

Hyperhomocysteinemia Association With Transient Global Amnesia: A Rare Case Report

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Abstract

Context: Transient global amnesia (TGA) is an intriguing condition that classically presents with an abrupt onset of temporary complete anterograde amnesia and partial retrograde amnesia. Most individuals who experience such a form of amnesia usually have only one attack but recurrent attacks are possible. Most attacks last for a few minutes or few hours and the ability to lay down new memories may also be affected but gradually improves, leaving only a dense amnesic gap for the duration of the episode. There has been some discussion about the etiology behind TGA; however, there has yet to be a consensus with regard to any significant association. **Case Report:** We report the case of a 65-year-old male presenting with a sudden onset of memory loss that is typical of TGA and who was found to have elevated homocysteine levels. There has only been one other case previously reported that discussed a possible correlation between hyperhomocysteinemia and TGA. It is yet to be determined if increased homocysteine level is a significant risk factor for attacks of TGA. **Conclusion:** Although it was first described more than half a century ago, it can still be misdiagnosed frequently as many physicians are not familiar with this condition. Furthermore, there are quite a few medical conditions that may cause sudden memory impairment, such as epilepsy and stroke, which make it difficult to distinguish them from this form of amnesia. The knowledge of these clinical identities is necessary for a high index of suspicion, which may lead to a meticulous medical evaluation as required for proper diagnosis.

Keywords: Dementia, homocysteine, hyperhomocysteinemia, memory, transient global amnesia (TGA)

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Introduction

Transient global amnesia (TGA) usually occurs as a solitary event; however, in some individuals it may recur with similar symptoms. Typically, TGA does not require specific treatment and most attacks resolve spontaneously within 1-8 h but less than 24 h.^[1] The etiology of TGA remains enigmatic although several possible mechanisms have been proposed, including arterial thromboembolic ischemia, vasoconstriction from hyperventilation, or venous congestion with Valsalva-like activities. During such an attack, although patients retain clear consciousness, intact cognition, and higher cognitive functions, they are disoriented with

regard to time and place and repeat the same questions, resulting in agitation and anxiety. Therefore, TGA can be very traumatic for some patients and the right diagnosis is important. Unfortunately, it remains unclear if there is any significant association or relationship between TGA and other conditions or if there is any laboratory value, such as homocysteine level, which may correlate to its diagnosis.

Case Presentation

In this case report, we illustrate the diagnosis of a 65-year-old male with a past medical history of hypertension who presented to the emergency department with complaints of headache, sudden onset of memory loss, and confusion. The patient, normally considered a very independent person, during his drive home from the restaurant had suddenly become confused, lost, and disoriented. He continued to drive on the highway for several hours, unable to recall his way back home or where he lived. After 4 h of being lost, he was able to find his way home. When his wife

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found him, he was disoriented and was unable to recall what had happened.

On physical examination, the patient was found to have a blood pressure of 115/83 mm Hg, heart rate of 88 beats per minute, and respiratory rate of 16 breaths per minute, and temperature of 98.4 F. Mini-mental state examination (MMSE) score was 27, with no apparent neurological deficits on physical examination.

Laboratory data on presentation were unremarkable on the chem 7 panel and the complete blood count panel showed cholesterol of 224 mg/dL (range: 100-199 mg/dL) and low-density lipoprotein (LDL) of 137 mg/dL (range: 0-99 mg/dL). Noncontrast computed tomography (CT) scan of the brain was conducted but it failed to illustrate any acute intracranial changes except mild diffuse cortical atrophy. Magnetic resonance imaging (MRI) of the brain was ordered and showed nonspecific periventricular and subcortical foci of altered signals on the fluid-attenuated inversion recovery (FLAIR)- and T2-weighted sequence without diffusion abnormality, and was negative for any acute intracranial pathology.

Further laboratory workup continued to be inconclusive, which consisted of a thyroid-stimulating hormone (TSH) of 3.21 uIU/mL (range: 0.45-4.5 uIU/mL), vitamin B12 of 492 pg/mL (range: 211-946 pg/mL), a normal folate level, and a negative urine drug screen. As there continued to be a lack of support or findings explaining the neurological deficits and vitamin B12 as well as other lab results such as folate, rapid plasma regain, thyroid stimulating hormone and others were found to be non-significant; the neurologist recommended testing homocysteine levels. As it has been linked to stroke and there are conflicting ideas on its association with dementia, homocysteine was obtained and was found to be elevated at 37.1 mcmol/L (range: 4-17 mcmol/L). Its increased levels may have been due to the patient's history of smoking and increased age; no other significant cause could be determined at the time. One day after observation, the patient showed cognitive and full neurological improvement and was thus considered stable for discharge with conservative management and further workup on an outpatient basis. Although no new incident of amnesia was reported by the patient, he was contacted for repeat homocysteine levels at a later date but failed to be compliant with his scheduled appointments.

Discussion

Homocysteine is a sulfur-containing amino acid that is a metabolite of methionine and plays a role in the critical biochemical intersection in the methionine cycle between

S-adenosyl methionine, the indispensable methyl donor, and vitamin B12 and folic acid. The regulation of homocysteine levels depends on the distribution between homocysteine remethylation and its transsulfuration to cystathionine.^[2] The levels are further impacted by the dietary intakes of methionine, folate, and vitamin B12 but some studies have shown that lifestyle factors such as coffee, alcohol, cigarette smoking, and physical inactivity may have some impact on modulating the levels as well.^[2] Furthermore, significant deficiencies in the homocysteine remethylation cofactors consisting of cobalamine, folate, and the transsulfuration cofactor vitamin B6 are commonly seen in the elderly population, with a resultant increase in the homocysteine level that may be correlated to advancing age.^[3] Only one other case has demonstrated a possible link of elevated homocysteine levels and TGA.

TGA, as seen in our patient, is usually accompanied by repetitive questioning, lack of focal neurological symptoms, and disorientation of time and place with attacks usually lasting for 1-8 h.^[4] During the time of the episode, the patient is unable to form new memories and thus, presents with anterograde amnesia, along with retrograde amnesia; however, he/she will remain fully communicative and alert throughout.^[4] Some differentials initially considered were seizures, acute confusional state, complex partial seizure, and transient ischemic attack. However, after other etiologies have been ruled out, rare causes must be taken into consideration.

The etiology remains controversial but current consensus suggests that the areas involved are the mediobasal temporal region, the hippocampus, and the parahippocampus; however, no agreement has been established behind its pathogenesis.^[4] Initially, it was thought that paradoxical embolus via a patent foramen ovale may be highly related to its etiology but Maalikjy *et al.*^[5] did not find a significant difference in its prevalence and patent foramen ovale. The migraine theory proposes that glutamate release in the hippocampus may result in depression and temporary dysfunction of the hippocampus resulting in TGA, as was seen in this patient.^[4] However, although the patient presented with the symptom of headaches that is also common in TGA, the highly elevated homocysteine level appeared to be the only significant laboratory-related factor.

A link between homocysteine and the disorders in the nervous system was first seen in patients with severe cystathionine beta synthase deficiency, which resulted in mental retardation, cerebral atrophy, and seizures.^[6] Homocysteine influences neuronal degradation and therefore, plays a role in psychiatric-

and age-related neurodegenerative disorders, especially as its levels have been found to increase with age.^[6] Concentrations of homocysteine were associated with approximately three times higher risk of white matter damage when compared to levels below 8.6.^[6,7] Increased levels of homocysteine have been correlated to a decline in memory scores in elderly subjects and worsening cognitive function, possibly as a result of cerebrovascular or direct neurotoxic mechanisms.^[6,8] In studies conducted with animals exposed to homocysteine, it was seen that an accumulation of this compound in the brain resulted in restricted growth, neural or cognitive dysfunction, and impaired brain energy metabolism.^[6,9]

Furthermore, homocysteine has been found to be a predictive factor for Alzheimer's disease. Several studies have shown that homocysteine is an independent risk factor for promoting dementia.^[2] Another hypothesis suggests that homocysteine may play a role as an excitatory neurotransmitter that competes with gamma-aminobutyric acid (GABA).^[2,10] Vascular dementia may be a result of an elevated level of homocysteine as it may further impact microvascular permeability by the attenuation of GABA receptors, which in turn activate disintegrin and metalloproteinase, resulting in disruption of the matrix in the blood-brain barrier.^[6] On the other hand, homocysteine levels can also be related to altered and low folate or vitamin B12 levels that may affect cognitive function. In our patient, these vitamins were found to be within normal limits. Semmler *et al.* presented the only other case discussing the possible association between a transient global amnesia-like episode in a patient with severe homocysteinemia.^[11] However, it is difficult to explain a definite correlation without more research and statistical analysis. Thus, though many sources have suggested a link between neurological function and homocysteine levels, no clear conclusion has been established on its etiology or regarding the connection between homocysteine level and TGA.

Hyperhomocysteinemia has been shown to be an independent risk factor for cognitive dysfunction but its causal relationship with TGA should be evaluated in further studies. More case-based studies and research need to be performed to assess whether this will also reduce the risk of cognitive disease and improve cognitive functioning. Individuals with TGA without any obvious cause should be investigated and treated for

elevated homocysteine levels. No final analysis has, at this time, been able to conclude on the causal relationship between homocysteine and cognitive dysfunction, most specifically in TGA.

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