DIFFERENTIAL DIAGNOSIS OF THE MAIN TRANSIENT GLOBAL AMNESIAS ATYPICAL CASE REPORT

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ABSTRACT

Objective*: Memory is one of man's most important cognitive functions. Various diseases can affect memory function and yield specific memory impairments. One of these conditions, transient global amnesia, is a peculiar type of memory loss with hallmark characteristics. However, the pathophysiological explanation for transient global amnesia remains controversial*

Methods*: Starting with the most significant data from the literature, we describe the most important features needed for diagnosing the three main clinical conditions that could mimic transient global amnesia. Then, we describe a retrospective series of cases of transient global amnesia.*

Results*: Among the cases observed, we focus on a case of transient global amnesia with features that distinguish it from the cases reported in the literature.*

Conclusion*: This paper describes the key features of transient global amnesia, discusses the main differential diagnoses from similar conditions and proposes a pathogenetic interpretation consistent with all of the hallmarks of the disorder (amnesia duration, lack of specific neuroradiological and electroencephalographic correlates or impaired sensitivity or motility, reversibility and benign prognosis of the amnesic episodes, and rare recurrence).*

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

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Introduction

Memory is one of man's most important cognitive functions and is how humans encode, consolidate, store and retrieve information. Memory is one of man's common features but varies widely from one individual to the next in terms of the various stages of memory processing. Memory is not always directly related to other cognitive skills, such as intelligence, perception, logic and reasoning. In addition, memory may vary widely within the same individual as well as among individuals. For example, the same individual may present with marked differences in memory performance coinciding with particular physiological and pathological events that may enhance or impair memory function.

Hypermnesia is the term used for an exceptionally exact or vivid memory associated with bipolar disorders. More common conditions observed in clinical practice are impaired memory, known as hypomnesia or amnesia (depending on

the severity). These conditions occur following head trauma or other brain insults (congenital or acquired illnesses, such as stroke, cancer, and metabolic or psychiatric diseases).

Memory changes may be transient or permanent, such as the ones encountered during acute short-lasting epileptic periods, transient but long-lasting pseudodementia or progressive irreversible dementia.

Methods

Starting with the most significant data from the literature, we describe the most important features needed for diagnosing the three main clinical conditions that could mimic transient global amnesia: transient global amnesia (TGA), transient epileptic amnesia (TEA), and transient ischemic attack (TIA). Then, we describe a retrospective series of cases of transient global amnesia.

Transient global amnesia

Acute attacks of transient memory loss are known as transient global amnesia (TGA), as defined by Fisher and Adams in 1964[1]. The estimated incidence of TGA is approximately 3 to 8 cases per 100,000 inhabitants per year[2], and the annual recurrence rate ranges from 6% to 10% and up to 26%[3]. The incidence in Rochester (Minnesota, USA) was reported to be 5.2 cases per 100000 inhabitants per year[4]. TGA usually affects adults or elderly subjects who are mainly 50-70 years of age. TGA is very rare in children and adolescents.

TGA risk factors include emotional distress, mood disorders or anxiety states, and the triggering factors include mental and physical stress, extremes of temperature, physical exertion, diagnostic procedures, administration of sedatives, and migraines (in a high percentage of cases). No consistent causal factors are identified in the great majority of cases.

The diagnostic criteria include (i) anterograde amnesia witnessed by an observer, (ii) no clouding of consciousness or loss of personal identity, (iii) cognitive impairment limited to amnesia, (iv) no focal neurological or epileptic signs, (v) no recent history of head trauma or seizures, and (vi) resolution of symptoms within 24 hours[5-7].

The hallmark of TGA is a loss of the ability to learn new information (anterograde amnesia), usually lasting 4-8 hours, with no clouding of consciousness, retention of memories acquired prior to the attack and no loss of personal identity. The condition shows no significant sexual prevalence, and there are no changes in motor, sensory or perceptive functions or other cognitive abilities. Patients appear to behave normally except for continually repeating the same questions even after receiving appropriate answers. At the end of the TGA episode, patients resume their usual behavior but continue to have a memory gap covering the duration of the TGA episode. Some authors include anterograde amnesia in the memory loss and also a variable limited loss of retrograde memory confined to the hours or days preceding TGA onset. TGA episodes resolve as suddenly as they appear for no apparent reason, and many patients complain of headache.

The strange feeling of malaise associated with TGA sometimes results in an erroneous diagnosis of psychiatric disease. However, when both patients and observers are unaware of the disease, TGA may pass unnoticed. In these cases, the only aspect of interest for the patient is the memory loss of events that occurred during amnesia, and the episode may not be clinically evaluated. Hence TGA may be underdiagnosed, especially when retrograde memory is spared.

TGA remains one of the most intriguing neurological conditions in terms of etiology despite the plethora of clinical and laboratory tests performed during the past fifty years. The two main hypotheses regarding the pathogenesis of TGA include cerebral ischemia and epilepsy that may be responsible for the key features of TGA.

Transient epileptic amnesia

The epilepsy hypothesis implicates transient epileptic amnesia (TEA), a temporal epilepsy variant characterized by isolated memory loss[8]. affecting both anterograde and retrograde memory, while apparently sparing other cognitive functions. TEA episodes are more common than TGA due to the typical recurrence of the attacks (similar to all other forms of epilepsy). In addition, a weak conservation of anterograde memory has been reported in patients with TEA. For example, TEA patients report realizing they did not remember during the attacks, whereas anterograde amnesia is reported as absolute during all episodes of TGA[9]. An even more important finding is that TEA episodes are often reported to last from 30 to 60 min, much longer than other temporal lobe seizures but much

shorter than TGA episodes. The longer duration of TEA compared to other temporal lobe seizures (usually a few minutes) is ascribed to a sort of temporal status epilepticus, as documented by occasional ictal EEG recordings[10] revealing temporal epileptic activity.

The prevalence of TEA episodes affects subjects of a similar age compared to subjects with TGA. However, TEA tends to affect males, while TGA exhibits no sexual prevalence. Because both forms affect similar age groups, the disorders could be construed as having a "meiopragy" effect of the mesial temporal structures that are probably involved in both clinical conditions. These structures are weakened by the onset of a reduced metabolic reserve and hence have a reduced safety margin against all possible insults within a vascular territory deemed to belong to "Snyder's watershed areas", which are at greater risk of ischemia or metabolic stress due to decreased blood flow.

Sixty percent of TEA seizures are accompanied by other events in addition to amnesia. Epileptic events occur much more frequently, and their clinical manifestations often involve other phenotypical features, such as dysperceptions/hallucinations and/or oroalimentary automatisms[11]. These features may be the expression of an irritative insult rather than a deficit. In this instance, EEG changes are common but limited to 60% of cases; the method is not very sensitive to epileptic activity in the deep mesial temporal structures. EEG changes, however, have never been documented in patients with TGA.

Although the epilepsy hypothesis can account for the sudden onset and resolution of TGA episodes, it does not seem to account for the duration of the amnesia (from a few to many hours), which could only be explained in the context of status epilepticus, a feature repeatedly ruled out in TGA even with ictal EEG recordings. Except for focal seizures, no epileptic manifestations have been described with preserved consciousness and maintained contact with the environment. In addition, metabolic triggering factors (such as hypoglycemia) have never been documented in patients experiencing TGA attacks.

Transient ischemic attack

The ischemia or vascular hypothesis appears to be a more convincing explanation of all the events characterizing TGA episodes. In this context, the cerebrovascular event most closely resembling TGA is a transient ischemic attack (TIA) in the territory most commonly involved in memory loss (the posterior cerebral artery and its branches and the choroid artery, which contributes to the hippocampal arteries). However, the overall clinical features of TIA are quite different due to the often concomitant cardiovascular risk factors (hypertension, diabetes, heart disease, heart valve disease, atheromatosis of brain vessels, and clotting disorders (alone or often in combination)), which have not been implicated in TGA. Furthermore, the two conditions have a different evolution and prognosis[4,12,13]. Experimental research designed to detect venous engorgement during the Valsalva maneuver (underlying episodic amnesia) was negative[14,15].

The limited area of vascular impairment, low incidence of recurrence, lack of specific neuroradiological changes arising during an amnesic episode, and the relatively young age at onset of TGA make this hypothesis unconvincing.

TIA episodes have a similar duration as TGA attacks, even though they tend to be shorter. However, TIA episodes are often recurrent, and unlike TGA, they tend to evolve into a stroke after varying time intervals. Moreover, neuroradiological investigations in acute patients and during longitudinal monitoring, as well as studies with large cohorts of TGA patients, have failed to confirm the systematic presence of vascular injury.

Personal case series

Our personal cohort of 12 TGA patients was observed over a period of 9 years (2006-2014). The cohort consisted of 7 men and 5 women aged 47 to 66. These patients had no significant cardiovascular risk factors. The only common symptom shared by all patients was migraine (with aura in 3 cases). The recurrence of pain varied from 3 attacks per month to six per year. All blood tests, ultrasound scans, EEG tests and neuroradiological investigations failed to reveal significant changes even after longitudinal monitoring.

All findings were consistent with the international literature in all patients except one. This 57-year-old man had no cardiovascular risk factors and was not hypertensive or diabetic. He had a normal weight and performed regular moderate physical activity. The patient had a history of smoking (c. 20 cigarettes/day) until the age of 35 (before the TGA episodes began). While feeling well on Christmas Eve, he suddenly presented with typical repetitive questioning. The patient was taken to the hospital

and was admitted for the appropriate tests (blood, heart, metabolic, neuroradiological and ultrasound investigations), which proved negative. At 3 pm, approximately 5 hours after the onset of symptoms, the TGA episode resolved spontaneously with a progressive complete recovery of memory.

Shortly before the amnesic episode, the patient reported feeling strange because he had always experienced December 24th as a special day associated with his childhood memories, very cold weather, and snow and/or fog in the mountainous region where he lived. This year on Christmas Eve, the day was warm enough to wear summer clothes, which resulted in a strong, peculiar sensation of unreal weather[16]. After this unusual isolated sensation at 10 am while exchanging Christmas greetings with a close friend, he was unable to recall anything until 3 pm, and he was surprised to find himself in a hospital bed.

The special feature of this case is that after the five hour memory gap, the patient was able to remember 3 occasions: having a telephone conversation (without remembering the content) with a person who noted nothing out of the ordinary; asking the doctor examining him what illness he had (without remembering the answer); and seeing himself inexplicably lying on a hospital stretcher alongside other patients (awaiting his neuroradiological examination). Generally speaking, TGA patients have a complete loss of memory throughout the amnesic episode. Presumably, this completeness does not apply to all cases, and our patient's anterograde amnesia was not complete. The patient has had no recurrences during the past 8 years.

Working hypothesis of TGA

A satisfactory interpretation of TGA should be compatible with the following:

- Amnesia duration
- Absence of specific and constant neuroradiological and/or electroencephalographic changes
- No disorders of consciousness
- No changes in sensitivity or motility, and no other cognitive changes other than memory loss
- Benign prognosis and reversibility of episodes
- Rare recurrence

A hypothesis embracing all these aspects could involve a migraine event. Migraine is a clinical finding commonly noted during history-taking in TGA patients. In many cases, migraine pain heralds and/or follows the amnesia, prolongs the feeling of malaise, and is well documented in the literature[17-20].

Migraine-related vascular changes can explain the changes that occur in hippocampal CA1 cells, which are selectively vulnerable to oxidative, pharmacological (benzodiazepines, antidepressants, neuroleptics and anticholinergic drugs), metabolic and hemodynamic stress induced by glutamate excitotoxicity involving high levels of calcium ions, for example, due to oligo-hypoxemia, thereby resulting in impaired long-term potentiation and increased long-term depression in CA1 cells, a decisive factor in memory loss[21].

All types of physical and mental stress lead to increased corticotropin-releasing hormone and corticosterone levels. Through receptors sensitive to mineralocorticoids and glucocorticoids, these hormones have depressive and destructuring effects on the CA1 cells and memory. A typical example of this condition is severe endogenous depression with contextual memory impairment (so-called pseudodementia)[22,23], but other conditions with different etiopathogenesis may contribute to cognitive impairment[24-31].

The clinical association between TGA and migraine was present in all patients in our series. The patients reported headache of varying severities at the end of the amnesic episode. Nonetheless, if TGA is an expression of a very common illness, such as a migraine, the rarity of TGA episodes and their recurrence awaits explanation. This event may be postulated to occur during an unusual type of migraine attack, i.e., not unilateral but bilateral ("bicranic attack") involving the bilateral temporomesial regions, which are strongly involved in memory function. A significant contribution to this hypothesis may be found in the research of Stillhard et al.[32] and Di Filippo and Calabresi[33]. These authors report a bitemporal hypoperfusion during TGA that was documented by diffusion-weighted imaging 2-3 days after the onset of symptoms or from the start of symptoms with sensitive 3T MRI systems[34,35].

The precipitating factors heralding an amnesic episode include recurrent triggers for migraine in subjects with a family and individual history of headache: a sort of "dysautonomic vascular dystonia" construed as a propensity toward reversible vasoconstrictor responses to mental and physical stress, temperature changes, and acute pain[4,36].

The occurrence of all the requirements listed for TGA seems to support our working hypothesis

on which to pursue future clinical, neuroradiological and experimental research (table 1).

	TEA	TIA	TGA
Onset	Acute	Acute	Acute
Age	variable	adult-elderly	50-60 years
Duration	30-60 minutes	minutes/hours	3-7 hours
Precedents	frequent	possible	rare
Symptoms	multiple	multiple	amnesia
Amnesia	anterograde	rare	anterograde>retrograde
Consciousness	impaired	spared	integral
Context	epilepsy	risk factors	indifferent
Instrumental signs	EEG	MRI, ECG, echocardio	none
Sequelae	anterograde amnesia	absent	anterograde amnesia
Treatment	antiepileptic drugs	antiplatelet/anticoagulant	none
Recurrence	frequent	frequent	rare

Table 1: summarizes the differential diagnoses among epileptic, cerebrovascular (TIA) and TGA attacks.

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