

[ORIGINAL ARTICLE]

Relationship between Cytotoxicity in the Hippocampus and an Abnormal High Intensity Area on the Diffusion-weighted Images of Three Patients with Transient Global Amnesia

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Abstract:

Objective An abnormal high intensity area (HIA) on diffusion-weighted imaging (DWI) indicates the presence of cytotoxic edema and has been reported to be observed in the hippocampus of patients with transient global amnesia (TGA). The appearance of an HIA on DWI is usually delayed after the onset of patients with amnesia in TGA; thus, the significance of the HIA was evaluated in patients with TGA.

Methods Three adult TGA patients who had a unilateral HIA on DWI (right, n=2; left, n=1) were enrolled. These patients were hospitalized due to acute-onset amnesia. Amnesia subsided within 24 hours of hospitalization in all three patients.

Results The HIA was confined to the upper lateral zone of the body in the unilateral hippocampus where the CA1 region exists. The lesions were confirmed after the improvement of amnesia in the three patients. The location of the lesions corresponded to the watershed area where the upper and lower hippocampal arteries were anastomosed.

Conclusion Cytotoxicity caused by glutamate-mediated calcium influx in the neurons of the CA1 region was recently reported in the pathogenesis of TGA. Based on the pathogenesis, the cytotoxicity was considered to have been caused by calcium overload throughout the entire CA1 region, and amnesia occurred due to this cytotoxicity. The cytotoxicity was more marked in the lesions because of the lower blood flow in the watershed area and was prolonged after the function of the CA1 region (excluding the watershed area) improved, which led to cytotoxic edema in the lesions.

Key words: transient global amnesia, diffusion-weighted imaging, CA1 region, watershed area

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Introduction

Transient global amnesia (TGA) tends to occur in middle-aged and elderly patients, and is characterized by the presence of selective anterograde and retrograde amnesia lasting up to 24 hours and the absence of other neurological signs or symptoms (1-7). TGA is associated with a marked reduction in the retrograde episodic memory, including executive functions and recognition (3). Patients with TGA typically repeatedly ask questions about where they are and why they

are there (8). Several causes of TGA have recently been proposed, including ischemia, hyperventilation-induced vasoconstriction, migraine, epilepsy, venous congestion, psychological disturbance, and metabolic disorders (i.e. glutamate-mediated calcium influx) (2, 5, 9). Amnesia has been demonstrated to be associated with the temporal lobe structures, including the hippocampus (2). In the coronal section of the body of the hippocampus, there are two layers: the cornu ammonis (Ammon's horn) and the dentate gyrus (5, 10). The former structure consists of four regions (CA1, CA2, CA3, and CA4). An abnormal high intensity area (HIA) in

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Table. Breakdown of the MRI Findings in Our Three Patients with Transient Global Amnesia.

Patient's number	Age/sex	Duration of amnesia (hours)	Duration between the onset and the MRI examination (hours)		The first MRI findings in the CA1 region			The second MRI findings in the CA1 region		
			First	Second	DWI	ADC map	FLAIR	DWI	ADC map	FLAIR
1	56/m	23	29	77	high	low	-	high	low	-
2	58/m	11	17		high	low	-	not performed		
3	57/f	22	12	74	-	-	-	high	low	high

DWI: diffusion weighted imaging, ADC: apparent diffusion coefficient, f: female, m: male, MRI: magnetic resonance imaging, FLAIR: fluid-attenuated inversion recovery

the CA1 region of the hippocampus has recently been reported on the diffusion-weighted magnetic resonance imaging (DW-MRI) of patients with TGA. This abnormal lesion in the hippocampus was exclusively localized in the lateral portion where the CA1 region exists (2, 5, 11). In previous reports on TGA, a delay in the detectability of the lesion in the CA1 region was noted (1, 2, 4, 9, 12-15). The lesion in the CA1 region was confirmed after a period of amnesia (1, 2, 4, 9, 12-15); however, the significance of the delayed appearance of the abnormal HIA on diffusion-weighted imaging (DWI) has not been previously investigated, based on the distribution of the arterial supply in the CA1 region. Thus, we examined three patients with TGA in whom an abnormal HIA was detected in the CA1 region on DWI, and evaluated the association between the delayed appearance of the abnormal HIA on DWI and the distribution of the arterial supply in the CA1 region.

Materials and Methods

Three patients with TGA in whom acute lesions were detected by MRI were enrolled in the study. The Institutional Research Review Board of Nihon University approved this study. Written informed consent was obtained from the patients or their representatives, and the privacy of the patients was strictly protected. Neurological examinations were performed by board-certified specialists (K.O., Y.S., S.K.) of neurology in our Division. MRI examinations were conducted using an Achieva system (1.5-T; Philips Medical Systems, Best, Netherlands). DWI were performed with the spin echo (TSE) echo planar imaging (EPI) method using an Achieva system [repetition time (TR)/echo time (TE) 4,000 ms/76 ms; slice thickness 5 mm; field of view (FOV) 230 mm×230 mm; matrix 104×140]. T2-weighted images were taken with the SE EPI method using an Achieva system (TR/TE 4,644 ms/100 ms; slice thickness 5 mm; FOV 230 mm×230 mm; matrix 384×247). Apparent diffusion coefficient (ADC) map images were taken with the SE EPI method using an Achieva system (TR/TE 1,500 ms/40 ms; slice thickness 5 mm; FOV 230 mm×230 mm; matrix 384×247). Fluid-attenuated inversion recovery (FLAIR) imaging was performed with the SE EPI method using an Achieva system (TR/TE 9,000 ms/110 ms; slice thickness 5 mm; FOV 230 mm×230 mm; matrix 384×247).

Results

Review of the clinical courses and MRI findings of the three patients (Table)

Patient 1

Patient 1 was a right-handed 56-year-old man with dyslipidemia. He had recently been overworked and had been tired for the past week. He was under stressful conditions at work. He suddenly became unable to remember the content of his breakfast or his workplace early in the morning. His family, who were worried about him, accompanied him to the station, where he forgot the name of his company and the commuter train that he would ordinarily take to work. He repeatedly asked his family about the name of his company and the commuter train. He was admitted to our division by his family on the evening of the same day. On admission, he was conscious, but became disoriented over time. He was hypertensive (156/115 mmHg) and afebrile (36.5°C). He was still unable to remember the location of his company or the station near his house. The other neurological findings were normal. He scored 20 points on the Hasegawa's Dementia Scale-Revised (HDS-R) (full score: 30 points). In the HDS-R, disorientation regarding the date was noted. Recall of the names of presented objects and backward recall of numbers were markedly impaired. He could not perform easy calculations. When asked to subtract 7 from 93, and 7 from 86, he answered 89 and 77, respectively. No areas of abnormal density were detected on brain computed tomography (CT) examinations on admission. After brain MRI on the second day of hospitalization (29 hours after onset), an abnormal HIA in the lateral zone of the body of the right hippocampus was observed on DWI (Fig. 1A). An abnormal low intensity area (LIA) was found in the same region on an ADC map (Fig. 1B). FLAIR and T2-weighted imaging revealed no areas of abnormal intensity in the hippocampus. Electroencephalography (EEG) conducted the day after hospitalization showed no epileptic discharges. Hippocampal infarction was suspected and he remained hospitalized. Argatroban hydrate was administered intravenously. In the early morning of the next day, the patient's amnesia and disorientation completely subsided, and he was able to perform easy calculations correctly. The total duration of amnesia was 23 hours. Brain MRI on the fourth

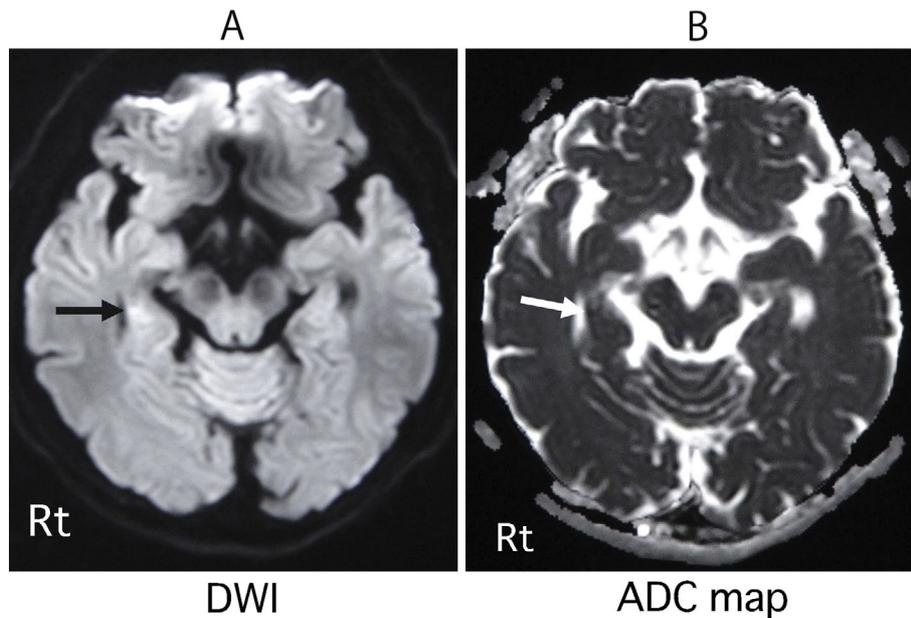


Figure 1. Brain MRI on the second day of hospitalization (Patient 1). A small high intensity area in the upper lateral zone of the body of the right hippocampus was found on DWI (A). An ADC map also revealed a small low intensity area in the same region (B). Rt: right, DWI: diffusion weighted imaging, ADC: apparent diffusion coefficient

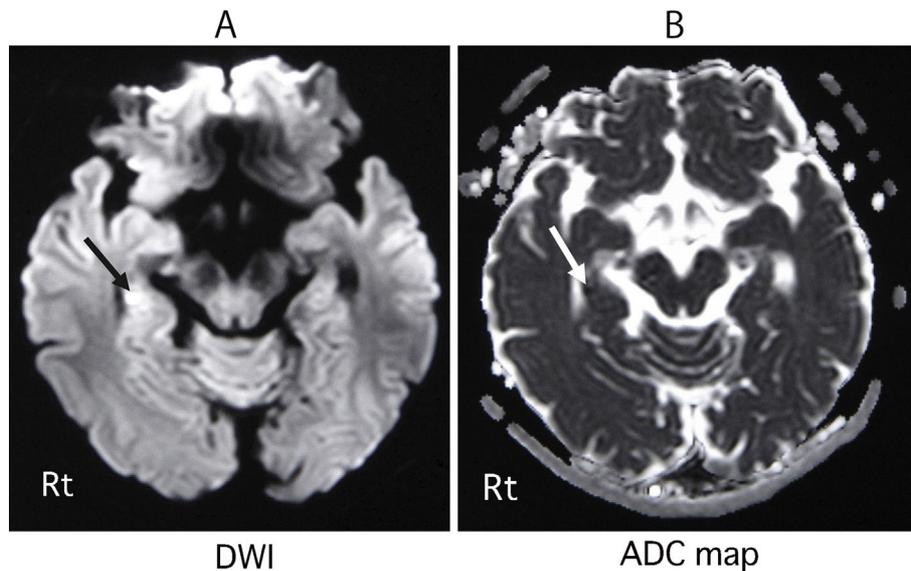


Figure 2. Brain MRI on the fourth day of hospitalization (Patient 1). A small high intensity area in the upper lateral zone of the body of the right hippocampus was observed on DWI (A). This lesion was a small low intensity area on an ADC map (B). The lesion was more evident on the second examination. Rt: right, DWI: diffusion weighted imaging, ADC: apparent diffusion coefficient

day of hospitalization (77 hours after onset) revealed an abnormal HIA in the hippocampus on DWI (Fig. 2A). An abnormal LIA was also found in the same region on a ADC map (Fig. 2B). This lesion was visualized more clearly (Fig. 2A and B) than the lesion that was observed on admission on both DWI and the ADC map (Fig. 1A and B). However, there were no abnormalities on FLAIR or T2 imaging of the hippocampus.

Patient 2

Patient 2 was a right-handed 58-year-old man with no relevant past history. He had worked hard and stayed at his company late every night for the last two weeks. One evening after finishing work, he suddenly became unable to remember the events of his day at work. Additionally, he was unable to remember some events from the previous day, and could not remember the way to his home from the nearby

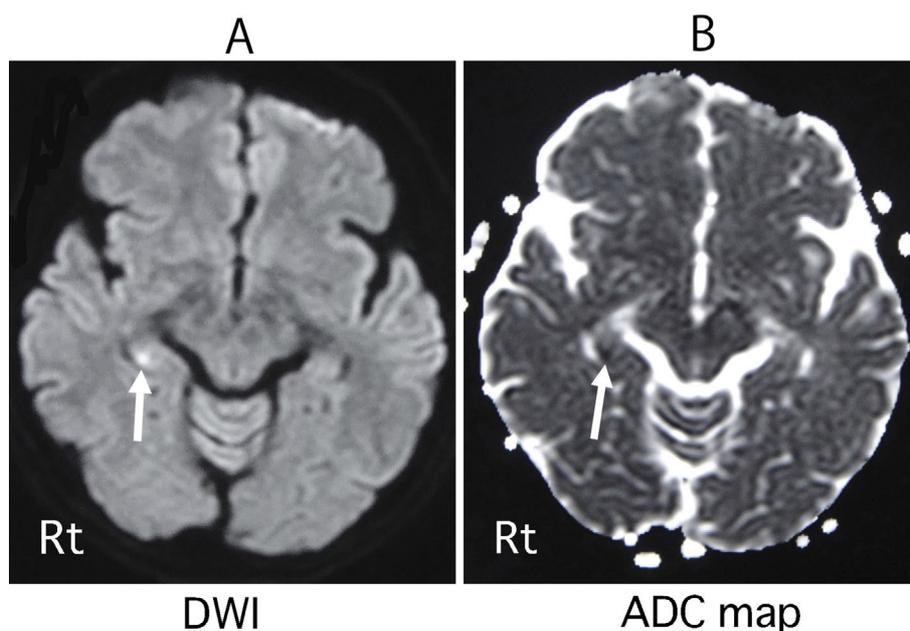


Figure 3. Brain MRI on the second day of hospitalization (Patient 2). A small high intensity area in the upper lateral zone of the body of the right hippocampus was observed on DWI (A). This lesion was a small low intensity area on an ADC map (B). The lesion was more evident on the second examination. Rt: right, DWI: diffusion weighted imaging, ADC: apparent diffusion coefficient

station or the location of his company. He repeatedly asked the same questions and was admitted to our hospital by his work colleagues the evening of the same day. Upon admission, he was conscious and his vital signs were within normal ranges (blood pressure, 133/85 mmHg; body temperature, 36.8°C). He talked with other people and obeyed simple commands, but was otherwise disoriented. He forgot the content of his dinner and his journey to the hospital by taxi. The other neurological findings were normal. He scored 25 points on the HDS-R. On the HDS-R, the date, persons, and places were correctly oriented, but the recall of names of presented objects was markedly impaired. No areas of abnormal density were detected on brain CT. He was suspected to have hippocampal infarction and was hospitalized. Argatroban hydrate was administered intravenously. Early in the morning of the next day, he exhibited neither amnesia nor abnormal disorientation regarding his location or the date. Brain DWI-MRI performed the next day (17 hours after onset) revealed an abnormal HIA in the lateral zone of the body of the right hippocampus (Fig. 3A). An abnormal LIA was observed in the same region on an ADC map (Fig. 3B). There were no areas of abnormal intensity in the hippocampus on FLAIR or T2-weighted imaging. EEG performed the next day showed no epileptic discharge. The duration of amnesia was 11 hours.

Patient 3

Patient 3 was a 57-year-old woman with familial hypercholesterolemia (HC) and diabetes mellitus (DM). She caught a common cold one week before admission. The cold gradually subsided, but general fatigue remained. In the morning, she suddenly became unable to remember to visit

the nearby hospital to receive medication for HC and DM as well as the name of the hospital or her history of regular ambulatory attendance of this hospital in the previous year. She could not remember the trip that she and her family had taken in the previous week, and repeatedly asked her family about the name of the hospital and the date on which she had gone on the trip. She was admitted to our hospital in the morning of the same day. Upon admission, her vital signs were within the normal ranges (blood pressure, 123/85 mmHg; body temperature, 36.8°C). She was conscious, but disoriented about the date and her location, and could not perform easy calculations. When asked to subtract 7 from 93, she answered 83. When she was re-asked the same question, she answered 84. She could remember the correct names of doctors or objects immediately after memorizing them, but not after ten minutes had passed. Repetition of figures, naming of objects, and reading of words were normal. Other neurological findings were normal. The brain MRI (12 hours after onset) and CT findings upon admission were normal. Hippocampal infarction was suspected and she was hospitalized. Ozagrel sodium was intravenously administered. Her recent memory and orientation improved by the early morning of the next day; however, she could not remember the events from the day of admission. She became able to perform easy calculations. DWI and FLAIR imaging from brain MRI examinations on the second day of hospitalization (74 hours after onset) showed an abnormal HIA in the lateral zone of the body of the left hippocampus (Fig. 4A and C). An abnormal LIA in the same region was observed on an ADC map (Fig. 4B). There were no areas of abnormal intensity on T2-weighted imaging. EEG performed

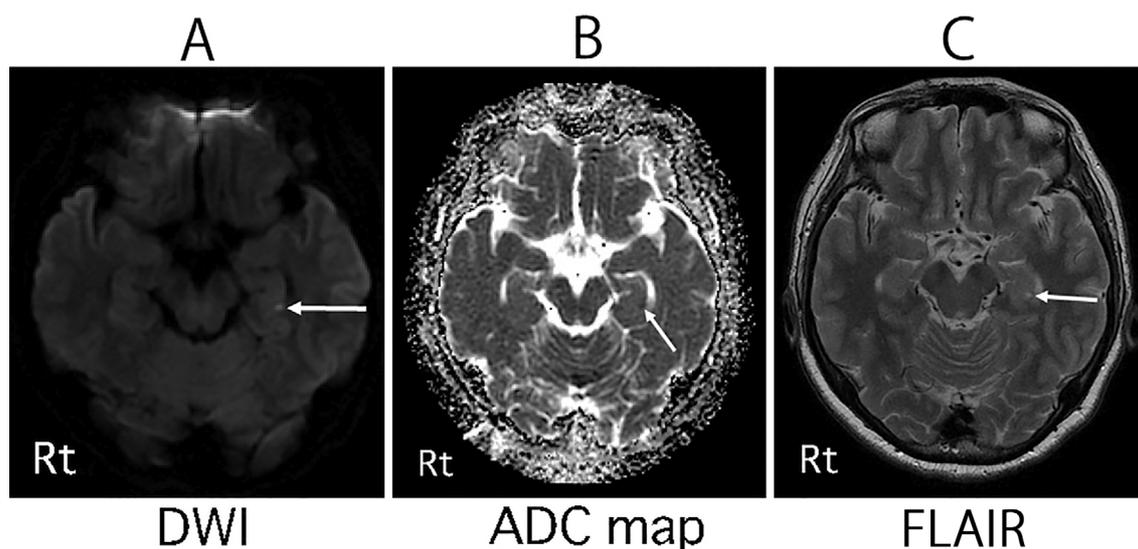


Figure 4. Brain MRI on the third day of hospitalization (Patient 3). A small high intensity area in the lateral region of the body of the left hippocampus was found on DWI (A). This lesion was a small low intensity area on an ADC map (B) and a small high intensity area on FLAIR imaging. Rt: right, DWI: diffusion weighted imaging, ADC: apparent diffusion coefficient, FLAIR: fluid-attenuated inversion recovery

the next day showed no epileptic discharge. The duration of amnesia was 22 hours.

Discussion

TGA is defined as a sudden-onset of selective anterograde and retrograde amnesia characterized by a loss of memory of recent events and an inability to retain new memories (16). Anterograde amnesia is more severe than retrograde amnesia (2). Patients with TGA are usually perplexed and disoriented about the time and their location, but exhibit no impairment of consciousness or personal identity (16). Amnesia subsequent to stressful events occurred abruptly, and then subsided within 24 hours in the three patients of the present study. No other remarkable neurological signs or symptoms were observed. These clinical features of our patients were consistent with the characteristics of TGA. In all three patients, the lesions in our patients were identified after their amnesia subsided, and were located in the lateral area of the body of the hippocampus and adjacent to the inferior horn of the lateral ventricle. We examined the mechanism underlying the appearance of HIAs in the CA1 region of the hippocampus on DWI, based on the hypothesized mechanism (cytotoxicity caused by glutamate-mediated calcium influx) and the distribution of the arterial supply in the hippocampus.

The hippocampus is divided into the anterior head (head), body, and posterior tail (tail) in the axial position (Fig. 5A) (10, 17). In the coronal section of the body, the hippocampus consists of the cornu ammonis (Ammon's horn) and the dentate gyrus (5). The cornu ammonis is subdivided into the CA1, CA2, CA3, and CA4 regions

(Fig. 5B) (5, 10). In the coronal section, the inferior horn of the lateral ventricle encompasses the upper zone of the CA1 region (Fig. 5B) (5). Thus, the lesions of the three patients were considered to be located in the upper lateral zone of the CA1 region of the hippocampus. However, there was a limitation in identifying the precise localization of the lesions in the hippocampus because coronal section MRI was not performed.

Autobiographical memory is a theoretical concept referring to the memory of personal events in an individual's life (11). The hippocampus plays a central role in episodic memory, including autobiographical memory, as neuroimaging data demonstrated hippocampal activation in autobiographical memory retrieval tasks, supporting that the hippocampus is an integral structure in the autobiographical network (11). Within the hippocampal memory system, the CA1 region relays direct and polysynaptic intrahippocampal circuits (11), and receives information from the parahippocampal postrhinal and medial entorhinal cortices (2). The CA1 region is essential for the retrieval of remote episodic memories (2). Postsynaptic output from neurons in the CA1 region projects to the entorhinal cortex throughout the subiculum (Fig. 5B) (2). Thus, dysfunction of the CA1 region disrupts the process of memory formation and affects the output relay function of the hippocampus (2). The CA1 region is characterized by an exclusive vulnerability to ischemia, metabolic and oxidative stress induced by hypoxia, β -amyloid neurotoxicity, and glutamate-mediated calcium influx (2, 3, 5, 12, 15, 18). The hippocampus is supplied by the hippocampal artery (Fig. 5B) (9, 19). The hippocampal artery diverges into the upper (dorsal) hippocampal artery and the lower (ventral) hippocampal ar-

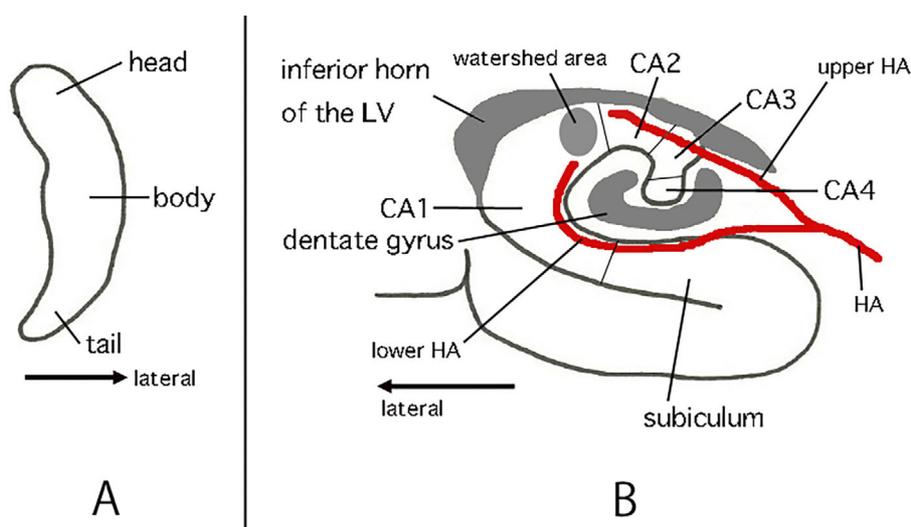


Figure 5. The anatomy and blood supply of the hippocampus. The hippocampus is divided into three portions (head, body, and tail) in the axial section (A). In the coronal section of the body, there are two gray matter areas (the cornu ammonis and the dentate gyrus). The cornu ammonis (Ammon's horn) consists of four regions (CA1, CA2, CA3, and CA4). The CA1 region is supplied by the lower hippocampal artery. The other regions (CA2, CA3, and CA4) are supplied by the upper hippocampal artery and several small arteries. The watershed area between the upper and lower hippocampal arteries is located in the upper part of the CA1 region (B). HA: hippocampal artery, LV: lateral ventricle

tery (9, 19). The CA1 region is supplied by the lower hippocampal artery (Fig. 5B) (5, 9, 19). The other regions (CA 2 to CA4 regions) are supplied by the upper hippocampal artery in addition to several small arteries (Fig. 5B) (9, 19). Moreover, the number of penetrating branches in the CA1 region is less than that in other regions (9, 19). The lower hippocampal artery reaches the upper lateral zone of the body of the CA1 region and anastomoses with the upper hippocampal artery (Fig. 5B) (9, 19), which indicates that arterial supply in this area is less than that in other areas in the CA1 region (9, 19). Accordingly, the upper lateral zone of the body of the CA1 region corresponds to the watershed area between the upper and lower hippocampal arteries (Fig. 5B) (9, 19).

An HIA on DWI indicates the presence of cytotoxic edema in the affected tissue, and is caused by ischemia, epilepsy, and encephalitis (2, 4). The ADC map mirrors the stage of cytotoxic edema (2, 4). In previous MRI studies of TGA, an HIA on DWI was usually accompanied by an LIA on an ADC map (4, 20). An LIA on an ADC map also indicates cytotoxic edema (4). The timing of the detection of an abnormal HIA on DWI is reported to be delayed after the period of amnesia in TGA patients (1, 13-15). The abnormal HIA on DWI is reported to appear at 24-48 hours after the onset of symptoms and to be detected for up to 7-10 days (2, 4, 15). This indicates that the initial appearance of the HIA on DWI was delayed by the period of amnesia. The maximum period for which the abnormal lesion was detectable was 48-72 hours after the onset (2, 4, 12). The maximum period for which the abnormal lesion was detectable was further delayed after the first appearance. In the first

MRI examinations in our study, HIAs were detected after the disappearance of amnesia in two of the three patients (Table). The duration between the onset and the first MRI examinations was the shortest in Patient 3; however, the HIA was absent, and amnesia was still present at the time of the first MRI examinations. During the second MRI examinations, HIAs were detected in two patients, excluding one patient in whom a second MRI was not performed (Patient 2). The lesion was more apparent than in the first examination (Patient 1). In the second examinations, the abnormal lesion appeared on DWI as well as ADC maps, whereas in the first examinations, no lesions were detected in the other patient (Patient 3). Abnormal lesions in the hippocampus were detected after amnesia had subsided in three patients (Table). This result was consistent with the delay in the detectability of the abnormal HIA on DWI of TGA patients (1, 13-15). The increase in high intensity on DWI in one patient (Patient 1) may have been related to a delay in the maximum of detectability of the lesions (2, 4, 12). In comparison to DWI, FLAIR imaging only revealed an HIA in one patient (Patient 3). FLAIR imaging reflected cytotoxic and vasogenic edema, and did not distinguish between the two conditions (21), whereas DWI reflected cytotoxic edema (2, 4). In our patient with an abnormal HIA on the FLAIR imaging, vasogenic edema was also considered in addition to cytotoxic edema.

A previous report on TGA assessed the laterality of the HIA in the DWI in the hippocampus (22). In this previous report, a TGA patient whose lesion was located on the right side predominantly exhibited visual memory impairment. In contrast, verbal memory was predominantly impaired in a

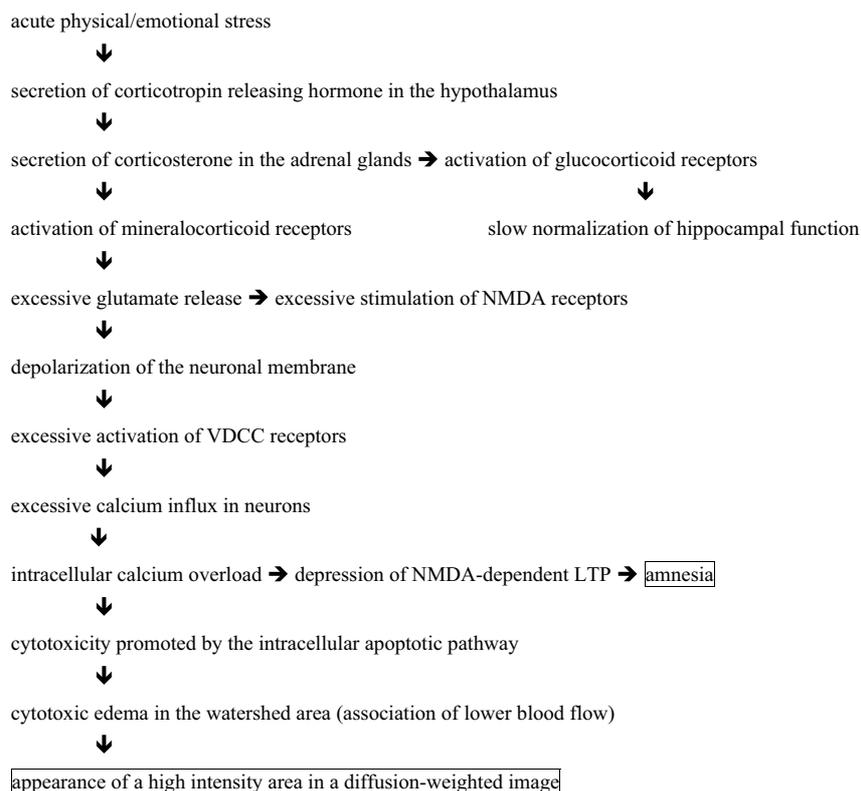


Figure 6. The probable pathogenesis in the CA1 region in our three patients. Corticosterone caused the excessive release of glutamate via the mineralocorticoid receptors. Glutamate overstimulated the NMDA receptors and depolarized the neuronal membrane. This depolarization activated the VDCC receptors, which led to the influx of calcium to the neurons. This condition caused cytotoxicity and inhibited LTP. The cytotoxicity of the neurons in the watershed area led to cytotoxic edema. NMDA: N-methyl-D-aspartate, LTP: long-term potentiation, VDCC: voltage-dependent calcium

TGA patient whose lesion was located on the left side, based on an analysis using the Wechsler Memory Scale-Revised (WMS-R) (22). The WMS-R was not employed in the examinations of our patients. Thus, visual memory and verbal memory were not compared.

Inability to perform simple calculations was observed in two patients. This finding was considered to occur due to dyscalculia or impairment of generalized attention during amnesia. Previous reports on calculations using functional MRI indicated the importance of the prefrontal cortex and the parietal lobe (23). In TGA patients, hypoperfusion was detected in the precuneus and in the superior area of the left parietal lobe in addition to the inferior area of the left temporal lobe (24). Involvement of the angular gyrus of the parietal lobe in TGA was also reported in a study using a three-dimensional stereotactic ROI template (25). It is possible that dyscalculia also occurred in two patients (Patients 1, 3) due to the involvement of the parietal lobe during the period of amnesia; however, measurements of the cerebral blood flow and functional MRI were not carried out. Accordingly, the inability to perform simple calculations was not directly caused by dyscalculia.

Recent research indicated hypersensitivity of the hypothalamus-pituitary-adrenal axis and higher cortisol levels due to stress in TGA patients (26). Glutamate-mediated

calcium influx in the neurons in the CA1 region has recently been reported to be involved in the pathogenesis of TGA (Fig. 6) (2, 4, 12, 15, 18). In this pathogenesis (Fig. 6) (27), acute emotional and behavioral stress induced an increase in the corticotropin-releasing hormone (CRH) levels in the hypothalamus, and CRH subsequently caused the release of the corticosterone in the adrenal glands (2, 28). Corticosterone entered the brain and bound to mineralocorticoid and glucocorticoid receptors (17, 29, 30), which are abundant in the neurons of the CA1 region (17, 29, 31). Corticosterone quickly enhanced glutamate release in the CA1 region via activation of mineralocorticoid receptors (Fig. 6) (30, 32). When corticosterone was excessively released, an excess of glutamate release also occurred (Fig. 6) (27, 33). Glutamate then activated N-methyl-D-aspartate (NMDA) receptors (27, 34). Activation of NMDA receptors induced long-term potentiation (LTP) of glutamatergic synaptic transmission in the CA1 region under normal conditions (2, 33). Depolarization of the membranous potential of neurons was induced by release of glutamate (Fig. 6) (35), and activated voltage-dependent calcium (VDCC) receptors (36). Activated VDCC receptors promoted calcium influx (27). In the condition of excessive glutamate accumulation in the extracellular space, the amount of intracellular calcium was increased

(Fig. 6) (33, 34, 37), which resulted in calcium-mediated cytotoxicity in the CA1 region (2, 3, 27, 33-36) leading to amnesia caused by the depression of NMDA-dependent LTP in the CA1 region (Fig. 6) (15, 27, 38). In the three patients in our study, stressful events prior to the occurrence of TGA may have induced the abovementioned pathogenesis (glutamate-mediated calcium influx) in the neurons of the CA1 region (15); however, the extent of lesions in the three patients did not involve the entire CA1 region. Cytotoxicity in the CA1 region was more prominent in the upper lateral zone of the body where the watershed area exists because the blood flow in this area was low. Consequently, cytotoxic edema was considered to have occurred in the confined lesions due to the prominent cytotoxicity that persisted in the lesions after the disappearance of amnesia. The delayed appearance of the confined HIAs in the CA1 region on DWI was likely due to the cytotoxicity caused by the glutamate-mediated calcium influx and the location of the watershed area in the CA1 region.

Acute glutamate-induced cellular stress has recently been considered in the pathogenesis of TGA (2, 4, 12, 15, 18). In our three patients, the occurrence of TGA was consistent with this hypothesis. Calcium overload caused cytotoxicity in the neurons throughout the entire CA1 region (2, 3, 27, 33-35). The extent of the lesions was limited to the upper lateral zone of the CA1 region where the watershed area exists (5, 9, 19). The cytotoxicity was prominent in the watershed area because of the lower blood flow, as shown on DWI, and caused cytotoxic edema in the lesions.

The authors state that they have no Conflict of Interest (COI).

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