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ORIGINAL COMMUNICATION

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Transient Global Amnesia

Evidence against vascular ischemic etiology from diffusion weighted imaging

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Abstract The etiology of Transient Global Amnesia (TGA) is still obscure. Diffusion-Weighted-Imaging (DWI) provides conflicting evidence concerning a possible vascular ischemic cause in mesiotemporal structures including the hippocampal region. The question remains open whether conflicting observations resulted from different observation times. DWI was performed at a time interval with known sensitivity for detection of ischemia. Ten patients (5 male, 5 female; mean age of 63 ± 9, range 41–71 years) with typical TGA were investigated at an average delay of 18 hours (range 6 to 44 hours) between onset of symptoms and magnetic resonance imaging (transversal DW-, T1W- and T2W-MRI). Five patients received apparent-diffusion-coefficient (ADC)-mapping. Cerebrovascular studies (ECG, TTE and extra/transcranial dopplersonographic and duplexultrasonic investigation) and EEG were normal in all patients. DW-MRI-sequences and ADC-maps, if performed, were normal in all patients. Conventional T2W-MRI in 3 out of 10 patients showed microangiopathic subcortical changes and lacunar strokes of older origin. We conclude that TGA does not result from a vascular ischemic etiology in the majority of cases.

Key words transient global amnesia · ischemia · diffusion weighted MRI · etiology

Introduction

Transient global amnesia (TGA) is clinically well defined. It is characterized by anterograde memory disturbance of sudden onset with impairment of orientation in space and time but undisturbed consciousness. Usually, the symptoms last for only a few hours followed by an almost complete restitution apart from a remaining short amnestic gap for the "core-period" of the episode [10]. However, the etiology of TGA remains obscure. [11, 18].

Several imaging studies have assessed patients during and upon recovery from the symptoms. CT and conventional MRI – have on very rare occasions demonstrated pathological alterations of heterogeneous nature in mesiotemporal structures. Results from SPECT and PET methods are ambiguous, too. In two early case reports a right prefrontal reduction of blood flow and oxygen consumption was found [4, 6]. Other studies, however, found reduced blood flow in mesial temporal areas unilaterally [13, 21] or bilaterally [27].

Diffusion-weighted magnetic resonance imaging (DWI) is a recently developed technique to detect cerebral ischemia in a very sensitive fashion [8, 17, 20, 29, 30] and within a short time after the event [20, 29, 30]. Depending on the duration of symptoms diffusion imaging is positive even in transient ischemic attacks [16]. Some case reports found postive DWI in mesiotemporal structures of patients with TGA [3, 22, 31]. However, in two recent series with 8 and 10 patients conflicting results of DWI were reported [7, 28] and it remains an open ques-

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tion whether TGA always results from the same pathology. One investigation reported an elevated DWI signal uni- or bilaterally in the temporal lobe in 7 of 10 patients with TGA [28] while the other did not find DWI signals in any of 8 investigated patients [7]. The latter report speculated whether the conflicting results might be due to differences in the time of examinations. In the study by Strupp et al. patients were tested with a delay of 36 hours to six days after the episode [28]. In contrast, Gass et al. investigated the patients between 1 and 16 hours after onset of symptoms [7]. In addition, both studies employed different MRI-protocols.

It was the goal of the current study to investigate diffusion weighted magnetic resonance imaging in TGA patients at a time interval with known sensitivity for detection of ischemic lesions.

Patients and methods

Patients

The study was conducted retrospectively on 14 patients with suspected transient global amnesia admitted to the neurology ward of the University of Ulm between January 1998 and January 2001. The duration of symptoms was found on admission from the accompanying persons, mostly family members. Diagnosis of TGA was verified retrospectively according to the criteria of Caplan [5].

The basic demographics are shown in Table 1. In all except two cases it was the first such event. One woman had had a similar episode about 5 years previously, which was classified as TGA as well. A second relapse was in a man reported to suffer from a similar attack about 3 years previously. The medical history of this patient included generalised epileptic seizures more than 20 years before admission. However, after years of antiepileptic drug treatment medication had been dropped and no further epileptic events occurred for more than 10 years up to onset of TGA. For this patient the routine electroencephalogram (EEG), EEG with photic stimulation, and the EEG upon sleep deprivation were normal. This subject therefore was included also in the final analysis. All other subjects had no history of epileptic seizures. Routine EEG and EEG with photic stimulation were normal in all subjects. None of the patients reported a recent head trauma and all had regular neurological and general internal examinations. Doppler and duplex sonographic investigation of the extra- and intracranial arteries did not show any high grade stenosis or thrombosis. Cardiac diagnostics with electrocardiogram, transthoracic and in two cases transesophageal echocardiographic examinations did not show any relevant pathological findings. One patient suffered from a previously unknown and asymptomatic intermittent tachyarrhythmia absoluta. All other patients did not show cardiac illness with high embolisation risk. None of the patients had suffered a stroke previously or was aware of preceding transient ischemic attacks (TIA).

None of our patients reported frequent headaches or migraine-like events in their own history. One patient noticed headaches prior to the episode and one other during the attack at the time of admission. Headache subsided within less than three hours. In both cases a lumbar puncture was performed to rule out meningitis. Also, lumbar puncture was performed on the patient suffering from a relapse of TGA to rule out chronic central nervous inflammatory disease. All these tests gave normal findings in all cases as well as routine laboratory-tests on admission of all other patients, thus excluding serious metabolic and electrolytical disorders or other serious health damages.

In none of our cases was emotional stress or physical exercise reported as a symptom-preceding event spontaneously or on inquiry. All patients left our hospital upon cessation of the episode and completion of the diagnostic procedure. Owing to the short in-hospital time and admission on weekends MRI was carried out in only 10 of 14 patients. Thus four patients were excluded as only CT was performed.

MRI

In total 10 out of the 14 suspected patients were examined by MRI using a 1.5 T clinical MR tomograph (Magnetom Symphony, Siemens, Erlangen, Germany) with echoplanar imaging capability using an extended stroke protocol: Transverse (repetition time(TR)/echo time(TE) 537/15ms; field of view (FOV) 230×230mm^2; matrix 192×256; slice thickness (SL) 5 mm; acquisition time (TA) 1:51min) and sagittal (TR/TE 466/15ms; FOV 230×230mm^2; matrix 192×256; SL 5 mm; TA 2:12min) spinecho T1w, transverse turbospin echo T2w (TR/TE 2850/115ms; FOV 230×201mm^2; matrix 224×512; SL 5 mm; TA 4:32min; echo train length (ETL) 5, transverse diffusion weighted echoplanar imaging (EPI; TR/TE 220/139ms; FOV 230×230mm^2; matrix 128×128; SL 5 mm; TA 0:18min; b = 1000sec/mm^2), transverse FLASH (TR/TE 584/18ms; flip angle (FA) 20°; FOV 230×201mm^2; matrix 168×128; SL 5 mm; TA 1:24min), coronal fluid attenuated inversion recovery (FLAIR; TR/TE/inversion time (TI) 9000/130/2400 ms; FOV 230×201mm^2; matrix 201×256; SL 5 mm; TA 1:38min), and time of flight MR angiography (TOF MRA) of the intracerebral arteries. In addition, quantitative apparent diffusion coefficient (ADC) maps were calculated on a voxel basis in six out of the eleven patients.

Table 1 Demographics, medical history, and further results.

Pat.Nr.	Age	Sex	Concomitant diseases	VRF	Headache?	EEG	CSF	Doppler	Relapse?
1	70	M		–	No	Normal	–	Normal	No
2	64	F		AHT	During	Normal	Normal	Normal	No
3	66	F		AHT	No	Normal	–	Normal	No
4	61	M		–	No	Normal	–	Normal	No
5	59	F		AHT	No	Normal	Normal	Normal	yes, 2nd
6	72	F	Epilepsia	–	No	Normal	Normal	Normal	yes, 2nd
7	41	M		–	Before onset	Normal	Normal	Normal	No
8	71	M		AHT	No	Normal	–	Normal	No
9	61	F		AHT	No	Normal	–	Normal	No
10	63	M		–	No	Normal	–	Normal	No

M male, *F* female, *VRF* vascular rsik factors, *AHT* arterial hypertension, *HLP* hyperlipoproteinemia. Headache is classified yes if there was headache along the episode or known frequent headache of any kind.

All images were displayed on a freestanding workstation and evaluated by two neuroradiological experienced reviewers (A. A., R. H.) for signs of fresh or older ischemic lesions with special interest in diffusion abnormalities and careful evaluation of the parahippocampal and hippocampal areas.

Results

In 10 patients transverse DW-MRI-Images with special regard to the mesiotemporal structures and the hippocampal regions on both sides were carried out. In none of these cases was a hyperintense signal detected (Fig. 1, Table 2). Similarly, in all 5 performed ADC maps normal results were found. Patients were examined with an average delay of 18 hours after onset of symptoms (range 6 to 44 hours, 5 out of 8 tested in between 8 to 24 hours) with most of them in the early recovery period (Table 2).

Additionally all patients received conventional transversal T1W- and T2W-MR imaging as well as sagittal T1W imaging. Corresponding to the missing pathological features in DW-MRI images all conventional pictures were normal without any sign of morphological changes in either temporal lobe. Nevertheless, there were signs of

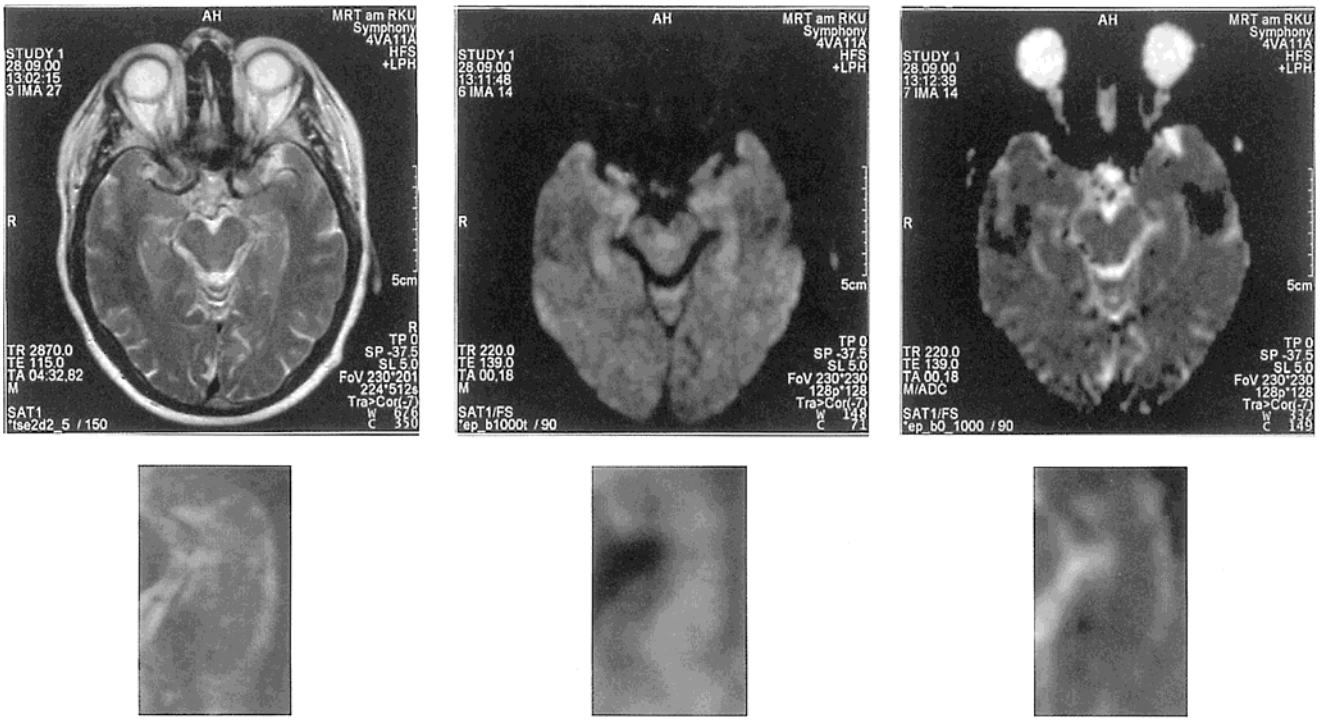

Fig. 1 Transverse T2w and diffusion weighted echoplanar imaging (DWI, b = 1000s/mm^2) with the corresponding ADC map of patient 2. Smaller images demonstrate the enlarged left mesiotemporal area. All images were performed 8 hours after onset of symptoms. Absence of hyperintense signals in DWI corresponds to normal ADC mapping without structural damages in T2w.

Table 2 Symptoms and results of DWI.

Pat.Nr.	Age	Sex	DWI (h)*	Total Duration of symptoms	DW-MRI finding	ADC map	Structural MRI
1	70	M	12		Normal	–	Normal
2	64	F	8		Normal	Normal	Normal
3	66	F	8		Normal	Normal	SMC
4	61	M	44		Normal	Normal	Normal
5	59	F	12		Normal	–	Normal
6	72	F	60		Normal	Normal	Cerebellar atrophy
7	41	M	8		Normal	–	
8	71	M	28		Normal	–	SMC
9	61	F	8		Normal	Normal	SMC
10	63	M	3		Normal	–	Normal

M male, *F* female, *SMC* subcortical microangiopathic changes, * after onset of symptoms. Headache is classified yes if there was headache along the episode or known frequent headache of any kind.

subcortical white matter changes in three cases due to an elevated microangiopathic risk-profile with arterial hypertension in these patients, of whom two additionally suffered from hypercholesterinemia.

Discussion

The etiology of the TGA-syndrome remains controversial [18]. One hypothesis has been transient cerebral ischemia. In support of this hypothesis is the sudden onset of the symptoms and case-based evidence from SPECT- and PET-imaging [13, 21, 27]. Similarly, symptoms mimicking transient global ischemia have been reported subsequent to cerebral angiography especially of the vertebrobasilar arteries, with well known risk of cerebral ischemias in the hippocampal formation and the mesiotemporal structures [31].

While a previous study reported DWI-hyperintense areas in 70 % of patients with spontaneous TGA [28] our study is in accord with Gass et al. [7], who did not show DWI-hyperintensities. Usually DWI is performed within several hours of onset of symptoms. In patients suffering from stroke DWI has been proven to be very sensitive and showed hyperintensity in about 94–100 % at 2 to 6 hours after onset of the symptoms [8, 20, 29, 30]. Even with transient ischemic attacks diffusion weighted hyperintense signals are observed in 50 % of patients rising to 70 % if symptom duration exceeds 12 hours [16]. In the present study the time between onset of symptoms and DWI was 18 hours. With a time interval of 18 hours the present study closes the gap in the studies performed by Gass et al. [7] and Strupp et al. [28]. We therefore conclude that the present study argues against an even transient ischemic origin of TGA.

DWI is known to be susceptible to artifacts such as "shine through" effects. Possible hyperintense signals on DWI therefore would have been needed to be verified by quantitative mesurements with the apparent diffusion coefficient (ADC) mapping to prove the significance of these findings. Even in spite of negative finding on the DWI-imaging, ADC mapping was performed in five of ten subjects in this study. In none of these investigations did the ADC map show a diffusion perturbance.

As diffusion-disturbances in DWI are etiologically rather unspecific it has been speculated that the pattern of changes found by Strupp, i. e. DWI-hyerintensities and failing equivalent pathological findings in conventional T2W- images, could alternatively indicate other than ischemic etiologies. Especially migraine was taken into consideration as precipitants and vegetative symptoms of migraine and TGA attacks overlap and patients with frequent headaches or known migrainic disease seem to be numerous in TGA patients [25, 32]. It has long been speculated that waves of spreading neuronal hypo- or depolarization cause especially the visual aura of migraine [2, 9]. In several animal models spreading depression was associated with brief reversible hyperintense DWI signal and positive ADC-signals [12, 14, 23, 26]. However, because of the regular ADC-maps in our study even a delayed onset due to a spreading-depression like syndrome is not supported. Moreover we have to emphasize that frequent headaches were not present in the medical history of our patients and only two of them accounted headaches just before or right upon the time of the amnestic syndrome.

Supported by ultrasonic investigations a Valsalva-maneuver was discussed as an underlying mechanism for TGA. High venous pressure could result in venous congestion [1, 18, 24] which might cause TGA via "transient venous ischemia" of the mesiotemporal structures. However, other known forms of venous congestion like venous-sinus thrombosis were demonstrated to cause at least transient DWI-abnormalities even with deep cerebral venous thrombosis [15, 19] so that such a mechanism is not supported either by our investigations. Beyond that no patient reported activities associated with a Valsalva-maneuver prior to the event.

In summary we conclude that the cause of TGA remains unidentified but a vascular ischemic etiology or spreading depression is highly unlikely in the majority of cases.

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