Transient global amnesia: hippocampal magnetic resonance imaging abnormalities

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Summary

Transient global amnesia (TGA) is an episodic dysfunction of declarative memory that usually resolves within 12 hours and whose underlying pathophysiological mechanisms are still unclear. Recent studies, on the basis of transient focal high-signal abnormalities in the hippocampus on diffusion-weighted imaging (DWI), suggest involvement of memory circuits in the temporo-mesial region. Out of a total of 65 patients presenting with acute or subacute TGA between May 2004 and May 2008, we retrospectively analysed 21 in whom a DWI sequence was performed. Five patients showed a focal hippocampal signal alteration both on DWI and on conventional T2; this alteration was no longer detectable on follow-up MRI two months later. The presence of transient DWI and T2 alterations in the hippocampal formation suggests that TGA could have a multifactorial, non-vascular aetiology. The presence of local susceptibility to neuronal metabolic stress emerges as a likely hypothesis.

KEY WORDS: diffusion-weighted imaging, magnetic resonance, transient global amnesia.

Introduction

Transient global amnesia (TGA) is a benign clinical entity characterised by sudden-onset, transient memory disturbances without alteration of consciousness or personal identity. These memory disturbances usually resolve within 24 hours without long-term sequelae and recurrence is uncommon. Three main hypotheses on the pathogenesis of TGA have been proposed: ischaemia, epilepsy, and migraine, but definite evidence in support of these mechanisms is lacking (1,2). A transient cerebral ischaemic insult is the hypothesis most commonly proposed. Diffusion-weighted imaging (DWI) has become a powerful tool in the evaluation of patients with suspected stroke owing to its sensitivity and specificity, even for small areas of acute ischaemia. DWI has also been applied to TGA in order to gain further insight into the pathophysiology of this enigmatic condition. DWI detects high-signal (3) abnormalities involving the hippocampal-diencephalic system, even only a few hours after the onset of TGA. Sedlazek reported that the lesions were usually localised to the upper portion of the hippocampus, which corresponds to the CA1 region, known to be susceptible to hypoxia (3). In recent careful serial magnetic resonance imaging (MRI) studies (4,5), the temporal evolution of DWI lesions in TGA was shown to be distinct from that of “classic” acute focal cerebral ischaemia (6,7) and no correlation was found between cerebrovascular disease and TGA (4,5). The aim of the present study was to assess the validity of the “vascular hypothesis” in a group of patients hospitalised for TGA at our institute.

Materials and methods

Between May 2004 and May 2008, 65 patients presenting with acute or subacute TGA were observed at our centre. The diagnostic criteria for TGA were the following (8,9): 1. presence of an anterograde amnesia; 2. amnesia witnessed by an observer; 3. no clouding of consciousness or loss of personal identity; 4. cognitive impairment limited to amnesia; 5. no focal neurological or epileptic signs; 6. no recent history of head trauma or seizures; and 7. resolution of symptoms within 24 hours. All the patients had a standard neurological examination on admission and follow up and underwent a structured interview to assess vascular and non-vascular risk factors (arterial hypertension, diabetes, hyperlipidaemia, smoking, acute myocardial ischaemia, arrhythmias, peripheral artery disease) and to establish the possible presence of a history of cardiovascular and/or neurological disease. A conventional brain MRI using SE and FLAIR images was performed in 29 out of 65 patients using a 1.5 Tesla scanner (Philips, Eindhoven, the Netherlands); 21 patients also underwent DWI with the following parameters: repetition time (TR) 3812 ms, echo time (TE) 91 ms, slice thickness (SL) 4 mm, GAP 1, NSA 1. In addition, quantitative apparent diffusion coefficient (ADC) maps were calculated on a voxel basis.
Focal signal alterations in the hippocampal region were identified by consensus between observers (E.A., A.P.). A punctate hyperintensity both on T2 and DWI had to be detectable and correspond to the decreased diffusion as seen in the ADC maps.

Results

Of the 29 patients submitted to conventional brain MRI, 21 (9 males, 12 females, mean age 66 years ± 7, age range 52-84 years) also underwent a DWI sequence, performed using a new 1.5 Tesla scanner. Fifteen of the TGA patients in the DWI group had hypertension; of these, nine also had also dyslipidaemia and three were smokers. No patient reported a history of cardiovascular and/or neurological disease. All the brain MRI studies were performed within 8 to 48 hours of the clinical onset.

Five patients showed, on DWI, small (1-2 mm) punctate high-signal lesions in the hippocampus unilaterally; in only three of them, possibly as an effect of scan timing, these were found to correspond to a focal hyperintensity on conventional T2-weighted images (Fig. 1). On transverse DWI, the lesions were found to be located in the lateral portion of the hippocampus in four of the patients and in the parahippocampal gyrus in the other, these locations corresponding to small areas of low signal intensity on the ADC map. All the lesions were unilateral and no side prevalence was observed (they were located in the right hippocampus in two patients and in the left hippocampus in the other three).

The punctate hippocampal signal alterations were not detected two months later in the two patients who underwent a follow-up brain MRI (Fig. 1, A3-B3). In four of the five TGA patients with focal hippocampal hyperintensity on DWI, small lacunar infarcts were also detectable on conventional MRI (in three patients in the subcortical frontal white matter bilaterally, and in one patient in the periventricular white matter and corona radiata).

Discussion

Clinical and experimental data show that hippocampal neurons are critically involved in the process of memory consolidation, fulfilling a relay function in direct and polysynaptic intrahippocampal circuits. Lesions to this area are sufficient to produce a clinically significant memory impairment (10,11). Several imaging studies found positive DWI in mesiotemporal structures of patients with TGA (4). The reported frequency of signal abnormalities on DWI in patients with TGA varies widely, from 0% to 84% (5). There are several possible explanations for this discrepancy among the literature results:

- the detectability of the lesion depends on MR scanner performance (being higher with 3.0 Tesla units) and on the sequences adopted;
- the low lesion detection rate on DWI during the first hours after the clinical onset could be due to the dimension of the lesion itself: in some cases the MR imaging section can be thicker than the lesion;
- not all the studies submitted all their patients to brain MRI with DWI at the same time from the clinical onset: the period ranged from within a few hours to 48 hours. The literature cites an instance in which a small percentage of hippocampal lesions were missed by radiologists due to a lack of experience (12).

Our data show unilateral and focal hippocampal punctate lesions on DWI in five of the 21 patients undergoing this investigation; a corresponding T2 signal alteration was found in three of them.

A signal alteration on DWI does not always indicate ischaemia; it has also been seen in other conditions such as multiple sclerosis, seizures, and venous thrombosis (13). In fact, DWI hyperintensity in these pathologies, not usually being either punctate or restricted to the hippocampus, does not signal the presence of cytotoxic oedema and it may be accompanied by signs of vasogenic oedema. The variety of potential pathophysiological processes and the lack of unequivocal circumstantial evidence make it extremely difficult to be certain of the pathophysiological mechanism of hippocampal lesions in TGA.

Other hypotheses, including thromboembolism, cerebral venous congestion induced by Valsalva-like activities, and vasoconstriction caused by hyperventilation (12), have been considered. As regards the thromboembolic hypothesis, some previous studies have shown no association between TGA and clinical vascular risk factors (i.e. high blood pres-
sure, hypercholesterolaemia, diabetes, obesity) (14): the incidence of vascular risk factors in patients with TGA is similar to or lower than that found in patients with transient ischaemic attack (TIA), and TGA patients do not show an increased risk of stroke or TIA compared with control subjects (1,15).

The literature to date contains no strong evidence of a single aetiology in TGA and Toledo et al. (4), on the basis of their experience, even cast doubt on the hypothesis of arterial ischaemia as a cause of TGA on account of the presence of delayed and reversible DWI lesions. Furthermore, the lack of significant carotid atherosclerosis and the low prevalence of cardioembolic disorders in their series are features that differ from what is usually observed in patients with TIA or minor stroke.

The majority of our TGA patients had only one cerebrovascular risk factor (hypertension), while only three had three risk factors (hypertension, dyslipidaemia, smoking); however, a history of previous strokes was not observed in any of the four patients with focal hippocampal hyperintensity on DWI who showed small lacunar infarctions (small ischaemic lesions) on their conventional brain MRI.

The complete and uniform reversibility of the focal hippocampal hyperintensity and the lack of post-lesion structural sequelae do not fit in with the time course and evolution of a classic ischaemic lesion, which starts with a cytotoxic (DWI/ADC) oedema and results in gliotic sequelae on T2 (16). In our study, all the five patients showed cytotoxic oedema on the first MRI examination carried out, but in the two patients who underwent a second brain MRI two months later, the hippocampal lesion was no longer detected at the follow up.

On these bases, we consider that the local anatomical and functional characteristics of the hippocampus, too, could play a role in the unusual timing of the lesion detection.

The hippocampal artery supplies an internal anastomosis that links an upper and a lower artery creating a watershed area called “the hypoxia-susceptible sector of Sommer” and it has previously been demonstrated that the CA1 region of the hippocampus is a brain area particularly vulnerable to ischaemia (17). The signal alteration observed on DWI and T2-W images is usually localised in this area. The Sommer sector of the cornu ammonis also shows a selective vulnerability to metabolic stress that, within one to three days of hypoxia, leads to glutamate- and calcium-induced apoptosis-mediated neuronal death of the affected neurons. On this basis, it is well known that a variety of stressful events including physical activity and emotional stress could precede TGA in many cases. Emotional arousal has been suggested to lead to metabolic disturbances, mainly enhanced glutamate release, which would in turn account for the increased energy requirements. Pantoni et al. (1) hypothesised that functional rather than organic mechanisms are involved in TGA, citing evidence for a possible role of anxiety, stress and emotional arousal. This could be the basis for the occurrence of transient changes in brain metabolism during TGA in older subjects with age-related small-vessel alterations (18). Lewis proposed another hypothesis (19): that there could exist a causal relationship between cerebral venous congestion due to Valsalva-like activities and TGA. In support of this hypothesis, Sander et al. (20), on the basis of a greater extent of internal jugular valve incompetence in patients compared to controls, suggested that TGA may be due to venous congestion and consequent venous ischaemia at the level of the bilateral diencephalic or hippocampal structures. In fact, they (20) examined the changes in the internal jugular venous flow pattern in patients with TGA and in age-matched and sex-matched controls using duplex ultrasonography during Valsalva manoeuvres. A retrograde flow component was seen more frequently in the TGA group than in the controls (21,22).

Our results, on the other hand, showed that the signal detected on DWI corresponded to decreased diffusion as seen in the ADC map and can thus be attributed, as an initial hypothesis, to cytotoxic oedema unrelated to a venous infarct (as the latter would have caused vasogenic-type oedema).

A DWI lesion is thus a non-specific finding with several possible underlying mechanisms, probably all leading to focal energy failure. The observed signal changes reflect a common pathway of CA1 neurons in response to acute glutamate-induced cellular stress. As Sledzczek pointed out (3), “high metabolic rates leading to relative hypoperfusion in the subcortical vascular borderzone in patients with mild vascular changes are associated with delayed ischaemic mechanisms. Similar processes occurring at a hippocampal level could be the natural history of sporadic TGA.”

In conclusion, our experience supports the recent literature results in patients with TGA. Conventional brain MRI and DWI demonstrated a focal reversible signal alteration in the lateral portion of the hippocampus both in patients with other signs of cerebrovascular disease and in patients without any other lesions.

Pathophysiological mechanisms other than focal ischaemia in cerebrovascular disease need to be explored further as causes of a temporal dysfunction in memory-related structures, as indicated by more recent reports (10,11).

It is very likely that TGA is caused by a combination of multiple aetiopathological factors.

Finally, our experience in a small group of patients using a 1.5 T scanner suggests the need for greater standardisation of brain MR sequences, in terms of both orientation and thickness, to allow an adequate prospective analysis, and for serial follow-up scans in order better to highlight the evolution and the pathogenesis of TGA.

References

5. Huber R, Aschoff AJ, Ludolph AC, Riepe MW. Transient global amnesia. Evidence against vascular ischemic etiolo-