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Transient Global Amnesia at the Emergency Department

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Abstract: Transient global amnesia (TGA) is a complex clinical syndrome characterized by sudden onset of an anterograde and retrograde amnesia that can last up to 24 hours, even if mild subclinical neuropsychological deficits may be detected. **Materials and Methods:** We performed a retrospective 9 year-study involving all patients with diagnosis of TGA evaluated at department of Emergency at the hospital of Esine (Vallecamonica, Brescia, Italy) January the 1st 2012 up to December 31 th 2020. Aim of the study is to evaluate preliminary epidemiological data of AGT in a small area of Lombardia. **Results:** 169 females and 117 men were considered, with mean age 67 ±10.9 (females 68.5±10.5, men 64.5±10.4). Number of patients discharged with diagnosis of transient global amnesia varied from 17 in 2012 to 40 in 2019.**Discussion**:In conclusion we performed one of the longest observational studies involving patients with transient global amnesia. Considering that it was retrospective and based ICD-9 code at hospital discharge, that misdiagnosed or miscoded patients could not be identified. Further data will be collected from General Practitioners archive who evaluated patients with mild symptoms.

Keywords: Amnesia, emergency unit, relapse.

INTRODUCTION

Transient global amnesia (TGA) is a clinical syndrome characterized by anterograde memory disturbance of sudden onset that lasts for 1 to 24 hours [Spiegel, D.R. *et al*., 2017]. The memory impairment of patients with acute TGA shows both reduction of anterograde and retrograde episodic memory, including executive functions. Studies evaluating risk factors for the development of transient global amnesia are still inconclusive, although it is suggested that various factors, such as migraine, focal ischemia, venous flow abnormalities, and epilepsy, may be involved in the pathophysiology and differential diagnosis of TGA [Spiegel, D.R. *et al*., 2017]. The brain area most responsible for TGA may involve a memory loop including the hippocampal CA1 region and the fornix column [Spiegel, D.R. *et al*., 2017].

We collected all the cases of TGA from January the 1st 2012 up to December 31 th 2020 discharged with diagnosis of Transieng Global Amnesia from Department of Emergency of Esine's Hospital (Valcamonica, Brescia- Italy). Aim of the study is to evaluate preliminary epidemiological data of AGT in a small area of Lombardia.

MATERIALS AND METHODS

ICD-9 (International Classification of Diseases, 9th revision - Clinical Modification) diagnostic code 351.0 and keyword ''amnesia globale transitoria'' (transient global amnesia, TGA) were used for database searching and filtering. All the included patients were evaluated by neurologist. Medical records of all subjects identified from source screening were reviewed to verify the diagnosis of TGA according to criteria proposed by Caplan [Spiegel, D.R. *et al*., 2017] and Hodges and Warlow (Spiegel, D.R. *et al*., 2017), aimed at excluding other causes of amnesia (posttraumatic, drug-induced, metabolic, degenerative, epileptic). All patients systematically underwent following examination to rule out other causes of amnesia: neurological evaluation (including an accurate history on drug assumption and head trauma), CT head scan, laboratory examinations (electrolytes, aspartate amino transferase, blood glucose, creatinine blood test and blood urea nitrogen, blood cells). Data were recorded in digital archives.

Patients were recommended to perform brain magnetic resonance imaging after discharge (except in case of specific contraindications such as pacemaker or other devices) in case of recurrent AGT or in case of pathological findings at brain CT, not so acute to justify in-hospitalization (for example incidental meningioma). We found n= 286 access at our emergency department (DEA) from January 2012 to December 2020. Clinical characteristics are summarized in table 1.

RESULTS

169 females and 117 men were considered, with mean age 67 ±10.9 (females 68.5±10.5, men 64.5±10.4). Number of patients discharged with diagnosis of transient global amnesia varied from 17 in 2012 to 40 in 2019. Despite SARS-CoV2 pandemia 33 patients received diagnosis of AGT

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In 2020. Clinical characteristics are summarized in table 1.

Few community-based studies determined the incidence of transient global amnesia, with annual incidence rate between 2.9 and 10.4/100,000; 23.5–32/100,000 for people aged 50 years and older. Furthermore, data on sex distribution of TGA are discrepant, with some studies reporting male, and other female prevalence [Brigo, F. *et al*., 2004] The female predominance noted in our study may derive, at least in part, from a relative overrepresentation of women among the elderly.

Considering that Vallecamonica population is estimated about 100.000 inhabitants (fonts: Istituto nazionale di STATistica –ISTAT 2017-2018) [3], we found an annual incidence higher than reported in literature (mean incidence 31.8/100.000), even if some evaluated patients were tourists and TGA relapses were also included and, as reported in figure 1, mean age of our patients at onset was > 60 years. From 2012 to 2020 we estimated that 226.780 patients were overall evaluated in our emergency room (mean value 25.197 evaluations/year). About 0.13 % of all the outcome diagnosis in our emergency department was of transient global amnesia.

DISCUSSION

As in previous studies emotional stress (instrumental exams, surgery, birth/death, work problems), physical effort (ie, bricolage, houseworks), and environmental stressors (ie, hot/cold water) were observed before an attack and have been related with AGT. State of anxiety triggered by personal conflicts, financial and health problems were also often reported to occur weeks prior to TGA [Portaro, S. *et al*., 2018]. In our population cohort 32.17% of events were preceded by trigger factors. In some cases patients declared not to remember them or refused to answer and no witnessed or caregivers were present at DEA.

Psychiatric comorbidities were found in 19.58% of our cohort. Patients with TGA are more likely to exhibit mood disorders such as anxious state [Serafetinides, E.A, 1994]. Some authors believe that stress-induced catecholamine release may lead to hypoxia or ischemia, whereas others believe that the neurotransmitters involved may affect the formation of memory [Portaro, S. *et al*., 2018]. Severe emotional reactions may contribute to the destabilization of the CA1 sector of the hippocampus via massive glutamate release [Spiegel, D.R. *et al*., 2016]. However, it has been shown that psychogenic amnesia can be also related to several mood disorders such as dissociative or post-traumatic stress disorder, anxious state, where the loss of memory could be considered as the result of a phobic personality and a defensive psychological reaction [Spiegel, D.R. *et al*., 2016].

Arterial hypertension is a prominent finding in patients with TGA and may be an associated risk factor, such as cardio-cerebrovascular disorders, as showed in previous studies. We performed diagnosis of transient global amnesia in 10 patients evaluated at department of emergency during hypertensive crisis [Obara, T. *et al*., 2020].

During last year (2020) we did not experience a significative reduction in TGA diagnosis. We didn't find patients with transient global amnesia and positivity for Coronavirus 19, but we also didn't find an increased number of patient with TGA during pandemia [Werner, R. *et al*., 2020], as reported in various studies. Perhaps some of them were evaluated by General Practitoners, avoiding department of emergency, perhaps due to fear of being infected.

Three patients were evaluated and discharged with TGA diagnosis and brain CT negative, but later performed magnetic brain MRI, showing left hippocampal stroke. There have been a few cases supporting the hypothesis that vascular ischemia is the cause of TGA. Ay et al. reported ischemic lesions in the left hippocampus and splenium of the corpus callosum of a patient with TGA [Kang, M.K. *et al*., 2021]. In a study of 86 TGA patients, DWI high signal lesions were identified in 10 out of 86 patients and all were hippocampal lesions [Kang, M.K. *et al*., 2021]. Ischemic lesions in memory-related brain structures also reported including thalamus, amygdale, fornix, mammillary bodies, and cingulate gyrus associated with the Papez circuit [Kang, M.K. *et al*., 2021]. Acute ischemic lesions were also found in the putamen and the corpus callosum. In other cases, focal ischemic lesion was found in the pons with delayed lesions in hippocampus and right frontal lobe [Kang, M.K. *et al*., 2021].

Brain CT at DEA revealed accidental findings in 45 patients (brain tumors, chronic cerebrovascular lesions, malformations). All of them, after being discharged, started neurological/neurosurgery evaluations.

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25 patients in our cohort after TGA developed cognitive impairment or Parkinson's disease (8.74%). In a 12-year follow-up study, the longest in the literature to date, TGA patients were compared with controls on endpoints of strokes, transient ischemic attacks, seizures, and mild cognitive impairment or dementia: TGA patients were not found to be at a higher risk of developing any of the included conditions than the control subjects [Arena, J.E. *et al*., 2017]. The yearly incidence of TGA is calculated as 3–8 cases per 100,000 people, but about a 6%–10% of patients will experience a second or third episode during life [Spiegel, D.R. *et al*., 2017]. 51 patients in our study reported 1-3 TGA relapses. Some of them were evaluated at department of emergency, others by General Practitioners. We hypothesized that, for many of them (29/51), anxiety disorder can be considered the most important trigger factor for new TGA events. 5 patients in our cohort with previous relapses developed neurodegenerative disorders during time. Neurological follow - up of all patients with previous history of TGA, especially with relapses, should be performed during time.

Table 1: characteristics of our study cohort

Epidemiological Characteristics	
Total number of patients	286
Gender: Females (%)Males (%) Total:	 169 (59.1%) 117 (40.9%) 186 (100%)
Age (mean, SD):F **M**	67 ±10.9 68.5±10.5 64.5±10.4
Number of patients discharged/year (%) 2012: 2013: 2014: 2015: 2016: 2017: 2018: 2019: 2020: total:	 17 (5.94%) 32 (11.19%) 27 (9.44%) 32 (11.19%) 37 (12.94%) 29 (10.14%) 39 (13.63%) 40 (13.99%) 33 (11.54%) 286(100.00%)
Trimester evaluation 1st January -31th March:1st April-30 th June: 1st July -30th September: 1st October-31th December: Total:	 73 (25.52%) 68 (23.78%) 78 (27.27%) 67 (23.43%) 286 (100%)
Clinical data	
Medical history hypertension: diabetes: cardiopathy: cerebrovascular disease: seizures history: liver diseases: autoimmune diseases: neurodegenerative disorders: infectious diseases of brain kidney disorders: respiratory diseases:	 147 15 30 11 3 3 3 2 2 2 2

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cancer (excluded brain tumors): brain tumor: meningioma prolactinoma psychiatric disorders: anxious personality: bipolar disorder: depression: adjustment disorder: more than 1 comorbidity:	14 4 3 1 56 49 3 3 1 16
Trigger factors for TGA Acute stressful events: Gastroenteric disorders:	 35 13

AD= Alzheimer's Disease, CAA = Cerebral Amyloid Angiopathy, CT= computer tomography, FTD = FrontoTemporal Dementia, SD= standard deviation, TGA = transient global amnesia.

CONCLUSION

we performed one of the longest observational studies involving patients with transient global amnesia. Considering that it was retrospective and based ICD-9 code at hospital discharge, that misdiagnosed or miscoded patients could not be identified. Further data will be collected from General Practitioners archive who evaluated patients with mild symptoms.

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