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ORIGINAL ARTICLE

Transient global amnesia and hippocampal diffusion restriction: an overlooked radiological finding

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Abstract

Transient global amnesia (TGA) is characterized by isolated sudden anterograde amnesia. Diffusion restriction can be observed in the hippocampus on DWI-MRI at varying rates in TGA patients. This study analyzes the prevalence and characteristics of the hippocampal diffusion restriction (HDR), its relationship with vascular risk factors, and the prevalence of lesions overlooked in routine reports. 91 patients diagnosed with TGA at a tertiary hospital between 2011 and 2022 were evaluated retrospectively. The mean age was 64.8 ± 7.3 years, and 63.7% of patients were female. 75.8% of the patients had at least one vascular risk factor. Focal diffusion restriction was detected in 17 patients (18.5%) on DWI-MRI, with only one being extra-hippocampal. 81.2% of HDR was detected when DWI-MRI scan was performed between 12 and 96 h after the onset of symptoms. HDR was detected most when the imaging was performed in 24 to 48 h ($p = 0.03$). There was no correlation between the duration of symptoms and the detection rates of HDR ($p = 0.55$). In 9 patients (53% of 17) diffusion restriction was not specified in routine radiology reports. Although focal ischemia, venous flow abnormalities, migraine and epileptic phenomena have been suggested in its etiology, TGA is a clinical condition of which pathophysiology has not been determined clearly. Signal changes observed in DWI-MRI has led to discussions that cerebrovascular etiology may play a role, yet more comprehensive studies are required to prevent and manage TGA. HDRs can be overlooked in routine reports. Therefore, the DWI-MRI images of patients with TGA should be examined vigilantly.

Keywords Transient global amnesia · Diffusion MRI · Hippocampal diffusion restriction · Differential diagnosis

Introduction

Transient global amnesia (TGA, 5–32/100 000) is a clinical syndrome characterized by acute anterograde amnesia not accompanied by any other neurological symptoms [1]. Although diagnostic criteria are available, given that there are no specific tests, the diagnosis is purely clinical [2, 3]. Different mechanisms are claimed as etiology of TGA, such as cerebrovascular (both focal ischemia and venous drainage abnormalities), migraine, and epileptic phenomena [1, 4, 5].

The hippocampus and the comprising temporal lobe are the main structures of memory. Diffusion restriction in hippocampus can be observed in 8 to 84% of patients with TGA in different populations and suggested as a putative cause [4, 6]. This study investigates the prevalence and characteristics of hippocampal diffusion restriction in patients diagnosed with TGA and their relationship with vascular risk factors as well as how frequently those lesions are underdiagnosed.

Methods

From 2011 to 2022, among all patients presenting to the neurology outpatient clinics or emergency department of Başkent University Hospital in Ankara, Turkey, 252 adult patients were preliminary diagnosed with TGA by a neurologist according to the diagnostic criteria of Caplan [3] and Hodges and Warlow [2]. Following the verification of diagnosis by the authors, the patients who applied to the hospital in 10 days subsequent to their complaints and who has DWI-MRI data were included in the study, retrospectively. One hundred sixty-one patients were excluded from the analysis either because they did not undergo a DWI-MRI scan at onset or MRI scans were performed more than 10 days after symptom onset or the diagnosis was different at the end of

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evaluation. The remaining 91 patients were included in the analysis. The data of the patients enrolled were analyzed retrospectively in accordance with institutional regulations as approved by the Başkent University Ethics Committee for Clinical Investigations (approval number: KA23/176).

Routine blood tests, an electrocardiogram, and an electroencephalogram (EEG) were performed in patients with TGA during the index hospitalization/evaluation. All MRI were obtained using a 1.5-Tesla scanner and all serial MRI included DWI sequences. A DWI scan was considered positive if the scan revealed an area of hyperintensity with a corresponding hypointensity on the ADC map in hippocampal area, named as hippocampal diffusion restriction (HDR). The region of hippocampus was also noted as head, body, or tail. All MRI scans were reviewed by either of three authors (II, ZK or GG) and compared with the routine radiology reports. Comorbidities were noted based on medical history. Accompanying MRI findings were recorded as white matter hyperintensities, silent ischemic infarcts, and cerebral micro bleedings. Antithrombotic treatments were recorded as acetylsalicylic acid, clopidogrel and anticoagulants (either oral or parenteral); time of the day as morning, noon, afternoon, evening, and night; triggers as physical effort, hot showers, psychological stressors, sexual intercourse, and infections. The patients were evaluated for carotid artery stenosis with MR angiography (MRA) or Doppler ultrasonography and the results were recorded as intima media hyperplasia, unremarkable stenosis, and stenosis of either < 50%, 50–70% or > 70%.

Statistical analyses were performed using the Statistical Package for the Social Sciences version 25 (SPSS, USA). The clinical characteristics of patients with TGA with diffusion restriction on hippocampus were compared with those with a normal brain DWI-MRI. The chi-square or Fisher's exact test was used for the categorical variables, the Student's *t* test and Mann–Whitney *U* tests were used for the continuous variables. Post hoc processes following chi-square test were based on the adjusted residual values calculated as the raw residuals divided by an estimate of the standard error Spearman's rank test was used for correlation analysis. *p* value less than 0.05 (two-sided) was appreciated as significant.

Results

Of 91 patients enrolled, 58 (63.7%) were female with an age of 64.8 ± 7.3 (mean ± SD) at the diagnosis. The median symptom duration was 180 min (IQR 240 min). The main cerebrovascular risk factors were hypertension (HT, 61.5%), hyperlipidemia (HL, 37.4%), and coronary artery disease (CAD, 13.2%). Detailed information of patients can be found in Table 1. Psychological stressors were the most common trigger (22.0%), followed by hot showers (16.5%) and physical effort (6.6%), while 51.6% of the patients did not define one. Migraine headache coincided in 8 patients (8.8%). TGA was most frequently diagnosed in winter (31.9%) and in the morning (34.1%). There was neither circadian rhythm ($p = 0.64$) nor seasonal variance ($p = 0.19$) in the cohort.

Diffusion restriction (DR) on DWI-MRI scans were detected in 17 patients (18.7%). All but one had positive DWI-MRI scan on hippocampus, consisting of 10 patients (62.5% of 16) with DR on right hippocampus, 3 (17.7%) on left hippocampus, and 3 (17.7%) on both hippocampi (Fig. 1).

The HDRs were located on the head region of 5 patients (31.2% of 16) and the body region of 11 (68.8%). It was remarkable that more than half of the cases (9 patients, 53% of 17 patients) were misreported as having normal DWI-MRI scans. DWI-MRI scans were performed in less than 12 h in 22 patients (24.2%), in 12 to 24 h in 25 (27.5%), in 24 to 48 h in 10 (11.0%), in 48 to 72 h in 8 (8.8%), in 72 to 96 h in 7 (7.7%) and in > 96 h of symptom onset in 19 (20.9%). It was found that the HDR was detected most when the imaging was performed 24 to 48 h after symptom onset ($p = 0.03$, chi-square test). There was no correlation between symptom duration and the detection rates of HDR ($p = 0.55$, Spearman's rank test). HDR detection was most common when the incident happened in the morning (53.3% of patients).

Considering one of the proposed mechanisms of hippocampal diffusion restriction is cerebrovascular disease (CVD), related risk factors were assessed. No difference was found between patients with negative and positive diffusion MRI regarding DM, CAD, HL ($p = 0.43$, 0.69 and 0.99, respectively, chi-square test). On the other hand, concomitant hypertension was significantly low in the HDR group ($p < 0.001$, chi-square test). Of 16 patients whom HDR was detected, 10 (62.5%) were antithrombotic treatment-naïve at the time of diagnosis, while 3 (18.8%) were on acetylsalicylic acid, 1 (6.3%) was on clopidogrel, 2 (12.5%) were on warfarin (INR levels were not in desirable range). Stenosis of internal carotid arteries (ICAs) were assessed in 68 patients (74.7% of total). 5 patients (5.5%) had < 50% stenosis, 2 patients (2.2%) had 50–70% stenosis, and one (1.1%) had > 70% stenosis on either of ICAs detected by MRA. Additional 6 (6.6%) patients had nonstenotic calcific plaques and 3 (3.3%) patients had intima media hyperplasia on doppler ultrasonography. 12 patients (75.0% of 16 with HDR) had no stenosis and the remaining 4 (25.0%) were not assessed with any vascular imaging modality. 61 patients (67.0% of all) were treated with acetylsalicylic acid, 12 (13.2%) with clopidogrel, 1 (1.1%) with dual antiplatelet treatment, and 6 (6.6%) with oral anticoagulants. Antithrombotic treatment was not initiated for 8 patients (8.8%) (Table 2).

Table 1 Clinical features and characteristics of patients with or without hippocampal diffusion restriction (HDR)

	With HDR ($n=16$)	Without HDR ($n=75$)	p value[¥]
Age (mean ± SD)	63.6 ± 5.8	65.0 ± 7.6	0.47
Female (n (%))	12 (75.0)	46 (61.3)	0.30
Symptom duration in minutes, (median (IQR))	210 (170)	180 (240)	0.55
	***n* (%)**	***n* (%)**	
Vascular risk factors			
Hypertension	3 (18.8)	53 (70.7)	*< 0.001**
Diabetes mellitus	1 (6.3)	9 (12.0)	0.69
Hyperlipidemia	6 (37.5)	28 (37.3)	0.99
Coronary artery disease	1 (6.3)	11 (14.7)	0.69
Migraine	2 (12.5)	6 (8.0)	0.63
Carotid artery stenosis (> 50%)	0 (0.0)	3 (4.0)	–
Cerebrovascular disease history	0 (0.0)	8 (10.7)	–
TGA history	1 (6.3)	8 (10.7)	0.99
Antithrombotic treatment at diagnosis			0.09
Acetylsalicylic acid	3 (18.8)	9 (12.0)	
Clopidogrel	1 (6.3)	1 (1.3)	
Warfarin	2 (12.5)	1 (1.3)	
Other	1 (6.3)	0 (0.0)	
Treatment-naïve	10 (62.5)	63 (84.0)	
Timing of MRI scan			0.03*
< 12 h	2 (12.5)	20 (26.7)	
12–24 h	6 (37.5)	19 (25.3)	
24–48 h	4 (25.0)	6 (8.0)	
48–72 h	0 (0.0)	8 (10.7)	
72–96 h	3 (18.8)	4 (5.3)	
> 96 h	1 (6.3)	18 (24.0)	
Accompanying MRI findings			0.055
White matter hyperintensities	7 (43.8)	49 (70.0)	
Silent ischemia	1 (6.3)	0 (0.0)	
Microbleeds	0 (0.0)	1 (1.4)	
None	8 (50.0)	20 (28.6)	

SD: standard deviation, IQR: interquartile range

[¥]Chi-square or Fisher's exact test were used for categorical variables. Symptom duration and age were compared using the Mann–Whitney U test and Student's t test, respectively

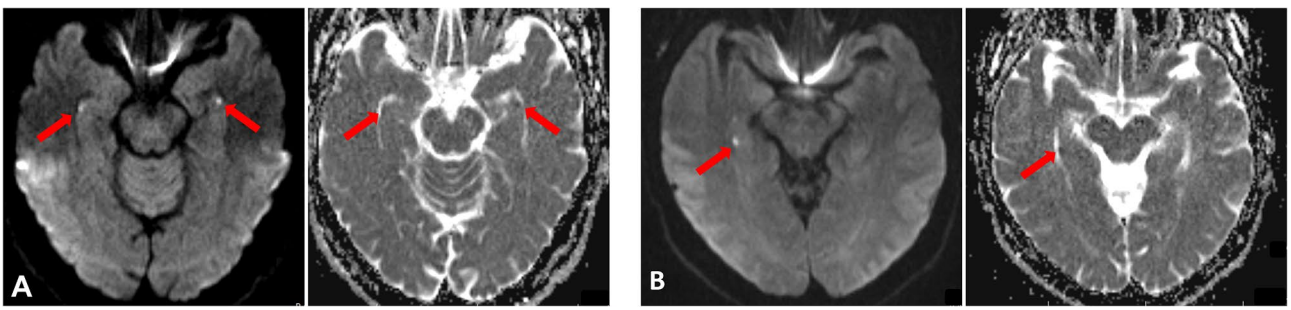

Fig. 1 Diffusion restriction on hippocampus, DWI-MRI, B1000 images. **A** Bilateral diffusion restriction (red arrows) as a hyperintense lesion on B1000 sequence with a corresponding hypointense lesion on ADC sequence at the head region. **B** Right unilateral diffusion restriction at body of hippocampus

Table 2 The rates of diffusion weighted imaging (DWI-MRI) and hippocampal diffusion restriction (HDR)

Imaging time	Patients with DWI-MRI (*n*, % of all)	Patients with normal DWI-MRI (*n*, % of patients with DWI-MRI)	Patients with HDR (*n*, % of patients with DWI-MRI)	*p* value
< 12 h	22 (24.2)	20 (26.7)	2 (9.1)	0.03
12–24 h	25 (27.5)	19 (25.3)	6 (24.0)	
24–48 h	10 (11.0)	6 (8.0)	4 (40.0)	
48–72 h	8 (8.8)	8 (10.7)	0 (0.0)	
72–96 h	7 (7.7)	4 (5.3)	3 (42.9)	
> 96 h	19 (20.9)	18 (24.0)	1 (5.3)	

77 patients (84.6%) were evaluated with an EEG in order to evaluate amnestic seizures. Of those patients, 72 (79.1%) had normal inter-ictal EEG findings, whereas 5 (5.5%) had nonspecific EEG changes. One of those 5 patients also had unilateral hippocampal diffusion restriction.

32 patients were lost to follow up after the index incident. Of the remaining 59 patients, 9 (15.3%) had another episode of TGA and 1 (1.7%) had stroke. The patients with recurrent TGA attacks had similar demographic and vascular risk factors compared with the rest of the population and one of them had HDR.

Discussion

In this retrospective study of 91 patients with unambiguous diagnosis of TGA, 17.6% have presented with hippocampal diffusion restriction. Only one of the patients had clinically silent, nonhippocampal lesion on DWI-MRI. Although various clinical entities such as status epilepticus, seizures, infections, inflammatory diseases, or acute ischemic infarction of hippocampus [7] may create an HDR, it is a valuable finding supporting TGA diagnosis, especially when it is not witnessed [8]. The studies from different centers detected HDR at varying frequencies [8–10]. Different sample sizes, imaging techniques or study groups from different ethnicities may be the reasons for this variability, so as misinterpretations of images by radiologists. Errors and discrepancies in radiological reports were stated to be encountered in 3–5% of studies, even at much higher rates in selected studies [11]. More than half of the patients in our study had a negative radiology report while their imaging showed HDR. A similar situation has also been reported previously suggesting that focal hippocampal diffusion restrictions can be overlooked in routine reports [6].

It is claimed that HDR develops in time, is temporary, and > 80% of the lesions were detected when the imaging was performed between in 12 and 96 h [12, 13]. Conforming these results, 81% of the patients in our cohort with HDR were imaged in the aforementioned time window. The location of lesions in hippocampus may differ, yet most studies defined them at body/CA1 region in parallel with our study [14, 15]. There was a preference for right-sided hippocampal lesions contrasting previous studies which requires further investigation [9, 10, 12, 16].

Except for hypertension, individuals with HDR had similar cerebrovascular risk factors compared with the cases with negative DWI-MRI scan that may weaken the theory of ischemic etiology of TGA. Existing studies have conflicting results regarding association of hippocampal DWI-MRI lesions with ischemia or stroke risk [17, 18]. Different studies agree that risk of a following ischemic stroke is similar to the general population following TGA [12, 14, 18]. In our cohort, the patients having cerebrovascular risk factors were put on antiaggregant therapy for primary prophylaxis to cerebrovascular disease even though TGA may not be associated with CVD directly. Antithrombotic treatment may not be necessary for patients without any vascular risk factors and a single TGA attack. HT was found to be protective for hippocampal focal ischemia which could be reasoned with preserved cerebral perfusion during the metabolically challenging situation creating TGA clinical findings. A recent case report pointed out unilateral hippocampal hypoperfusion 3 h after TGA symptom onset as a potential mechanism [19]. Migraine was previously reported to be a risk factor for TGA [20], yet these data could not be confirmed in our study given that less than 10% of patients have migraine headache.

Our study may be presented with limitations such as small sample size, lack of some of the information regarding triggers or chronological variations due to retrospectively collected data. Also, a minority of patients had a follow-up MRI, thus some patients who developed hippocampal diffusion restriction at later time points might be left out as having negative DWI-MRI results.

Overall, our study demonstrated that there was no association between patient characteristics, cerebrovascular risk factors except for hypertension, chronological variation, symptom duration and presence of hippocampal diffusion restriction in patients diagnosed with TGA. These results suggest that HDR may be an imaging finding related to the disease nature rather than a risk factor for further ischemic events. In view of the fact that hippocampal diffusion

restrictions may be overlooked, the DWI-MRI images of patients suggesting diagnosis of TGA should be examined vigilantly.

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Author contributions II and ED conceptualized and designed the study. II, ZK, GG, and BA gathered and analyzed the data. ED supervised the analyses. II, ZK, and ED wrote the manuscript. All authors read and commented on the manuscript critically.

Data accessibility The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical statement and declarations The work has not been published previously, it is not under consideration for publication elsewhere, its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

This study was approved by Research Committee and Ethics Committee of Baskent University (project No: KA 123/176).

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