Hiroshima J. Med. Sci.
Vol. 59, No. 4, 77~81, December, 2010
HIJM 59–14

Serial Changes in Delayed Focal Hippocampal Lesions in Patients with Transient Global Amnesia

Hiroki UENO[1)*], Hiromitsu NAKA[2)], Tomohiko OHSHITA[1)], Shinichi WAKABAYASHI[3)] and Masayasu MATSUMOTO[1)]

1) Department of Clinical Neuroscience and Therapeutics, Hiroshima University, Graduate School of Biomedical Sciences, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan
2) Department of Neurology, Suiseikai Kajikawa Hospital, 8-20 Showamachi, Naka-ku, Hiroshima 730-0046, Japan
3) Department of Neurosurgery, Suiseikai Kajikawa Hospital, 8-20 Showamachi, Naka-ku, Hiroshima 730-0046, Japan

ABSTRACT

The etiology of transient global amnesia (TGA) is not well understood. MR studies, including studies using diffusion-weighted imaging (DWI), have been used to investigate the pathophysiology of TGA, and focal hippocampal lesions have been detected in some studies. The aim of this study was to investigate serial changes in MR images from the patients with TGA. In seven TGA patients, serial MRI scans (from the same day of the onset to several days after the onset of symptoms) using a 1.5-T MR unit were prospectively evaluated. In four patients, the duration of TGA was over 12 hr. Three of those patients showed small punctate hippocampal hypersensitivity with decreased ADC values on DW images. These lesions were detected in the postacute phase (a time window of 24 - 48 hr after the onset of symptoms). In follow-up studies performed several days after the onset of symptoms, DWI lesions had disappeared in the subacute phase (7-10 days after the TGA episode). The delayed hippocampal lesion on DW images with 1.5-T MRI in patients with TGA appears to be associated with longer duration of symptoms, to persist for several days and to disappear in the chronic phase.

Key words: *TGA, Transient global amnesia, DWI, Hippocampus*

Transient global amnesia (TGA) has a sudden onset of anterograde and retrograde amnesia accompanied by repetitive questioning. Other than amnesia, there are no neurological deficits. Attacks last minutes or hours, rarely longer than a day, with gradual recovery. Patients are usually middle-aged or elderly and otherwise healthy. TGA is thought to be a benign syndrome, but some neuropsychological studies have suggested long-term memory disturbance persisting after a TGA episode[2,4,6,7,11)].

TGA has been reported to be associated with several pathological factors, although there are still no consistent pathophysiological findings. Several studies using DWI have been unable to detect abnormalities in the acute phase of TGA[5,9,14)]. In a recent study, Sedlaczek and colleagues found that most patients with TGA have small punctate DWI lesions in the lateral aspect of the hippocampal formation, which were rarely noted within 24 hr but were detected with high sensitivity 24 to 48 hr after the onset of symptoms[25)]. The observed DWI lesions show high detectability within a time window of 48-72 hr after the onset of TGA[5,9,10,22,25,27)]. However, there have been few detailed reports on serial changes in these delayed hippocampal lesions revealed by DWI. In this study, we prospectively analyzed serial MR images, including DW images, from patients with TGA obtained by using a 1.5-T MR unit.

MATERIALS AND METHODS

Seven patients (5 women and 2 men, aged 57 to 83 years) with clinically identified TGA who presented to our hospital underwent MRI. All patients satisfied the diagnostic criteria for TGA[3,8)]. The patients presented with clinical symptoms of TGA that had begun 2 to 9 hr before the first MRI examination. All patients underwent neurological, neuropsychological and MRI exami-

*Corresponding author and reprints: Hiroki Ueno, MD, PhD; Department of Clinical Neuroscience and Therapeutics, Hiroshima University, Graduate School of Biomedical Sciences, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan
Tel.: +81-82-257-5201 Fax: +81-82-505-0490 E-mail: hirokiueno@hiroshima-u.ac.jp

nation. Electroencephalography was performed in five (Patients 1, 2, 3, 6, 7) of the seven patients. Several follow-up MRI studies were performed in the postacute phase (24-72 hr after onset) and the subacute phase (3-10 days after onset) of TGA. Patients with detectable DWI lesions in the postacute phase underwent MRI examination 3 to 10 days after the onset of TGA. Clinical data of the patients are summarized in Table 1. All patients had had their first TGA at the time of admission. All symptoms lasted less than 24 hr and disappeared without any disability remaining, other than partial amnesia for the episode. During the follow-up period (2-11 months), none of the patients presented with stroke, epileptic seizure, or recurrent TGA.

All of the patients were examined using a 1.5-T clinical MR unit (SIEMENS, MAGNETOM Symphony), and the whole brain was scanned with a slice thickness of 5 mm and a 1.5-mm interslice gap. The imaging protocol consisted of axial T2-weighted fast spin-echo sequences (TR/TE = 4000/93; field of view, 220 × 192.5; matrix, 256 × 256), axial fluid-attenuated inversion recovery (FLAIR) spin-echo sequences (TR/TE = 9000/110; field of view, 220 × 182.2; matrix, 256 × 256), axial diffusion-weighted imaging with echo-planar spin-echo sequences (TR/TE = 4500/123; field of view, 220 × 220; matrix, 128 × 128; b values, 0 and 1000 s/mm^2) with subsequent maps of apparent diffusion coefficient (ADC), and intracranial MR angiography (3D time-of-flight sequence; TR/TE = 35/7.15; flip angle 25°).

RESULTS

In four (Patients 1, 2, 3, 7) of the seven patients, the durations of the TGA episodes were over 12 hr. In three (Patients 1, 2 and 3) of those four patients, focal hyperintense lesions with decreased ADC values on DW images in the lateral hippocampus were detected on day 2, in a time window of 24-48 hr after onset (Table 2). In the other four patients, hyperintense signals were not detected in the acute and postacute phases. Two patients (Patients 1 and 3) showed hippocampal DWI lesions on the right side and one patient (Patient 2) showed the lesion on the left side. In contrast to these three lesions on DW images, abnormalities on conventional T2-weighted MR images or FLAIR images were not detectable in any patients. Other abnormal lesions including silent infarction were not observed.

Several days after the episode, in two (Patients 1 and 2) of the three patients with detectable DWI lesions, the lesion remained hyperintense on DW images and ADC values were reduced in the 3rd MRI study in Patient 1 (92 hr after onset) (Fig.) and Patient 2 (90 hr after onset). In the follow-up MRI study performed about one week (7-10 days) after symptom onset, lesions had disappeared on DW images and ADC maps with FLAIR and T2-weighted images remaining normal in these three patients. In the other four patients, no

Table 1. Clinical data of the patients

Patient No.	Age (years)	Sex	Cerebrovascular risk factors	Antiplatelet treatment	MRA	EEG
1	57	M	HT	+	normal	normal
2	83	F	HL, rt. thalamic infarction	+	normal	normal
3	59	F	HL	-	normal	normal
4	60	F	-	-	normal	not done
5	53	M	-	-	normal	not done
6	71	F	HL	-	normal	normal
7	58	F	-	-	normal	normal

MRA, MR angiography; EEG, Electroencephalography; HT, arterial hypertension; HL, hyperlipidemia; Present is indicated by + and absent is indicated by -.

Table 2. MRI changes

Patient No.	Duration of TGA, hr	Focal hippocampal hypersensitivity with decreased ADC values on serial DW images (hours from symptom onset to MR study)			
		0 -24 hr	24 -72 hr	3 -4 days	day 7-
1	12	normal (2)	Rt. (25)	Rt. (92)	normal (235.5)
2	12	normal (4.5)	Lt. (28.5)	Lt. (90)	normal (176)
3	21	normal (9)	Rt. (33)		normal (168)
4	4	normal (6)	normal (50)		
5	9	normal (4, 15)	normal (62)		
6	11	normal (5)	normal (54)		
7	12	normal (8.5)	normal (43)		

TGA, transient global amnesia; ADC, apparent diffusion coefficient

lesion was detected in follow-up scans. These four patients (Patients 4-7) with no detectable lesions on DW images did not undergo further MRI studies in the chronic phase of TGA.

DISCUSSION

Diffusion-weighted imaging has been used to investigate the pathophysiology of TGA. In three recent long-scale studies using DWI, abnormalities in the hippocampal formation were detected in 84% of the patients (Sedlaczek et al)[25], in 36% of the patients (Winbeck et al)[27] and in 71% of the patients (Bartsch et al)[1]. In our study, similar hippocampal abnormalities were detected on DW images in 43% of the TGA patients. Furthermore, as in recent studies[1,25], most of these DWI lesions, which were not detected in the acute phase within 24 hr of symptom onset, were detected on the second day after symptom onset. Since the DWI

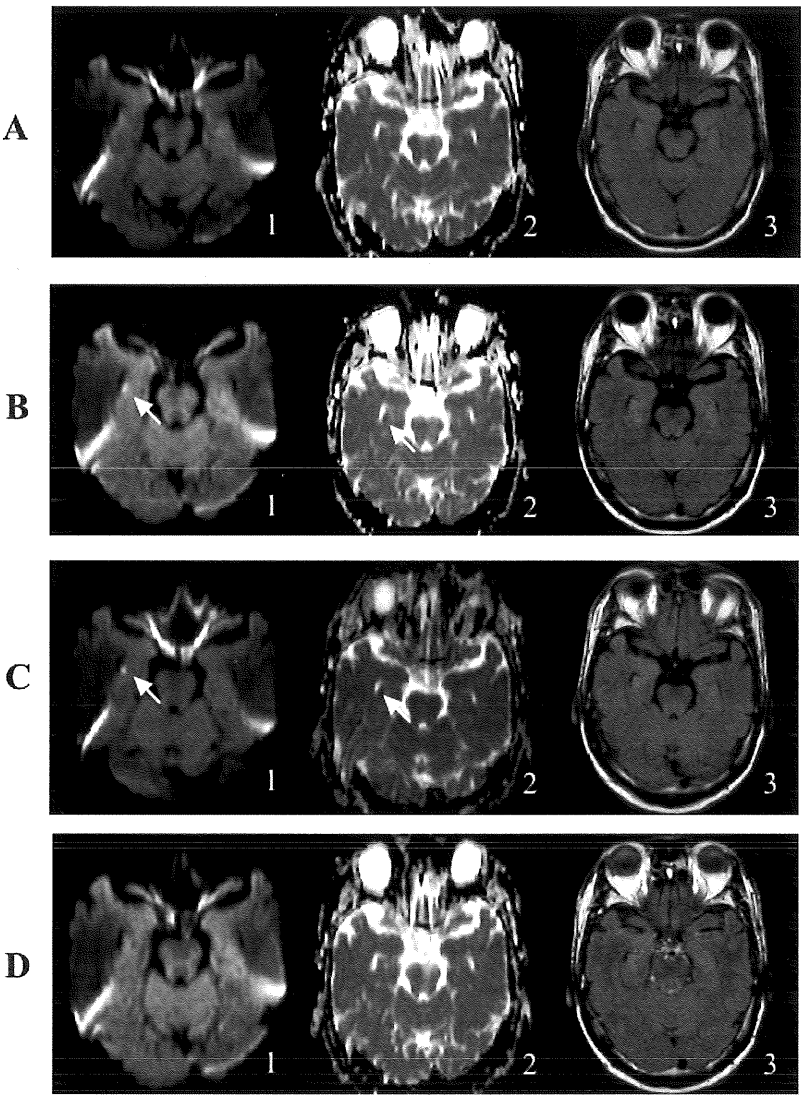

Fig . MR images from a patient with TGA (Patient 1) obtained 2 hr after onset (A-1, 2, 3). Diffusion-weighted image (DWI) (echo-planar spin-echo sequence; b = 1000 sec/mm2) (A-1), apparent diffusion coefficient (ADC) map (A-2) and fluid-attenuated inversion recovery (FLAIR) image (A-3) were normal. After 25 hr, a hyperintense lesion was observed in the right parahippocampal gyrus on a DW image (B-1 arrow), while the same region showed low intensity on an ADC map (B-2 arrow). Hyperintensity on a DW image (C-1) and reduced ADC values (C-2) remained after 4 days. After 10 days, the lesion had disappeared on a DW image (D-1) and ADC map (D-2). No abnormality was noted on a FLAIR image in the corresponding region (D-3).

lesions with decreased ADC were observed in hippocampal structures, it is possible that an ischemic change occurred in memory-relevant structures. It has been shown that the sector of Sommer (CA1) had a selective vulnerability to cellular metabolic stress, such as hypoxaemia and ischemia, that led to glutamate and calcium-induced and apoptosis-mediated 'delayed neuronal death' of the affected neurons several days after hypoxia[12,20,22]. Some animal experiments of delayed neuronal death show that transient ischemia causes neuronal death selectively in the hippocampus 2-4 days[18,19]. It has been hypothesized that hypoperfusion in the hypoxia-susceptible sector of Sommer (CA1), which is the vascular borderzone, followed by delayed ischemia may cause TGA[25]. In addition, it has been reported that brain stem infarction in the posterior circulation territory could be reliably visualized by a combination of DW-MRI and T2-weighted imaging beginning 12 hr after the ischemic attack[13], which may be connected with a delayed DWI lesion in the hippocampal area.

Recently, Bartsch and colleagues[1] studied the time courses of hippocampal DWI lesions in TGA patients using 3-T MR imaging, and they found that follow-up studies performed 10-20 days after the episode did not show any persistent DWI signal changes or corresponding T2 lesions. Their results are supported by the results of our study in which punctate small DWI lesions had disappeared about 7-10 days later and it was not possible to identify a corresponding region on T2-weighted images or FLAIR images. The increased signal intensity on DW images and decreased intensity on ADC maps in the hippocampus in the postacute phase of TGA suggest an ischemic event, but the time course of these lesions differs from that of usual ischemic lesions. These reversible findings suggest that there is no profound neuronal loss or degeneration in the affected hippocampal area.

The symptoms of TGA usually last 4-6 hr[28]. Compared with previous DWI studies, this series includes the cases with relatively longer durations of symptoms (more than 12 hr). There has been no report on the association between the detection of hippocampal lesion on DW images and the duration of symptoms in patients with TGA. The delayed hippocampal lesion on DW images in patients with TGA appears to be associated with longer duration of symptoms.

One of the current hypothesis of the cause of TGA is that venous congestion leads to venous ischemia of memory-relevant structures and high venous pressure and increased venous return towards the superior vena cava induced by Valsalva-like activities might lead to ischemia[16]. In this study, patients had no episode of Valsalva-like activity such as stressful reaction and pain before the attacks. Another possible pathophysiological mechanism other than a haemodynamic vascular mechanism is cortical spreading depression in migraine[8,17,20]. However, our patients had no medical history of migraine, and it has been suggested that there is no association between TGA and migraine[24].

Our study has a limitation. We examined using a 1.5-T clinical MR unit and DWI parameter with the same b-value of 1000 s/mm^2. Lee et al reported that 3.0-T MRI showed 11 out of 32 TGA patients with hippocampus lesion, whereas 1.5-T MRI detected no lesion in any of 11 TGA patients[15]. Weon et al reported that the lesion detection rate of the initial DWI was higher for b = 2000 or 3000 (54%) than for b = 1000 (38%)[26]. It remains possible that the detection rate of hippocampal lesion on DWI in the present patients with TGA varied with the following factors: high field strength MRI, high b-value and section thicknesses.

The pathophysiologic characteristics of TGA remain to be elucidated. A delayed ischemic mechanism and reversible hypoperfusion mechanism may be a clue to elucidate the pathophysiology of TGA.

ACKNOWLEDGEMENTS

We thank Dr. Junko Ikeda and Dr. Yasuyo Mimori for providing clinical information.

(Received October 27, 2010)
(Accepted November 29, 2010)

REFERENCES

1. **Bartsch, T., Alfke, K., Stingele, R., Rohr, A., Freitag-Wolf, S., Jansen, O. and Deuschl, G.** 2006. Selective affection of hippocampal CA-1 neurons in patients with transient global amnesia without long-term sequelae. Brain **129**: 2874-2884.
2. **Borroni, B., Agosti, C., Brambilla, C., Vergani, V., Cottini, E., Akkawi, N. and Padovani, A.** 2004. Is transient global amnesia a risk factor for amnestic mild cognitive impairment? J. Neurol. **251**:1125-1127.
3. **Caplan, L.** 1985. Transient global amnesia. p.205-218, *In* JAM Frederiks (ed). Handbook of Clinical Neurology. Elsevier Science. Amsterdam.
4. **Gallassi, R., Stracciari, A., Morreale, A., Lorusso, S., Rebucci, G.G. and Lugaresi, E.** 1993. Transient global amnesia: neuropsychological findings after single and multiple attacks. Eur. Neurol. **33**:294-298.
5. **Gass, A., Gaa, J., Hirsch, J., Schwartz, A. and Hennerici, M.G.** 1999. Lack of evidence of acute ischemic tissue change in transient global amnesia on single-shot echo-planar diffusion-weighted MRI. Stroke **30**:2070-2072.
6. **Hodges, J.R. and Ward, C.D.** 1989. Observations during transient global amnesia. A behavioural and neuropsychological study of five cases. Brain **112**: 595-620.

7. **Hodges, J.R. and Oxbury, S.M.** 1990. Persistent memory impairment following transient global amnesia. J.Clin.Exp.Neuropsychol. **12**:904-920.
8. **Hodges, J.R. and Warlow, C.P.** 1990. Syndromes of transient amnesia: towards a classification. A study of 153 cases. J.Neurol.Neurosurg.Psychiatry **53**:834-843.
9. **Huber, R., Aschoff, A.J., Ludolph, A.C. and Riepe, M.W.** 2002. Transient Global Amnesia. Evidence against vascular ischemic etiology from diffusion weighted imaging. J. Neurol. **249**:1520-1524.
10. **Jeong, Y., Kim, G.M., Min, Song, Y. and Na, D.L.** 2003. A tiny hippocampal ischemic lesion associated with transient global amnesia. Cerebrovasc. Dis. **16**:439-442.
11. **Kessler, J., Markowitsch, H.J., Rudolf, J. and Heiss, W.D.** 2001. Continuing cognitive impairment after isolated transient global amnesia. Int.J.Neurosci. **106**: 159-168.
12. **Kirino, T.** 2000. Delayed neuronal death. Neuropathology **20**:S95-97.
13. **Kuker, W., Weise, J., Krapf, H., Schmidt, F., Friese, S. and Bahr, M.** 2002. MRI characteristics of acute and subacute brainstem and thalamic infarctions: value of T2- and diffusion-weighted sequences. J.Neurol. **249**:33-42.
14. **LaBar, K.S., Gitelman, D.R., Parrish, T.B. and Mesulam, M.M.** 2002. Functional changes in temporal lobe activity during transient global amnesia. Neurology **58**:638-641.
15. **Lee, S.Y., Kim, W.J., Sun, S.H., Oh, S.H. and Lee, K.Y.** 2009. Higher lesion detection by 3.0T MRI in patient with transient global amnesia. Yonsei Med. J. **50**:211-214.
16. **Lewis, S.L.** 1998. Aetiology of transient global amnesia. Lancet **352**:397-399.
17. **Melo, T.P., Ferro, J.M. and Ferro, H.** 1992. Transient global amnesia. A case control study. Brain **115**:261-270.
18. **Ohtsuki, T., Matsumoto, M., Kitagawa, K., Mabuchi, T., Mandai, K., Matsushita, K., Kuwabara, K., Tagaya, M., Ogawa, S., Ueda, H., Kamada, T. and Yanagihara, T.** 1996. Delayed neuronal death in ischemiac hippocampus involves stimulation of protein tyrosine phosphorylation. Am.J.Physiol. **271**:1085-1097.
19. **Okamoto, M., Matsumoto, M., Ohtsuki, T., Taguchi, A., Mikoshiba, K., Yanagihara, T. and Kamada, T.** 1993. Internucleosomal DNA cleavage involved In ischemia-induced neuronal death. Biochem.Biophys.Res.Commun. **196**:1356- 1362.
20. **Olesen, J. and Jorgensen, M.B.** 1986. Leao's spreading depression in the hippocampus explains transient global amnesia. A hypothesis. Acta Neurol. Scand. **73**:219-220.
21. **Quintana, P., Alberi, S., Hakkoum, D. and Muller, D.** 2006. Glutamate receptor changes associated with transient anoxia/hypoglycaemia in hippocampal slice cultures. Eur.J.Neurosci. **23**:975-983.
22. **Sander, K. and Sander, D.** 2005. New insights into transient global amnesia: recent imaging and clinical findings. Lancet Neurol. **4**:437-444.
23. **Schmidt-Kastner, R. and Freund, T.F.** 1991. Selective vulnerability of the hippocampus in brain ischemia. Neuroscience **40**:599-636.
24. **Schmidtke, K. and Ehmsen, L.** 1998. Transient global amnesia and migraine. A case control study. Eur.Neurol. **40**:9-14.
25. **Sedlaczek, O., Hirsch, J.G., Grips, E., Peters, C.N., Gass, A., Wohrle, J. and Hennerici, M.** 2004. Detection of delayed focal MR changes in the lateral hippocampus in transient global amnesia. Neurology **62**:2165-2170.
26. **Weon, Y.C., Kim, J.H., Lee, J.S. and Kim, S.Y.** 2008. Optimal diffusion-weighted imaging protocol for lesion detection in transient global amnesia. AJNR Am. J. Neuroradiol. **29**:1324-1328.
27. **Winbeck, K., Etgen, T., von Einsiedel, H.G., Rottinger, M. and Sander, D.** 2005. DWI in transient global amnesia and TIA: proposal for an ischaemic origin of TGA. J.Neurol. Neurosurg. Psychiatry **76**:438-441.
28. **Zeman, A.Z. and Hodges, J.R.** 1997. Transient global amnesia. Br.J.Hosp.Med. **58**:257-260.