

Lack of Evidence of Acute Ischemic Tissue Change in Transient Global Amnesia on Single-Shot Echo-Planar Diffusion-Weighted MRI

A. Gass, MD; J. Gaa, MD; J. Hirsch, PhD; A. Schwartz, MD; M.G. Hennerici, MD

Background and Purpose—There is uncertainty concerning the etiology of transient global amnesia (TGA). Previous CT and MRI studies have indicated that permanent structural abnormality is rare in TGA. Diffusion-weighted (DW) MRI is very sensitive to early ischemic parenchymal changes and has recently demonstrated embolic infarction in the posterior cerebral artery territory in 2 TGA patients. We report the findings of DW MRI in 8 patients in acute stages of TGA.

Methods—Conventional and echo-planar DW MRI was performed in 2 patients in the active phase and 6 patients in the recovery phase (1 to 8 hours after cessation of anterograde memory dysfunction) of spontaneously occurring TGA.

Results—None of the patients showed signs of hyperintensity on DW images or hypointensity on quantitative apparent diffusion coefficient (ADC) maps to suggest regional decreases of water mobility or acute T2 changes on transverse or coronal slices.

Conclusions—We were unable to detect ADC or acute T2 changes with echo-planar DW MRI in patients with TGA, which suggests that mechanisms other than ischemic infarction may cause TGA. We did not identify spreading depression-associated changes of the ADC. Further refinement of MRI sequences may be necessary to detect subtle or transient signal change in brain parenchyma. (*Stroke*. 1999;30:2070-2072.)

Key Words: amnesia ■ hemiplegia ■ magnetic resonance imaging ■ stroke

Transient global amnesia (TGA) refers to a benign syndrome of sudden-onset alteration of behavior dominated by a temporary dysfunction of anterograde and recent retrograde memory lasting for several hours or even few days, with preservation of alertness, attention, and self-identity, without further neurological symptoms or signs. Although TGA is a well-documented clinical entity, there is uncertainty concerning the etiology and localization of neuronal dysfunction in TGA.^{1,2} Previous CT and MRI studies have indicated that permanent structural abnormality is rare in TGA, but altered perfusion has been demonstrated in various brain regions with positron emission tomography and single-photon emission CT.^{3,4}

Diffusion weighted MRI (DW MRI) has been a current focus of interest. It can detect early changes related to ischemia and abnormal brain activity. Cytotoxic cell swelling can be demonstrated before a net increase in parenchymal water causes T2-weighted (T2W) changes in stroke patients.⁵ TGA is a well-recognized potential complication after posterior circulation angiography, and recently small, acute embolic ischemic lesions were detected with echo-planar DW MRI in the medial basal temporal lobe in a patient with TGA after vertebral artery angiography.^{6,7} Another case study⁸

demonstrated 2 tiny foci of acute ischemia in the splenium of the corpus callosum and in the left parahippocampal gyrus in a patient with spontaneous onset of TGA. Strupp et al⁹ recently described signal changes in DW images without the subsequent development of permanent lesions, which suggests a mechanism other than infarction in TGA. In experimental models of focal ischemia with periinfarct depolarization and of spreading depression and epilepsy, transient reductions of the apparent diffusion coefficient (ADC) have been detected with DW MRI.¹⁰⁻¹² On the basis of those results, one may assume that DW MRI has the potential to detect permanent or transient ADC changes associated with ischemic tissue changes or irregular electrical activity in patients with TGA.

Subjects and Methods

Eight patients with spontaneous onset of TGA (6 women and 2 men, aged 56 to 77 years) who presented to the emergency room underwent MRI. All patients (and, additionally, in patients 6 and 8, a relative) gave written informed consent. The study had been approved by the local ethics committee.

All patients had been brought to the hospital by relatives or neighbors, and a reliable history was obtained from at least 1 witness in all cases. There was sudden-onset amnesia without disturbance of

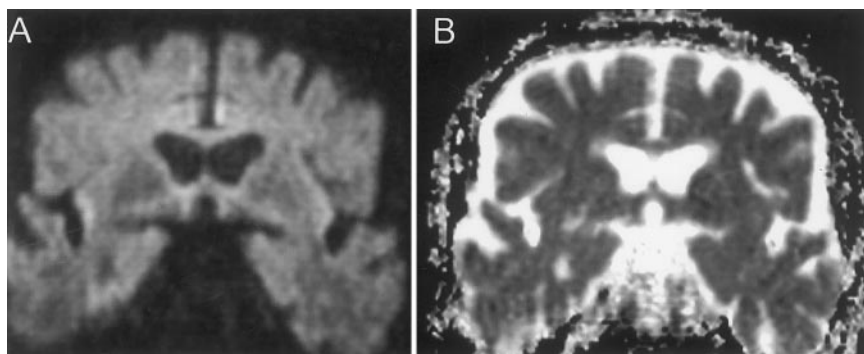
Received March 26, 1999; final revision received July 8, 1999; accepted July 9, 1999.

From the Departments of Neurology (A.G., J.H., A.S., M.G.H.) and Radiology (J.G.), Klinikum Mannheim, University of Heidelberg (Germany).

Correspondence and reprint requests to Dr A. Gass, NMR Research, Neurology/Radiology, Klinikum Mannheim, Theodor Kutzer Ufer, 68137 Mannheim, FR Germany. E-mail gass@neuro.ma.uni-heidelberg.de

© 1999 American Heart Association, Inc.

Stroke is available at <http://www.strokeaha.org>



Normal coronal DW image (average of 3 diffusion-sensitized directions, $b=1000$ s/mm²) (A) and map of the ADC (B) of patient 6.

vigilance or cognition. There was no history of head trauma or previous stroke. Patient 1 reported having occasional episodes of migraine since her twenties until 15 years ago, and patients 3 and 5 reported occasional tension headaches (Table). All patients had normal neurological examinations, except for the memory deficit, and normal routine medical examinations (physical examination, ECG, conventional or transesophageal echocardiography, and laboratory tests). Doppler and duplex studies excluded significant obstructive lesions or sources of artery-to-artery embolism in extracranial and intracranial arteries. Routine surface EEG failed to reveal focal or generalized abnormalities.

At the time of MRI, patients 6 and 8 were in the acute phase at 5 and 6 hours, respectively, after sudden onset of memory disturbance. They continuously asked where they were and what had happened, and were still unable to form very basic new memories. Both recovered over the next 6 hours.

Patients 1, 4, and 7 were in the early recovery phase 1 to 3 hours after TGA. They were able to form new memories, but they still could not recall recent events and were still worried and anxious.

Patients 2, 3, and 5 were examined in a later phase 6 to 8 hours after cessation of anterograde amnesia; however, they still showed incomplete recovery from retrograde amnesia.

MRI was performed with a 1.5-T Magnetom Vision (Siemens Medical Systems) with echo-planar hardware (gradient power 25 mT/m, rise time 83 mT/m/ms). A standardized MRI protocol was used, with transverse, coronal, and sagittal localizing sequences. This was followed by transverse continuous 5-mm images, field of view (FOV) 240 cm aligned with the hippocampus; proton density, T2W (turbo spin echo [SE] 2620 ms/14 ms/85 ms/5 mm/FOV 240); T1W (SE 530 ms/12 ms/5 mm); DW (echo-planar SE TR 4000 ms/TE 144 ms, 24-cm FOV, 5-mm slice thickness, 128×128 matrix, 5 b values=0 to 1000 s/mm², diffusion gradients in 3 orthogonal planes) in transverse oblique plane aligned with the hippocampus and in 2 coronal sequences angulated perpendicular to the hippocampus with

differing phase-encoding directions in order to evaluate the medial temporal lobes without artifact.

Maps of the ADC were obtained by a linear least-squares fit on a pixel-by-pixel basis after averaging of the direction-dependent DW images. The directionally independent trace of the diffusion tensor (ADC/3) was determined.

ADC maps and DW (isotropic, $b=1000$ s/mm²), T2W, and T1W images were analyzed for acute and chronic abnormalities (Figure). The ADC was determined by region-of-interest (0.5 cm² to 1.0 cm²) analysis.

Results

None of the patients showed parenchymal hyperintensity on DW images or hypointensity on ADC maps that would suggest regional decreases of water mobility on transverse or coronal slices. The ADC in normal-appearing white and gray matter and in the hippocampus ($ADC=0.77\pm 0.04\times 10^{-5}$ cm²/s) were within the normal range (as established for previous stroke studies, $ADC=0.75\pm 0.06\times 10^{-5}$ cm²/s).

Patients 3, 5, 7, and 8 also had unremarkable T1W and T2W studies. In patients 1, 2, and 4, only very slight punctate subcortical white matter changes were seen on T2W images. In patient 6 there were subcortical hyperintense periventricular lesions. There were no signs of major tissue destruction in corresponding areas on T1W images.¹³ The number of hyperintense T2 lesions were compatible with the age of the patients. There was no indication of previous territorial infarction.

Discussion

Evidence of acute ischemic lesions in the posterior cerebral artery territory (right hippocampus, medial basal temporal lobe, splenium of the corpus callosum, and in the left parahippocampal gyrus) has recently been demonstrated with echo-planar DW MRI in a patient with postangiographic TGA and in a second patient with spontaneous-onset TGA. In both patients an embolic mechanism of ischemic changes was presumed. Although we used a very similar DW MRI technique and have demonstrated even very small embolic stroke lesions previously, we found no evidence of embolic lesions in 8 patients with TGA.¹⁴ Transverse and coronal calculated maps of the ADC and DW images showed no indication of acute ischemic tissue change. This is in line with earlier studies which show that structural changes are rarely found in TGA patients.^{2,4}

Although TGA may be caused by embolic infarction, our negative results confirm that TGA may instead be a consequence of different etiologies. Shared pathophysiological mechanisms of migraine and TGA have repeatedly been

Clinical Details of Patients With TGA

Patient/Age/Sex	Duration of TGA, h	TMRI, h*	Risk Factors/Migraine†
1/63/F	10	2	—/M
2/70/F	4	6	HT/—
3/61/M	7	8	—/TH
4/74/F	8	1	—/2nd TGA episode
5/56/F	8	8	—/TH
6/77/F	9	During episode	HT/—
7/71/M	5	1.5	—/—
8/66/F	12	During episode	—/—

*Time of MRI after TGA.

†Vascular risk factors/migraine history. M indicates migraine; HT, hypertension; and TH, tension headache. Minus sign indicates absence of risk factor or migraine.

suggested. It is interesting to note that in a recent MRI study in patients with migraine auras, no ADC abnormalities to suggest spreading depression or ischemia could be demonstrated, while on hemodynamically weighted (perfusion-weighted) MRI there were signs of regional hypoperfusion.¹⁵ In TGA transient abnormalities of tissue perfusion have also been detected with single-photon emission CT and positron emission tomography.^{16–18} Perfusion-weighted MRI was not part of our study but should be a useful adjunct in future studies of TGA.

Spreading depression has been demonstrated with DW MRI in experimental models of focal ischemia but not yet in human stroke.^{10,11} We did not identify a regional transient ADC decrease suggesting spreading depression. Experimental work^{11,19} has demonstrated that in spreading depression the ADC reduction (20% to 30% reduction) is usually less pronounced than in ischemic tissue damage when anoxic depolarization occurs (50% to 60% reduction). Although echo-planar DW MRI has been shown to be very sensitive in detecting the ADC decrease of even small ischemic lesions, a higher spatial resolution using segmented echo-planar sequences and serial measurements may be better suited than single-shot echo-planar DW MRI to detect spreading depression. Echo-planar-specific artifact (chemical shift artifact, N/2 artifact, susceptibility artifact) has to be taken into consideration when interpreting DW images.²⁰ Although such artifact usually, in our experience, does not obscure lesions in the medial temporal lobes or at the base of the skull (as analyzed in a recent study of 105 stroke patients),²¹ we used 3 echo-planar DW studies in transverse and coronal planes to provide best visualization of the medial temporal lobes.

Our negative findings contrast with the findings of Strupp et al.,⁹ who report widespread transient hyperintensities on DW images in 7 of 10 TGA patients 3 to 25 hours after TGA and in 1 patient at the time of TGA. These image abnormalities were believed to be consistent with spreading depression. They used steady-state free precession (SSFP) DW images with a single diffusion gradient direction. Surprisingly, no diffusion anisotropy effects were visible in those images. The potential diffusion changes were determined by visual interpretation without the opportunity to quantitatively analyze the ADC, which is crucial to distinguish diffusion effects from other complex factors that influence image contrast.²² The steady-state free precession sequences are known to be susceptible to contrast influences due to slice profile effects, uncertainties due to relaxation times, and other tissue motions.²³ Therefore, it is conceivable that these technical reasons are responsible for the differing results of our studies. There also is some possibility that DW MRI changes occurred with a delay, as patients were examined later (hours to days after the onset of TGA).

Despite using up-to-date MRI technology, we were unable to detect signs of ischemic tissue change in acute stages of TGA on DW MRI, which suggests that mechanisms other than ischemic infarction may also cause TGA. We did not identify changes of the ADC associated with spreading depression. Further refinement of MRI sequences may be necessary to detect subtle or transient ADC change in brain parenchyma.

References

1. Caplan LB. Transient global amnesia. In: *Handbook of Clinical Neurology, Vol 1: Clinical Neuropsychology*. Amsterdam, the Netherlands: Elsevier; 1985:205–218.
2. Hodges JR, Warlow CP. Syndromes of transient amnesia: towards a classification: a study of 153 patients. *J Neurol Neurosurg Psychiatry*. 1990;53:834–843.
3. Kushner MJ, Hauser WA. Transient global amnesia: a case control study. *Ann Neurol*. 1985;18:684–691.
4. Ladurner G, Skvarc A, Sager WD. CT in transient global amnesia. *Eur Neurol*. 1982;21:34–40.
5. Warach S, Gaa J, Siewert B, Wielopolski P, Edelman RR. Acute human stroke studied by whole brain echo planar diffusion-weighted MRI. *Ann Neurol*. 1995;37:231–241.
6. Meder JF, Mourey-Gerosa I, Blustajn J, Lemaigen R, Devaux B, Fredy D. Transient global amnesia after cerebral angiography. *Acta Radiol*. 1997;38:273–274.
7. Woolfenden AR, O'Brien MW, Schwartzberg RE, Norbash AM, Tong DC. Diffusion-weighted MRI in transient global amnesia precipitated by cerebral angiography. *Stroke*. 1997;28:2311–2314.
8. Ay H, Furie KL, Yamada K, Koroshetz W. Diffusion-weighted MRI characterizes the ischemic lesion in transient global amnesia. *Neurology*. 1998;51:901–903.
9. Strupp M, Bruning R, Wu RH, Deimling M, Reiser M, Brandt T. Diffusion-weighted MRI in transient global amnesia: elevated signal intensity in the left mesial temporal lobe in 7 of 10 patients. *Ann Neurol*. 1998;43:164–170.
10. Gyngell M, Back T, Hoehn-Berlage M, Kohno K, Hossmann KA. Transient cell depolarisation after permanent middle cerebral artery occlusion: an observation by diffusion-weighted MRI and localised 1H-MRS. *Magn Reson Med*. 1994;31:337–341.
11. Roether J, de Crespigny AJ, D'Arceuil H, Mosley ME. MR detection of cortical spreading depression immediately after focal ischemia in the rat. *J Cereb Blood Flow Metab*. 1996;16:214–220.
12. Zhong J, Petroff OAC, Pleban LA, Gore JC, Prichard JW. Reversible, reproducible reduction of brain water apparent diffusion coefficient by cortical electroshocks. *Magn Reson Med*. 1997;37:1–6.
13. Gass A, Oster M, Cohen S, Daffertshofer M, Schwartz A, Hennerici M. Assessment of T₂- and T₁-weighted MRI brain lesion load in patients with subcortical vascular encephalopathy. *Neuroradiology*. 1998;40:503–506.
14. Gass A, Hennerici M, Gaa J, Schwartz A. Rapid recovery from left hemiplegia. *Lancet*. 1997;349:772–772.
15. Cutrer FM, Sorensen AG, Weisskoff RM, Ostergaard L, Sanchez del Rio, Lee EJ, Rosen BR, Moskowitz MA. Perfusion-weighted imaging defects during spontaneous migrainous aura. *Ann Neurol*. 1998;43:25–31.
16. Baron JC, Petit-Tabue MC, Le Doze F, Desgranges B, Ravenel N, Marchal G. Right frontal cortex hypometabolism in transient global amnesia. *Brain*. 1994;117:545–552.
17. Sakashita Y, Kanai M, Sugimoto T, Taki S, Takamori M. Changes in cerebral blood flow and vasoreactivity in response to acetazolamide in patients with transient global amnesia. *J Neurol Neurosurg Psychiatry*. 1997;63:605–610.
18. Goldenberg G, Podreka I, Pfaffelmeyer N, Wessely P, Deecke L. Thalamic ischemia in TGA: a SPECT study. *Neurology*. 1991;41:1748–1752.
19. Hoehn-Berlage M, Eis M, Back T, Kohno K, Yamashita K. Changes of relaxation times (T₁, T₂) and the apparent diffusion coefficient after permanent middle cerebral artery occlusion in the rat: temporal evolution regional extent, and comparison with histology. *Magn Reson Med*. 1995;34:824–834.
20. Edelman RR, Wielopolski P, Schmitt F. Echo-planar MR imaging. *Radiology*. 1994;192:600–612.
21. Gass A, Gaa J, Sommer A, Hirsch J, Hennerici MG, Georgi M, Schwartz A. Echoplanare diffusionsgewichtete MRT in der Diagnostik des akuten Schlaganfalls: Möglichkeiten und Grenzen bei der Interpretation auffälliger Bildbefunde. *Radiologe*. In press.
22. Warach S, Boska M, Welch KMA. Pitfalls and potential of clinical diffusion-weighted MR imaging in acute stroke. *Stroke*. 1997;28:481–482.
23. Buxton RB. The diffusion sensitivity of fast steady-state free precession imaging. *Magn Reson Med*. 1993;29:235–243.