

Risk factors of transient global amnesia

Three case reports

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Abstract

Introduction: Transient global amnesia (TGA) is characterized by a sudden onset of anterograde and retrograde amnesia, sometimes associated with mild subclinical neuropsychological deficits and vegetative symptoms, lasting for days after the episode. Migraine history, cardiovascular risk factors, and emotional stress are considered possible risk factors. TGA usually occurs during the seventh decade of life, that is, when risk factors and concomitant pathologies have a higher incidence.

Case Presentation: We report 3 cases of TGA triggered by different causes (cardiovascular risk factors, emotional stress, and orgasm) with an unusual young onset (patient 1 was a 40-year-old woman, patient 2 was a 21-year-old woman, and patient 3 a 32-year-old man). The patients underwent neuroimaging and cardiovascular examination, and neuropsychological evaluation, without important abnormalities. TGA completely recovery within 1 to 7 days.

Conclusions: The occurrence of different precipitating events and accurate questioning (in the absence of head trauma) seem to be key features in making the diagnosis of TGA, besides a complete neuropsychiatric and cardiovascular assessment.

Abbreviations: MMPI = Minnesota Multiphasic Personality Inventory, MRI = magnetic resonance imaging, MTHFR = methylenetetrahydrofolate reductase, SCID = structured clinical interview for DSM-IV, TEA = transient epileptic amnesia, TGA = transient global amnesia, TIA = transient ischemic attack.

Keywords: transient epileptic amnesia, transient global amnesia, transient ischemic attack

1. Introduction

Transient global amnesia (TGA) is characterized by a sudden onset of an anterograde and retrograde amnesia, often associated with executive function and recognition impairment, lasting up to 24 hours and not otherwise associated with other neurological deficits.^[1–3] The presence of mild subclinical neuropsychological deficits and vegetative symptoms may also occur, and they can last for days after the episode. The main risk factors for TGA are considered migraine history,^[1] cardiovascular risk factors, that is, ischemic heart disease, carotid atherosclerosis, and psychophysical stress.^[4,5]

TGA was described for the first ever time in 1964 by Fisher and Adams, who reported on 17 patients with sudden onset anterograde amnesia and confusion that resolved within a few hours.^[6] Diagnostic criteria for this clinical syndrome were

carried out in 1990 by Hodges and Warlow:^[7] that is, attacks must be witnessed; presence of anterograde amnesia during the attack; cognitive impairment is limited to amnesia; no clouding of consciousness or loss of personal identity; no focal neurological signs/symptoms; no epileptic features; attack must resolve within 24 hours; no recent head injury or active epilepsy.^[7]

TGA usually occurs during the seventh decade of life (mean age: 61–67.3 years), that is, when risk factors and concomitant pathologies have a higher incidence,^[8–11] with a peak observed around the age of 62,^[12] and it is more frequent in females.^[12]

Herein, we report 3 young patients presenting TGA, ascribed to different conditions and neuroradiological presentation.

2. Case report 1

The patient was a 40-year-old woman, born from nonconsanguineous parents. Family history was positive for cardiovascular and cerebrovascular diseases (her father died at 51 years due to an ischemic cardiac attack; her mother suffered from high blood pressure and cerebrovascular disease) and for inflammatory autoimmune diseases (sister affected by psoriatic arthritis). The patient was a strong smoker since adolescence (about 40 cigarettes/daily). Twenty-four hours before medical consult, she started to become repetitive, asking the same questions, mainly concerning the memory loss itself. Such episode lasted about 2 hours, and was followed by headache, without memory about it. Thus, she was prescribed low weight heparin, and submitted to a neurological assessment. At the evaluation, she complained of easy irritability, difficulty to gain weight, feeling of pounding, flushing with profuse sweating, and a feeling of “internal tremor.” Neurological examination was normal. Blood test, including thyroid function evaluation, coagulative and autoim-

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mune screening, were within the normal range. She was heterozygous for the C677T and the A1298C mutations in the methylenetetrahydrofolate reductase (*MTHFR*) gene. A brain magnetic resonance imaging (MRI) showed the presence of diffuse subcortical gliotic lesions in frontal, parietal, temporal, paratrigenal areas, bilaterally, which were confluent at the frontal level. Electroencephalography revealed slow waves at the central-frontal and temporal areas. Cardiac screening, including electrocardiography, echocardiography, transcranial Doppler, visual evoked potentials, and neck vessels Doppler ultrasound, was normal. She was prescribed aspirin at the dosage of 75 mg daily. After 6-month follow-up, she was clinically and neuro-radiologically stable, presenting episodic nocturnal awakenings, and irritable mood. Neuropsychological assessment showed subclinical neuropsychological deficits, in particular for mild alteration in long-term memory, searching words and problem-solving, together with low anxiety and depressed mood. At 1-year follow-up, there were no abnormalities at the neuropsychological assessment.

3. Case report 2

The patient was a 21-year-old woman. Family history was negative for neurological and cardiovascular diseases. At the age of 17, she started to complain lipothymic episodes, characterized by generalized asthenia, profuse sweating, blurred vision, and feeling of air starvation, with a spontaneous recovery. A complete cardiac assessment was normal, as well as the tilt test. Blood assessment was normal, including prolactin, thyroid, and homocysteine tests. One month before our evaluation, after an intense psychological stress due to continuous bickering with her boyfriend, her parents referred an episode of loss of consciousness lasting about 10 minutes, not in line with previous episodes and not associated with any movements at the 4 limbs, nor tremors, nor loss of urine nor *morsus*. Because of such episode (diagnosed as nonepileptic psychogenic seizure), she was admitted to a Neurology Unit presenting amnesia related to that specific event, associated with a retrograde amnesia concerning the 2 years before the episode. Such symptoms lasted about 1 week. Neurological assessment was normal (apart from brisk reflexes), together with electroencephalography and brain MRI performed at symptoms onset and repeated at the 6-months follow-up. Neuropsychological assessment did not disclose anxiety or depressed mood; verbal memory, all field of attention, verbal fluency, executive functions were normal. Personality tests, that is, MMPI-2 and SCID-II were also normal.

4. Case report 3

The patient was a 32-year-old man. Family history was negative for neurological and cardiovascular diseases. Since adolescence, he suffered from migraine treated with anti-inflammatory drugs, as needed. He came to our observation because of an episode of TGA lasted 2 hours, triggered by orgasm. There was no alteration in level of consciousness reported at any time during the episode. There was no suggestion of other loss of specific neurologic function. Medical history was unremarkable, apart from the migraine headache. The patient did not report alcohol abuse, and he denied any form of illicit drug use. Blood tests, including prolactin, thyroid, and male sexual hormones, were all normal. Neurological examination was normal, as well as electroencephalography and brain MRI performed the week after the episode and at the 6-month-follow-up. Neuropsychological assessment

did not show anxiety or depressed mood; verbal memory, all domains of attention, verbal fluency, executive functions were normal. Personality tests, that is, MMPI2 and SCID-II were also within the normal range.

5. Discussion

Close precipitating events for TGA are considered emotional stress (i.e., triggered by gastric endoscopy, birth/death announcement, and difficult/exhausting workday), physical effort (i.e., gardening, house work, and sawing wood), physical exertion (including sexual activity), and water contact/temperature change (i.e., hot bath/shower and cold swim). Remote precipitating events, with onset reported weeks prior to TGA, are considered anxiety triggered by conflict at home or work, health problems, and financial stressors.^[7,12]

According to Hodges and Warlow, TGA patients may be divided into 3 different categories: pure TGA, probably epileptic amnesia, and probably TIA. In the pure TGA, it has been shown that the majority of attacks lasted 1 to 8 hours. Pure TGA can be excluded if there are focal neurological symptoms, such as ataxia, limb weakness, and sensory disturbances. Moreover, differential diagnosis is mandatory before considering a TGA diagnosis.

The main syndromes that should be ruled out are transient epileptic amnesia (TEA) and ischemic events and TIAs.

TEA occurs upon awakening, usually lasts ~1 hour, and it is characterized by interictal retrograde amnesia/incomplete anterograde amnesia, and patient may present temporal lobe features such as olfactory/gustatory hallucinations and/or oral automatisms. Interictal electroencephalography is abnormal in 1/3 of cases, while the other 2/3 show focal slowing or normal findings.^[1,10,13–15] Moreover, TEA has a higher recurrence rate than TGA.^[10,13,15]

Ischemic events and TIAs must be excluded before diagnosing TGA, since there is a different therapeutic approach. Specifically, ischemic events and TIAs are most commonly associated with focal neurological deficits, which by definition rule out the TGA diagnosis. However, differential diagnosis may be more difficult when there is unilateral, isolated hemispheric infarction of the hippocampus or thalamus, or ischemia involving the hippocampus, caudate, or fornix.^[16–18] Thus, accurate neuroimaging is mandatory, since TGA does not typically show acute changes on brain imaging, apart from T2-hyperintense punctate lesions in the lateral hippocampal regions in the subacute phase ~48 to 72 hours after TGA symptoms' onset, lasting up to 7 to 10 days.^[19–27] On the other hand, there are cases of TGA with bilateral and even multifocal hippocampal involvement and cases with ischemic or hemorrhagic damage to other brain regions.^[18,28–32]

This is the case of our patient 1, in which gliotic lesions are diffuse in the brain, supporting a cerebrovascular cause but without risk factors for cerebrovascular disorders, apart from being a strong smokers and the slight ATIII increase.

Patients with TGA are more likely to exhibit irritability or anxiety.^[33] 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.^[34–39] Severe emotional reactions may contribute to the destabilization of the CA1 sector of the hippocampus via massive glutamate release.^[40] However, it has been shown that psychogenic amnesia can be linked to several psychiatric disorders including post-traumatic stress disorder and dissociative disorders, where the loss of memory could be

considered a defensive psychological mechanism, often associated with a phobic personality trait.^[40]

This seems the pathophysiology involved in the case report 2, in which psychogenic causes seem to play a major role. In fact, the precipitating trigger was the onset of psychological stressor in a young female presenting a subjective indifference to the memory loss experienced, as previously reported.^[41] Such psychological insult appears to disturb the affective learning circuit between amygdala, hippocampus, striatum, and prefrontal cortex, by transitorily affecting the inhibitory effects on the amygdala, thus inducing a disruption in memory formation.^[40]

It is worthy to note that physical or psychological precipitating factors seem to be responsible for up to 90% of TGA episodes.^[10] Among them, orgasm has been reported rarely as a precipitant of TGA. In 1964, Fisher and Adams reported a case of a man whose episode began during orgasm,^[6] but other authors also reported on recurrent TGA episodes induced by sexual activity.^[42] However, the overall recurrence rate is very low, and our case 3 belongs to such group of uncommon causes of TGA.

The occurrence of a distinct precipitating event and repetitive questioning (in the absence of head trauma) seem to be key features in making the diagnosis of TGA. However, considering such pathophysiological variability, when facing TGA, if the clinical picture remains unclear, neuropsychological testing and/or other neurological tests, that is, electroencephalogram and brain MRI, a prompt follow-up monitoring clinical condition, together with cardiovascular, neurophysiological (electroencephalography) and neuroradiological (brain MRI) assessments can be helpful to establish a right treatment (pharmacological or psychological support).

Fortunately, the natural course of TGA is usually benign, self-limited, and without long-term residual sequelae, but a prompt diagnosis is mandatory to properly approach such clinical entity.

Author contributions

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