, brain CT scans were normal in all patients, while DWI-MR showed typical hippocampal lesions in 4.26% of patients. EEG showed slightly decreased temporal lobe activity in 9.72% of patients (10).

Panton et al. found that as many as 17.6% of TGA patients also suffered from migraines (17). A 2015 retrospective study in France reported that out of 8,821 migraine patients, six experienced a TGA episode during their attack (20). A German study found no evidence of an increased incidence of TGA in migraine patients despite a higher prevalence of both migraine and tension headaches in TGA patients (21). In contrast to our study, a 2014 cohort study conducted in Taiwan found that patients with a history of migraines had an earlier onset of TGA (56.6 years) compared to the control group (61.4 years), and this difference was statistically significant (22). Cardiovascular risk factors were present in similar percentages in our study and in Panton et al. (17). The latter study showed a significantly higher presence of cardiovascular risk factors in control cases with a history of TIA compared to patients with TGA. A 12-year follow-up study, the longest published to date, showed no statistically significant difference in the incidence of any cardiovascular events for TGA patients (10). In a case-control study conducted in Munich in 2000, Valsalva maneuver-associated activities were a trigger of TGA in 10 (48%) patients. The onset of acute pain was the only event that was not recorded in our study but preceded amnesia in two individuals in that study (23). In C.M. Fisher's study, sexual intercourse preceded the onset of TGA more frequently in males than in females (24). We identified one male and one female patient with such medical histories. The male had a recurrent post-coital TGA episode spaced 3 years apart. This contributing factor may often go undocumented due to the reluctance of patients and their families to provide such information.

Numerous studies have shown that TGA patients are more likely to have psychiatric comorbidities. In Panton et al., 39.2% of TGA patients also had a psychiatric illness, compared to 13.7% in the control group with a history of TIA (17). The most comprehensive study to date was conducted in Italy in 1997. Potential phobic personality traits were examined in 51 TGA patients, with 82% exhibiting pathological reactions to fear-inducing situations (25). In Quinette et al., 21.2% of patients had a history of anxiety or depression, and 29% experienced emotional stress before the onset of amnesia (18). Summarizing data from 49 articles, Jeong et al. identified 89 patients with medical procedure-related TGA. They documented various medical procedures, but these did not include colonoscopy or vaccination, as was seen in our TGA patients (26).

Depending on the patient follow-up period, the annual recurrence rate of TGA was between 2.9% and 26.3%. In an Australian study, 16% of patients had a recurrent episode, which was almost double compared to our study. The study authors noted that a significant percentage of patients with recurrent episodes had depressive disorders, a family history of dementia, or head trauma (27).

A primary limitation of this study involves the possibility of an outpatient diagnosis of TGA. Since other studies have shown a higher incidence, the incidence may be slightly higher. There is also the potential for misdiagnosis due to common differential diagnostic dilemmas. Additionally, there may be a lack of awareness regarding this disorder. Another limitation of this study is its retrospective design, which hinges on the quality of medical record keeping. The lack of a control group to compare the prevalence of risk factors is also a drawback. Finally, following an extensive literature review, we may conclude that the results of our study are in line with previous research. Considering the dearth of TGA research in Croatia, our findings could serve as a stepping stone for further analysis of this population, hopefully leading to advancements in this elusive field of medicine.

Acknowledgements

The analysis of TGA incidence at University Hospital Centre Split between January 1, 2015 and December 31, 2019, showed that between 2015 and 2019, the incidence of TGA in Split-Dalmatia County was 6.12/100,000 people, regardless of sex. TGA was more common in women. The median age at diagnosis was 65 years. TGA occurred more frequently in the morning and the median duration was 1 hour. Retrograde amnesia was present in 23.7% of patients, and the recurrence rate was 8.6%. The most common associated symptoms were headache, nausea, and vertigo. The etiology of episodic short-term memory dysfunction may be multifactorial and requires further investigation for clarification.

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