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Case Report
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Recurrent TGA Complicated with Migraine with Bilateral Hippocampus NAA Peaks Reduction: A Case Report

*Yu F[1], Yu H-M[1] and Zhang B-W[1,2]**

[1]Department of Neurology, First Affiliated Hospital of Dalian Medical University, China

[2]Department of Psychology, Dalian Medical University, China

Abstract

Transient Global Amnesia (TGA) is a transient memory disorder of unknown etiology. Most patients are likely to experience only one TGA episode in their lifetime, we have herein reported a patient with recurrent TGA complicated with migraine, whose hippocampal Magnetic Resonance Spectroscopy (MRS) show a reduced bilateral N-Acetyl-Aspartate (NAA) peak, as rarely reported previously.

Keywords: Transient global amnesia; Migraine; Magnetic resonance spectroscopy; N-acetyl-aspartate peak

Introduction

Transient Global Amnesia (TGA), first described in 1956, is characterized by isolated episode anterograde and sometimes retrograde amnesia of less than 24 h and without focal neurological deficits. It has been suggested that focal ischemia, migraine, venous congestion, and epileptic phenomena are involved in the pathogenesis of TGA, and migraine is one of the most compelling relative factors associated with developing TGA [1]. Generally, TGA attacks only once in most cases, but 5.4% to 27.1% of TGA patients will experience recurrence [2,3]. In recent years, migraine has also been seen as an important influencing factor in TGA recurrence, and there are some cases [4] suggested that TGA occurs as either "an aura" or "a sequel" to migraine. Hippocampus hyperintensity on Diffusion-Weighted Imaging (DWI) reflects the diffusion limitation of the structure related to memory which is thought to be associated with the focal transient perturbation of hippocampus circuits. Few reports have addressed the imaging of patients with recurrent TGA complicated with migraine, and we have herein reported a case of recurrent TGA patient with migraine, who showed hippocampus hyperintensity on brain MRI, aiming to try to understand the pathophysiological mechanisms of recurrent TGA patients complicated with migraine.

Case Presentation

A 62-year-old woman with a sudden memory disorder 3 h before her emergency visit, presented with repetitive questioning about her immediate circumstances (e.g., "What am I doing here?"; "Has the car stopped?"). Symptoms similar to this time have occurred twice at 6 years ago and 1 year ago, and recovered completely the next day after sleep and had no memory of the course during the onset. She only had a medical history of migraine for ten years that manifested fluctuation-like pain in the right posterior occipital and often occurred at cold, cough, fatigue and when summer and autumn alternations. She had no diabetes or hypertension and did not smoke or drink. During the attack, her personality, cognition involving semantic language, visuospatial discrimination, and writing ability were all preserved, and there was no impairment in the state of consciousness, and no obvious seizure activity. Physical examination showed limbs strength, sensation, reflex and coordination were normal. CHA2DS2-VASc scores were three (history of TGA, female). Blood tests revealed no significant abnormality. No significant abnormality was observed in the head Computed Tomography (CT) scan. MRI performed at three days after onset revealed a recent right hippocampus punctate hyperintensity on DWI with corresponding lesion in the T2-weighted MR image (Figure 1), and MRS sequence showed the decrease of NAA peak in bilateral hippocampus (Figure 2, 3). Fazekas' score was one which represented only minor cerebral microangiopathy in this patient. Because this patient had Valsalva-like activities related migraine, we also done contrast-enhanced Transcranial Doppler (c-TCD) examination which showed no shunt during normal breathing and mild shunt (1 microbubble appeared 11 sec after the starting of injection) during the

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Correspondence:
Bing-Wei Zhang, Department of Neurology, First Affiliate Hospital of Dalian Medical University, No. 222, Zhongshan Road, Dalian, Liaoning Province 116011, China

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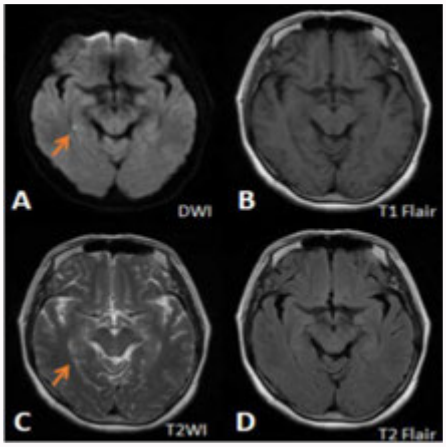


Figure 1: MRI imaging of patient at three days after onset (A-D). The red arrow point to a recent ischemic lesion in the right hippocampus area.

Valsalva Maneuver (VM) procedure (Figure 4). Aspirin and statins were given for secondary prevention, and the patient had complete symptom resolution the next day after sleep and had no TGA or stroke recurrence during six months follow-up.

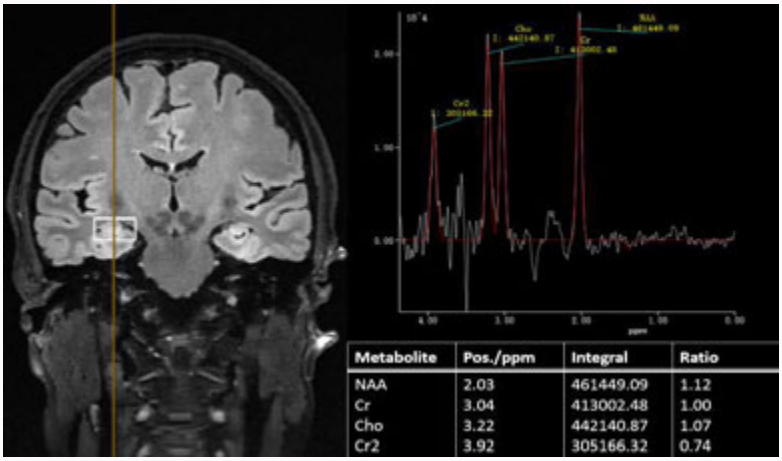
Discussion

Although TGA was previously considered as a subtype of TIA because both are characterized by a sudden reversible loss of function, it was recently believed that many TGA patients did not belong to TIA. The risk factors of TIA are atherosclerotic risk factors, for example, age, hypertension, diabetes mellitus and cerebral microangiopathy. However, it is reported in the literature [2,5] that age and cerebral microangiopathy are protective factors for TGA recurrence, and TGA patients have a lower prevalence of hypertension, diabetes, and lipid disorders compared with TIA patients. Liampas et al. [5] raises a pathophysiological hypothesis that the interaction between angiotensin II type-1 and N-methyl-D-aspartate receptors may be an important reason for traditional risk factors for cerebrovascular diseases have emerged as protective factors for TGA recurrence. This patient was a 62-year-old female patient with no history of smoking, alcohol consumption and hypertension or diabetes mellitus, with a normal head MRA, which was consistent with the reports on the risk and protect factors for TGA recurrence.

The most compelling study in TGA risk factors, come from a large-scale population-based study in 2014 [6], who demonstrated people with migraine were more prone to TGA than those without migraine, with the incidence rate ratio of 2.48. No associations were found between migraine subtypes and TGA. Studies [1] have shown that the most frequent trigger factors of TGA were emotional stress, physical effort, Valsalva-like activities and water contact or temperature change. In this case, three episodes of TGA attacks were triggered by cough or fatigue, which may be related to the temporary reduction in cerebral blood flow by VM. It is worth noting that Valsalva-like activities are the trigger factors of TGA, migraine is a risk factor of TGA, and migraine may be associated with unclosed foramen ovale, so here is an interesting hypothesis about the pathogenesis of TGA that the unclosed foramen ovale mediates paradoxical embolism under Valsalva-like activities and causes migraine, which also causes local cerebral ischemia and eventually triggers TGA. However, further attempts to verify the causal relationship between patent foramen ovale and TGA have since failed [7], and the result of the c-TCD examination in this patient also do not fully support patent foramen ovale. In addition, some scholars [8] believe that TGA may be sequelae in migraine patients due to the activity throughout the cerebral cortex was suppressed in migraine patients, and the depression will extend to the hippocampus, thus leading to transient memory dysfunction. Spiegel [9] has also reported that migraine may contribute to the destabilization of the CA1 filed of the hippocampus by releasing massive glutamate. However, the current evidences can only prove an association between migraine and TGA but not causality and further experimental researches are needed to prove the causal relationship between them.

A recent systematic review yielded TGA recurrence rate of 13.5% by an analysis of nine cohorts consisting of 1,989 patients [4]. Andreas et al. [2] predicted that patients older than 70 years old and with mild microangiopathy were subjected to about 25% risk of recurrence within the median latency period of four years. Oliveira et al. [3] reported patients with recurrent TGA versus single TGA had more hippocampus hyperintensity on DWI (p=0.001). There are some retrospective studies [3,4] showing that young, without significant microangiopathy, with migraine and history of depression or dementia have an increased recurrence risk of TGA.

TGA is mainly a clinical diagnosis and hippocampus hyperintensity on brain MRI also assist in the diagnosis of TGA



Metabolite	Pos./ppm	Integral	Ratio
NAA	2.03	461449.09	1.12
Cr	3.04	413002.48	1.00
Cho	3.22	442140.87	1.07
Cr2	3.92	305166.32	0.74

Figure 2: MRS sequence showed the decrease of NAA peak in the right hippocampus.

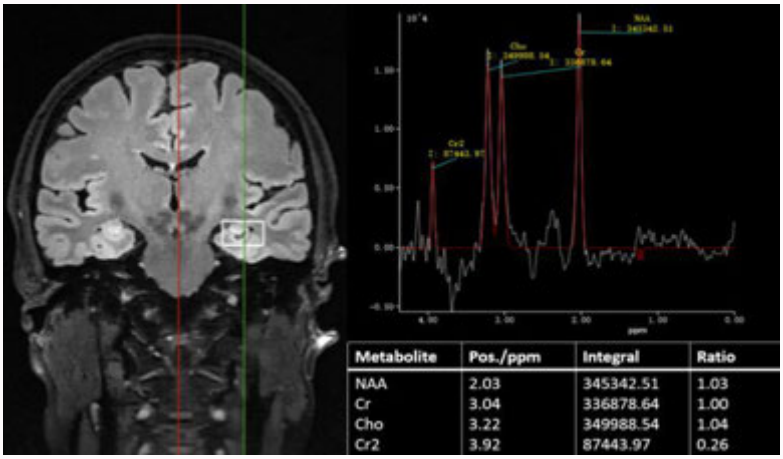


Figure 3: MRS sequence showed the decrease of NAA peak in the left hippocampus.

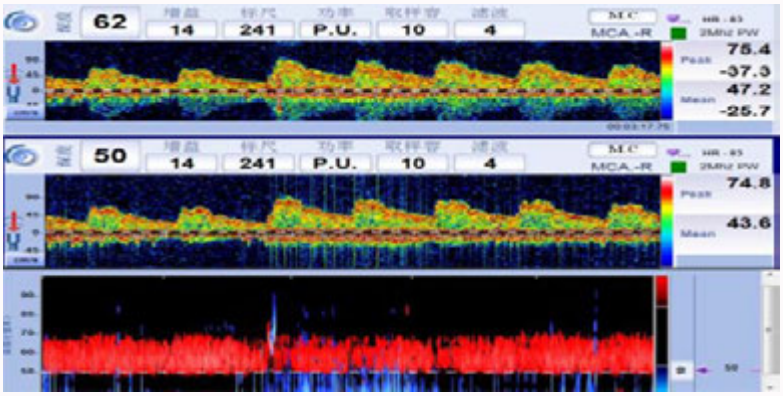


Figure 4: The contrast-enhanced Transcranial Doppler (c-TCD) examination show no shunt during normal breathing and mild shunt (1 microbubble appeared 11 seconds after the starting of injection) during the Valsalva Maneuver (VM) procedure.

from a neuroanatomical perspective. Lesions were considered to be located in CA-1 sector of the hippocampal cornu ammonis when they were detectable in both DWI and T2-weighted images which had been speculated to play a key role in the pathophysiology of TGA [10]. While TGA does typically not show acute changes on brain imaging, DWI or T2-weighted imaging may reveal hippocampal regions from 48 h to 72 h to 7 to 10 days after onset, and studies suggest that delayed neuronal injury of the hippocampus may cause the delayed appearance of the lesions on image findings [1]. In this case, the patient completed brain MRI at three days after onset showed a DWI lesion with corresponding lesion in the T2-weighted MR that revealed a recent right-side hippocampal lesion (Figure 1), a region known to be critically involved in the process of memory consolidation and to be vulnerable to metabolic stress, and MRS sequence of hippocampus completed at eight days after onset showed the decrease of NAA peak in bilateral hippocampi (Figure 2). As we know that MRS provides information of metabolic alterations within brain structure from a clinical perspective, and NAA is one of the highest concentration of molecules in the Central Nervous System (CNS), which is a marker of neuron integrity and viability [10], however there are no relevant reports of decreased NAA peak on the hippocampal MRS of TGA patients as yet. Bartsch et al. [10] reported hippocampal MRS of diffusion lesions showed a lactate peak which indicated acute metabolic stress of hippocampal CA-1 neurons while long-term metabolic sequelae were lacking. There is only one punctate hypersignal in DWI, but both hippocampi have decreased NAA peaks, indicating that the hippocampal dysfunction that triggers TGA is far greater than the range shown by DWI. This phenomenon supports the hypothesis that TGA with migraine is not of TIA origin. In view of the fact that there are few reports addressing MRS pattern in TGA, it is difficult to verify whether the decrease of NAA peak in bilateral hippocampus is representative and whether the pathophysiologic correlation between these lesions and episode of TGA is established, and more studies should be investigated.

The limitation of this case is lacking MRS sequences in the early stage of the onset and the follow-up, therefore we could not identify the alteration of NAA peak in the whole course of TGA.

In summary, we have herein presented a case of recurrent TGA complicated with migraine, who had a typical DWI lesion with corresponding lesion in the T2-weighted MR that revealed a recent right-side hippocampus lesion and relatively rare decreased NAA peaks in the bilateral hippocampus on MRS. Although TGA is generally a benign course, patients with recurrence risk factors and abnormal imaging examinations should be noticed by neurologists and scheduled for a long-term follow-up. Therefore, more studies are needed to investigate the relationship between migraine and recurrent TGA and DWI/MRS sequences of TGA patients at each stage of the

onset, which may shed light on the pathophysiological bases of TGA.

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