

# High-field, T2 reversed MRI of the hippocampus in transient global amnesia

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**Abstract—Objective:** To investigate the fine structural integrity of the hippocampus in patients with transient global amnesia (TGA) using high-resolution T2 reversed (T2R) MRI. **Methods:** The authors performed detailed structural analysis of the hippocampus in 15 patients who had recovered from an episode of TGA and 150 randomly recruited normal volunteers across the adult age spectrum using high-resolution T2R MRI obtained on a 3.0-T system. An additional 100 subjects, with stroke or tumor, were similarly studied and served as disease controls. **Results:** The overall incidence of hippocampal cavities detected in normal volunteers increased with age but never exceeded 40%, whereas the incidence in disease control group was 31%. They were always unilateral. In contrast, cavities were found in all 15 patients with TGA (100%), an incidence higher than in normal or disease controls ( $p < 0.05$ ; Ryan's multiple comparison test), and were bilateral in eight patients (53%). The cavities in all but one of the normal volunteers (99%) and all disease controls (100%) were crescent shaped and  $\leq 2$  mm in width. The cavities in 14 of 15 patients with TGA (93%) were considerably larger ( $>3$  mm in width), and five of the patients had giant cavities ( $>5$  mm in width). Most of the cavities in patients with TGA had a rounded shape and resembled pathologic cavities described in specimens of hypoxia-related CA1 necrosis. **Conclusion:** The data indicate that transient global amnesia may not be a benign entity. Delayed neuronal loss within CA1 area of Lorente de No may represent its important sequel.

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The term transient global amnesia (TGA) was introduced in 1958 to describe a behavioral syndrome characterized by one or more episodes of acute-onset, circumscribed anterograde amnesia typically lasting from 2 to 8 hours, during which level of consciousness and personal identity are preserved.<sup>1</sup> During TGA, patients are unable to encode new information into long-term memory but are able to interact with the examiner and perform normally on other cognitive tasks outside the memory domain.<sup>2</sup> Patients with TGA often show concern about their amnesic deficit during the episode but subsequently are unable to remember details of the attack. TGA is considered benign. Patients with TGA show rapid subsequent recovery of memory, and most exhibit no residual damage on conventional CT or MRI.<sup>3–6</sup>

Various potential etiologic factors have been proposed for TGA, including ischemic, epileptic, and migrainous. There is similar prevalence in risk factors for TIAs and TGA.<sup>3,5–7</sup> However, the vascular hypothesis, whether vasospastic, thromboembolic, or hemorrhagic in nature, has thus far lacked consistent identifiable abnormal structural abnormalities. Although there are no correlative data regarding the prevalence of epileptic syndrome and TGA, migraine and precipitating events have been proposed as risk

factors for TGA due to their relatively high association with TGA.<sup>5,6,8,9</sup> Because spreading depression is considered an important pathogenetic mechanism in migraine, it is thought that TGA may share this mechanism.<sup>7,8</sup> Nevertheless, there is no convincing evidence of a single etiology for TGA.

TGA has received interest because of its relation to the neurosubstrates of memory. Memory abnormalities during TGA have been postulated to be caused variously by transient dysfunction in diencephalic or mesial temporal structures. Indeed, PET and SPECT have suggested hypoperfusion in TGA.<sup>10–14</sup> Recent studies using diffusion-weighted imaging (DWI) also indicated that delayed abnormalities around the lateral hippocampus can be found in patients with TGA.<sup>15</sup> Nevertheless, there is no consensus on the anatomic structures affected in TGA.

One drawback of noninvasive studies in patients with TGA has been the limited anatomic resolution of conventional imaging methodologies. We recently demonstrated that detailed anatomy of fine structures can now be obtained in humans with a high-field (3.0 T) system.<sup>16–19</sup> In this study, we investigated the structural integrity of the hippocampus in 15 patients who met clinical criteria for TGA using high-field T2 reversed (T2R) MRI.

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**Table 1** Summary of patient data

Patient no.	Age, y	Sex	Duration, h	Interval between symptoms and MRI	Cavity $\geq 3$ mm detected on T2R MRI	Conventional MRI	Other medical	Witness
1	62	F	3	4 y	Right	Normal	None	Spouse
2	64	M	20	8 mo	Bilateral	IWMC	High cholesterol	Spouse
3	69	M	24	35 d	Bilateral	Normal	HTN	Spouse
4	57	F	6	19 d	Bilateral	Left parietal infarct	High cholesterol	Children
5	59	F	2	13 d	Left	Normal	HTN	Co-worker
6	77	F	24	18 d	Bilateral	Normal	HTN	Daughter
7	70	F	4	40 d	Bilateral	Normal	None	Spouse
8	21	M	24	21 d	Bilateral	Normal	HTN, arrhythmia	Friends
9	66	M	2	7 d	Bilateral	IWMC	None	Friend
10	56	F	6	7 d	Left	IWMC	None	Spouse
11	66	F	20	2 mo	Bilateral	Normal	None	Friends
12	69	F	18	6 d & 3 mo	None	Right frontal infarct	Atrial fibrillation	Spouse
13	47	M	3	12 d	Right	Normal	None	Spouse
14	62	F	8	35 d	Right	Normal	None	Neighbor
15	56	M	6	43 d	Bilateral	IWMC	HTN, DM,	Friends

T2R = T2 reversed; IWMC = ischemic white matter changes; HTN = hypertension; DM = diabetes mellitus.

**Methods.** *Patients with TGA.* Fifteen patients with TGA, nine women (age range, 57 to 77 years) and six men (age range, 21 to 69 years), were evaluated using high-field T2R MRI. All patients met the proposed clinical diagnostic criteria for TGA<sup>6,20</sup>: a witnessed episode of anterograde amnesia, variable retrograde amnesia, preservation of immediate memory and personal identity, absence of cognitive deficits other than amnesia, absence of accompanying focal neurologic signs, absence of epileptic features, absence of disturbance of consciousness or history of recent head injury, alcohol or drug abuse, and resolution within 24 hours of the start of amnesic symptoms, although variable amnesia for the duration of the attack may persist. Any patients with a known major medical condition including myocardial infarction or cerebrovascular accident were excluded. Patients who exhibited more than two episodes of amnesic syndrome were also excluded from this study. All patients were examined by at least one neurologist during the TGA episode. Included in their initial evaluation were brain CT or conventional MRI, EEG, and routine chemistries and complete blood counts (table 1).

*Normal volunteers.* Through community advertising, 150 normal healthy volunteers were recruited. Inclusion criteria were a normal developmental history and a normal Mini-Mental State Examination and neurologic examination. Exclusion criteria were a neurologic diagnosis, history of head trauma, past neurosurgical intervention, cardiovascular disease, hypertension, diabetes mellitus, or hyperlipidemia. Subjects were divided into three age groups: young (18 to 40 years), middle age (41 to 59 years), and senior (60 to 80 years). There were 62 young (32 female, 32 male), 54 middle-age (27 female, 27 male), and 34 senior (17 female, 17 male) subjects.

*Disease controls.* Fifty patients with brain tumors (meningioma, 18; glioma, 10; acoustic neurinoma, 6; metastasis, 5; cavernous angioma, 4; hemangioblastoma, 2; pituitary adenoma, 2; craniopharyngioma, 1; chordoma, 1; central neurocytoma, 1) of the age range of 22 to 68 years (mean age, 52.5; 29 females, 21 males) and 50 patients with stroke (putaminal hemorrhage, 19; thalamic hemorrhage, 10; striatocapsular infarction, 17; cortical infarction, 4) of the age range of 42 to 72 years (mean age, 59.2; 15 female, 35 male) were included as disease controls.

*High-field T2R MRI.* A Signa 3-T (GE Medical System, Waukesha, WI) research imaging system with a superconductive magnet operating at 3.0 T (Magnex; Abingdon, Oxon, UK) was

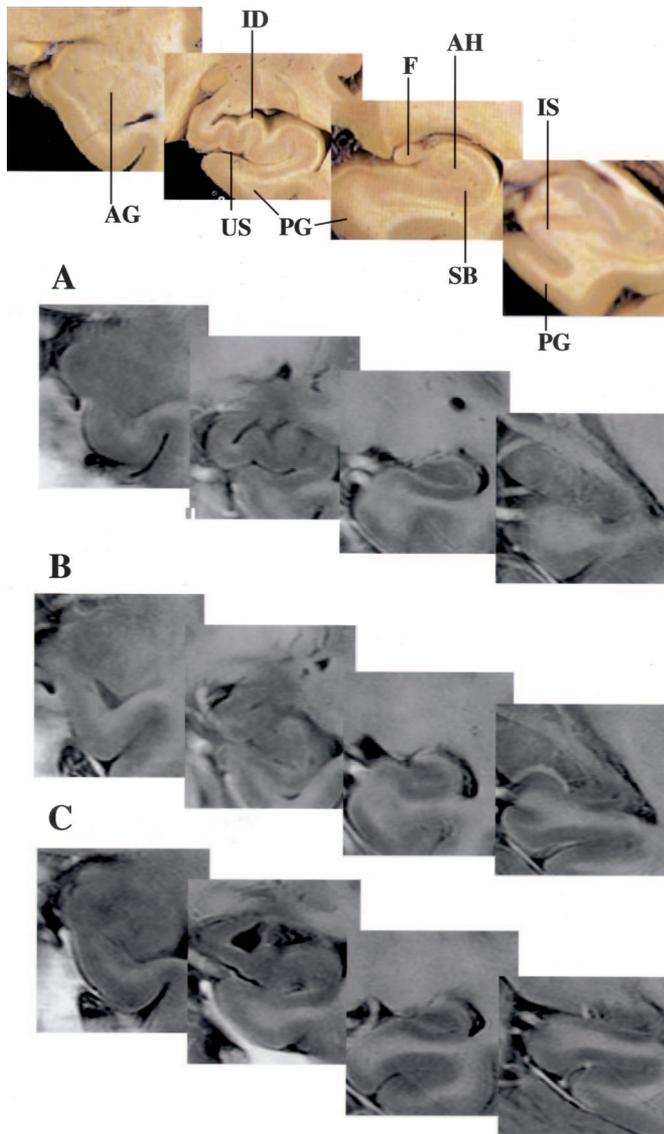
used to perform all T2R MRI studies. Subjects were imaged according to the human research guidelines of the Internal Review Board of the University of Niigata. Written informed consent was obtained from all subjects.

Data were obtained using a fast spin-echo sequence (FSE) and the following parameters: repetition time, 4,000 msec; echo time, 17 msec; field of view, 12 × 12 cm; matrix size, 512 × 512; and echo train, 12. Considering the specific absorption rate, the number of slices in a single FSE session were limited to five slices (5-mm slice thickness, 2.5-mm interslice gap). These slices started at the level of the hippocampal head and continued up to the caudal-most aspect of the hippocampal body. Raw data were obtained using 256 phase-encoding steps (NEX = 8) and zero-filled into 512 data points. The total scanning time necessary to obtain five slice images was 12 minutes. After conventional two-dimensional Fourier transformation, the gray scale of images was inverted and given an expanded window range (T2R images).

Coronal images of the hippocampus (figure 1) were analyzed by two independent experienced neurologists in blinded fashion. Findings of the CA1 area were classified into four categories as shown in table 2 (no, small, large, and giant cavity) according to the size of the cavity in width (b in figure 2A). No discrepancy was found between the two image evaluators. Statistical assessments were performed by applying Ryan's multiple comparison tests. Significance was taken as a two-tailed value of  $p < 0.05$ .

**Results.** The findings of the normal volunteers, disease controls, and patients with TGA are summarized in table 2. The overall incidence of cavities in the CA1 field of the hippocampus detected in normal volunteers increased with age. The highest incidence was found in the senior group. But even in this group, the incidence never exceeded 40%. The size of cavities found in all but one of the normal volunteers and disease controls were always  $\leq 2$  mm in width (b in figure 2A). Cavities were single, crescent-shaped structures along the deep aspect of the vestigial hippocampal sulcus.

Representative images of a patient with TGA (Patient 11) are shown in figure 2C. Single representative hip-



**Figure 1.** Examples of four consecutive slices of the hippocampus used for evaluation (left to right, frontal to caudal). (A) young age; (B) middle age; (C) senior age group. Photographs of actual brain slices of the corresponding areas are shown in the top row. AG = amygdala; ID = internal digitations; US = uncal sulcus; PG = parahippocampal gyrus; AH = Ammon horn; SB = subiculum; F = fimbria; IS = isthmus.

pocampal images of all patients with TGA are shown collectively in figure 3. Cavities were found in all 15 patients (100%). The incidence was higher than that of normal volunteers or disease controls ( $p < 0.05$ ; Ryan's multiple comparison test). In all but one (Patient 12) of the 15 patients (93%), the cavities were larger ( $>2$  mm in width) than those seen in normal volunteers. Five patients (Patients 3, 4, 7, 8, 11) had giant ( $>5$  mm) cavities. Most cavities had a noncrescent, rounded appearance and resembled cavities described in pathologic specimens of hypoxia-related CA1 necrosis. In eight patients (53%), lesions were found bilaterally (Patients 2, 3, 4, 6, 7, 9, 11, 15).

**Table 2** Summary of MRI findings

Age group	Cavity detection, no. (%) of cases	Size,* mm		
		Small ( $\leq 2$ )	Large (3–5)	Giant ( $>5$ )
Young (18–40 y) (n = 62)	14 (22.6%)	13	0	1†
Middle (42–59 y) (n = 54)	14 (26.0%)	14	0	0
Senior (60–80 y) (n = 34)	13 (38.2%)	13	0	0
Tumor (22–68 y) (n = 50)	13 (26.0%)	13	0	0
Stroke (42–72 y) (n = 50)	18 (36%)	18	0	0
TGA (21–69 y) (n = 15)	15‡ (100%)	1‡	9‡	5‡

\* Width (b in figure 2A).

† In-depth poststudy interview of this subject disclosed that she had an incidence of prolonged loss of consciousness in a swimming class in high school.

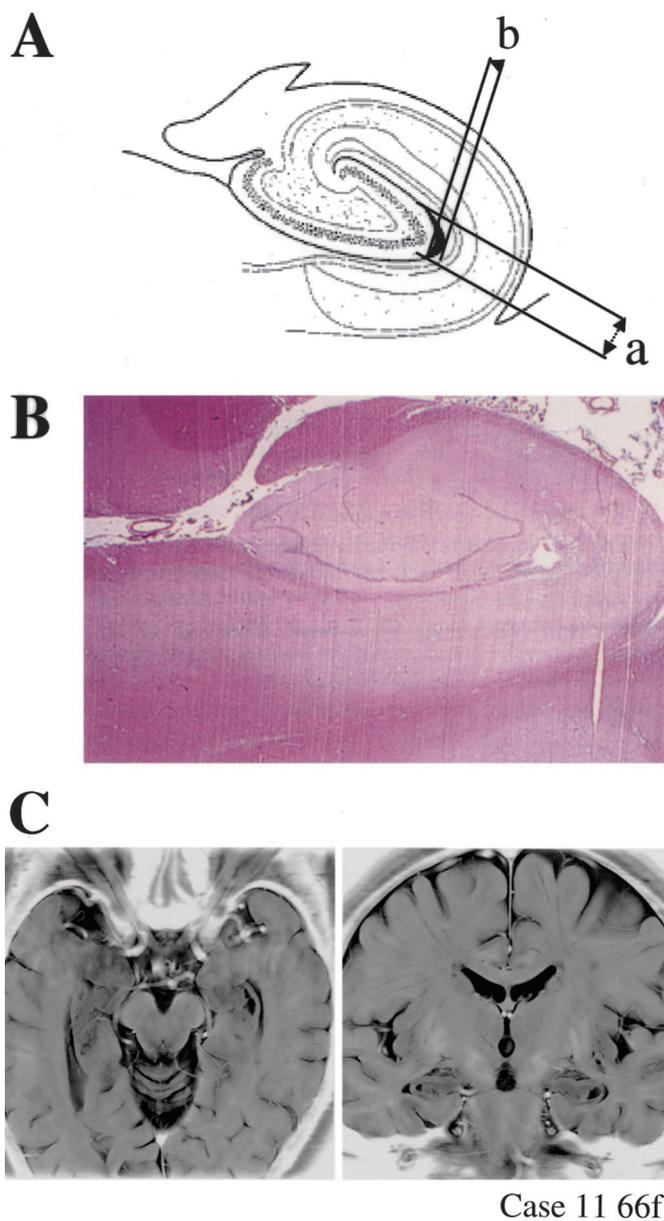
‡  $p < 0.05$ ; Ryan's multiple comparison test.

n = number of cases.

**Discussion.** The current study with high-field T2R technique provides better anatomic resolution than other imaging techniques. Indeed, the T2R technique has improved anatomic resolution of the CNS in the clinical setting, including such structures as the individual branches of the trigeminal nerve off the semilunar ganglion, the indusium griseum, and moyamoya vessels.<sup>16–19</sup>

Incidental cavities are occasionally found within the hippocampus in patients who undergo imaging studies. Such cavities are often considered normal and may represent physiologic or residual cavities of the vestigial hippocampal sulcus.<sup>21,22</sup> The current study demonstrated that, in the normal population, residual cavities of the vestigial hippocampal sulcus are frequent. The overall incidence of cavity detection in patients with TGA, however, far exceeds that in controls. In addition, the size of the cavities seen in patients with TGA is distinctly larger than that seen in controls.

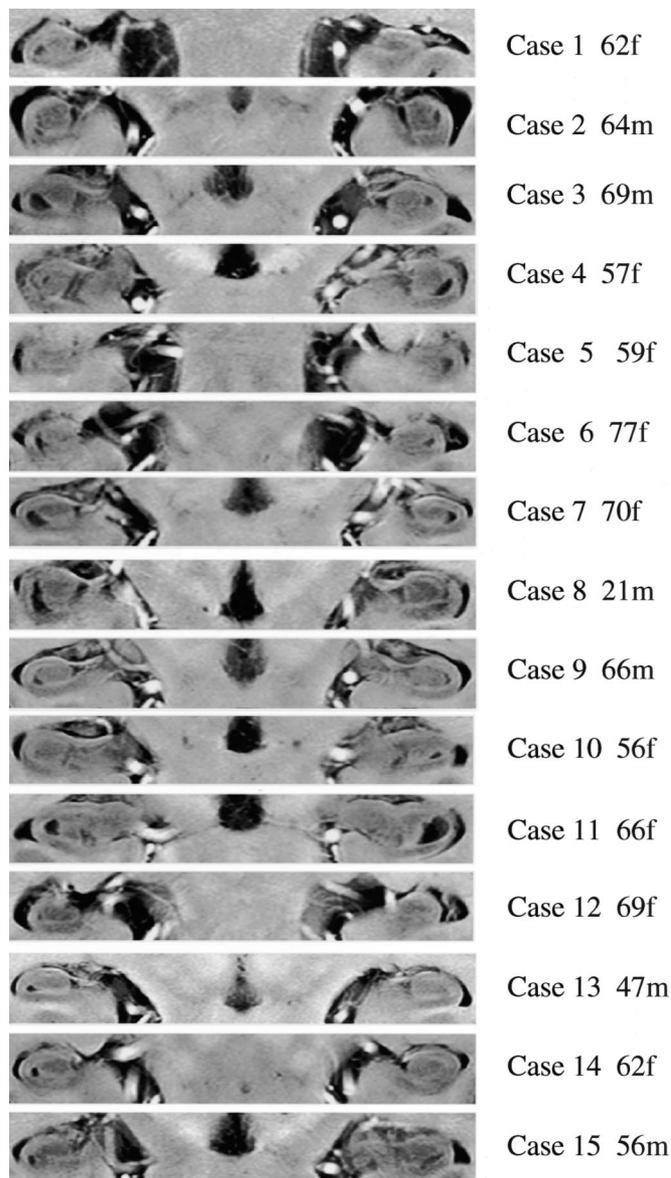
Whether the cavities in this study represent the result of intraparenchymal pathology or significantly enlarged residual cavities of the vestigial hippocampal sulcus is uncertain. Nevertheless, even if the findings constitute the latter, considering the Kellie-Monroe doctrine,<sup>23</sup> which states that loss of parenchymal tissue results in a compensatory increase in adjacent CSF space, it appears likely that the higher incidence of cavity detection and larger cavity size found in patients with TGA represent an indirect sign of parenchymal loss in the hippocampus adjacent the hippocampal sulcus.<sup>24</sup> In either case, the current study strongly suggests that underlying processes affecting the hippocampus in patients with TGA are likely to be focal in the area adjacent to the



**Figure 2.** (A) Schematic drawing of a residual cavity of the vestigial hippocampal sulcus, redrawn based on the schema of Duvernoy,<sup>30</sup> and incidental residual cavity, <2 mm in width, seen on T2 reversed MRI (arrow; width indicated by b). (B) A case of transient global ischemia (a 49-year-old man who had cardiac arrest, with 7 weeks of survival) showing a lesion in CA1 area of Lorente de No. (From Graham and Lantos.<sup>24</sup>) (C) Representative coronal and axial images of a patient with bilateral large cavitory lesions (Patient 11).

apex of the hippocampal fold, which is distinctively different from those disease processes affecting hippocampal neurons diffusely, such as those seen in hippocampal sclerosis or Alzheimer disease.<sup>24</sup>

The anatomic distribution of the abnormal lesions suggests several possibilities. As noted, these cavities strongly indicated that causative processes occur exclusively in the vicinity of the apex of the hippocampal fold, an area histopathologically identified



**Figure 3.** T2 reversed images at the level of the body of the hippocampus of Patients 1 to 15. Except for the cavity seen in Patient 12, all cavities are larger than those seen in normal volunteers.

as the Sommer sector. Neurons of the Sommer sector have been shown to be selectively vulnerable to ischemic or hypoxic/anoxic insults. Limited neuronal loss leading to cavity formation in this region is recognized by pathologists as typical of premortem hypoxia or ischemia rather than infarction due to thromboembolic vascular occlusion, which results in nonselective necrosis of all cell types.<sup>24</sup> Furthermore, neurons in the Sommer sector, especially the CA1 neurons of Lorente de No, are known to be selectively vulnerable to mechanisms relating to delayed cell death.<sup>25,26</sup> Therefore, the extent of hippocampal damage recognized on pathologic examination becomes more evident as the interval between insult and the histopathologic examination increases. It

thus appears plausible, given the morphologic similarities between the lesions detected in our study and those seen on pathology (see figure 2B) that the imaged lesions are the result of a hypoxic or ischemic event. These findings are also compatible with a recent report of delayed abnormalities detected by DWI.<sup>15</sup>

It is known that venous obstruction may result in frank cerebral infarction (venous infarction), the underlying molecular mechanism of which is believed to be heterogeneous, including vasogenic edema due to intimal vessel damage, insufficient tissue perfusion due to increased cranial pressure, and a decline in cerebral blood flow.<sup>27</sup> Similarly, neural dysfunction due to venous congestion, especially neurons in the hippocampal area, has been postulated as a pathogenetic mechanism of TGA.<sup>28,29</sup> DWI studies indicate that changes in diffusion characteristics similar to those seen in acute ischemia can also be observed associated with venous congestion. To our knowledge, no specific studies designed to follow the changes of delayed neuronal death associated with venous congestion have appeared in the literature. It is, however, highly plausible that, similar to ischemia or hypoxia, venous obstruction of the hippocampal area may indeed trigger pathologic cascades leading to delayed neuronal death in the CA1 region. Although it remains speculative, a recent observation of delayed abnormalities in DWI in patients with TGA<sup>15</sup> may reflect a similar pathologic phenomenology.

Assuming that delayed Sommer sector neuronal cell death may indeed be a pathophysiologic mechanism in TGA, we analyzed our patients for risk factors. A hypoxic cause was not tenable because none of the patients had a hypoxic/anoxic event. Although purely conjectural, an ischemic mechanism seems tenable in 11 of our 15 patients with TGA who had identifiable risk factors for vascular disease, including seven for microvascular disease. Nevertheless, no potential risk factor could be identified in the remaining four patients. These patients also did not have any apparent risk factors leading to venous obstruction or congestion such as hypercoagulopathy, dehydration, and physical restraints.

Until clearly defined, TGA should be considered as caused by various etiologic factors. The current study, however, demonstrated potential structural abnormalities in the Sommer sector of the hippocampus in most of the cases and suggested that delayed neuronal loss within CA1 area of Lorente de No may represent an important sequel of TGA.

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