Keywords: FDG-PET; memory; postoperative change; selective amygdalohippocampectomy; temporal lobe epilepsy

Abbreviations: AED = antiepileptic drug; FDG = [^{18}F]-fluorodeoxyglucose; IQ = intelligence quotient; MTLE = mesial temporal lobe epilepsy; SAH = selective amygdalohippocampectomy

Introduction

Mesial temporal lobe epilepsy (MTLE) with hippocampal sclerosis is the most common localization-related epilepsy in adults. MTLE is characterized by epileptic activity arising from the mesial temporal region where there are neuropathological changes. MTLE is also associated with broad temporal lobe functional abnormalities, shown by an alteration of cerebral glucose metabolism and neuropsychological deficits such as memory dysfunction. Moreover, neuroimaging studies using [^{18}F]-fluorodeoxyglucose (FDG), [^{11}C]-flumazenil PET or magnetic resonance spectroscopy have shown that functional abnormalities extend beyond the temporal lobe (Arnold *et al.*, 1996; Hammers *et al.*, 2002; Mueller *et al.*, 2004).

For patients with medically intractable MTLE, surgery is one of the more favourable options in order to achieve good seizure control (Wiebe *et al.*, 2001). Anterior temporal lobectomy, where the anterior one-third of the temporal lobe is resected, has been a standard surgical procedure because the anterior part of the temporal lobe was considered to be a functionally 'silent area' (Gibbs *et al.*, 1948; Falconer *et al.*, 1955). However, recent FDG-PET and neuropsychological studies have described a postoperative decrease in cerebral glucose metabolism and associated cognitive impairments following anterior temporal lobectomy (Lee *et al.*, 2002; Joo *et al.*, 2005*b*; Tellez-Zenteno *et al.*, 2007). Decreased glucose metabolism inside and outside the remnant temporal lobe is assumed to be the result of deafferentiation following the massive resection of anterior temporal structures (Joo *et al.*, 2005*b*).

Selective amygdalohippocampectomy (SAH) has been advocated as a less-invasive surgical procedure in order to preserve postoperative cerebral functions. Trans-sylvian SAH, however, resulted in postoperative verbal memory decline in patients with MTLE of the language-dominant hemisphere (Gleissner *et al.*, 2002; Gleissner *et al.*, 2004; Morino *et al.*, 2006; Helmstaedter *et al.*, 2008). One hypothesis is that the procedure disconnects the long-tract fibres that pass through the white matter of the temporal stem, such as the uncinate fasciculus or the cholinergic projection fibres from the nucleus basalis of Meynert (Selden *et al.*, 1998; Ikeda *et al.*, 2005; Helmstaedter *et al.*, 2008).

It is thought that subtemporal SAH could offer an alternative procedure that prevents damage to the lateral temporal neocortex and temporal stem white matter (Hori *et al.*, 1993; Park *et al.*, 1996). Recent studies indicate that subtemporal SAH results in the preservation or improvement of postoperative cognitive function in patients with intractable MTLE (Hori *et al.*, 2003; Mikuni *et al.*, 2006; Hori *et al.*, 2007). A preliminary study suggested that subtemporal SAH preserving the basal temporal language area achieved good seizure control and improved verbal memory in patients with MTLE in the language-dominant hemisphere (Mikuni *et al.*, 2006). Although such neuropsychological studies suggest that cerebral function improves after subtemporal SAH, the neural substrate for this remains unclear.

The purpose of the current study was to evaluate the effects on cerebral glucose metabolism and memory function of subtemporal SAH that preserved the basal temporal language area in patients with medically intractable MTLE. Elucidating the functional changes in the human brain after the selective removal of an epileptogenic lesion is of both clinical and neuroscientific interest.

Patients and Methods

Patients

All patients over the age of 16 years who underwent subtemporal SAH for intractable MTLE with hippocampal sclerosis between 2002 and 2006 at Kyoto University Hospital were considered potential candidates for the study. Among them, 15 patients met the inclusion criteria for this study (8 left MTLE patients and 7 right MTLE patients). All patients underwent preoperative and postoperative neuropsychological testing. All but two patients (Patients 6 and 14) consented to undergo postoperative FDG-PET. The interval between surgery and postoperative assessment was 1–5 years (mean 2.6 years). The results of the neuropsychological tests 1 year after surgery in five patients with dominant-side MTLE have been reported elsewhere (Mikuni *et al.*, 2006).

The inclusion criteria were as follows: (i) medical history and seizure semiology consistent with MTLE, such as epigastric, autonomic or psychic auras, followed by motor arrest, progressive clouding of consciousness, oro-alimentary or manual automatisms and autonomic phenomena; (ii) a unilateral epileptic focus in the anterior temporal regions confirmed by prolonged video-electroencephalography (EEG) monitoring and (iii) unilateral hippocampal sclerosis detected by conventional 1.5 T MRI and glucose hypometabolism determined by FDG-PET in the affected side of the temporal lobe in accordance with the EEG findings. The exclusion criteria were as follows: (i) focal neurological abnormalities on physical examination or psychiatric diseases; (ii) significant past medical history suggesting causes of temporal lobe epilepsy other than MTLE with hippocampal sclerosis (that is, encephalitis or severe head trauma); (iii) MRI abnormalities including significant brain atrophy outside the mesial temporal lobe; (iv) epileptic paroxysms in the extratemporal area on EEGs and (v) a full-scale intelligence quotient (IQ) <65.

The preoperative full-scale IQ was significantly lower in patients with dominant-side MTLE than in those with non-dominant-side MTLE. There were no statistical differences between the two groups with respect to the male/female ratio, level of education (number of years), duration of the disease, age at surgery, postoperative interval or number of seizure-free patients within each group. At postoperative evaluation, the numbers or dosages of antiepileptic drugs (AEDs) remained unchanged from the preoperative state in seven patients, decreased in six patients (based on >2 years freedom from seizures) and increased in two patients because of poor seizure control.

Table 1 Patients' data

Patient No.	Age (years) at surgery, Sex	Age (years) of onset	Language-dominant side	Resected side	Pathological findings	Postoperative interval (years)	Seizure outcome (Engel's class)	AEDs (mg) preoperetion	AEDs (mg) postoperation
Dominant side resection									
1	25, F	7	L	L	HS	4.0	I	C (900), V (800), P (325)	C (850), V (700), P (325)
2	22, F	8	L	L	HS	1.2	I	C (800), P (212.5), N (1), M (2.5), A (500)	Unchanged
3	39, F	8	L	L	HS	3.9	III	C (900), V (800), M (10), Z (150)	C (900), V (800), M (10), P (100), G (200), A (500)
4	30, M	21	L	L	HS	5.0	I	C (800), M (20)	C (200), M (20)
5	25, M	9	L	L	HS	1.3	I	C (700), P (250)	Unchanged
6	24, F	4	L	L	HS	1.0	I	C (600), A (625)	Unchanged
7	28, F	4	L	L	HS	2.8	III	C (800), P (300), D (6)	C (1000), P (350), D (6)
Nondominant side resection									
8	31, F	11	L	R	HS	3.4	I	V (600), N (2), M (5)	V (200), N (1.5), M (2.5)
9	25, F	15	L	R	HS	4.6	I	C (900)	C (500)
10	38, M	20	L	R	HS, FCD	4.1	I	C (900), V (400), P (250), M (2.5)	C (600), P (225), M (2.5)
11	19, F	10	L	R	HS	1.3	I	P (200), V (800)	Unchanged
12	16, M	11	L	R	HS	2.4	I	C (1000), P (200), M (2.5)	C (800), P (200), M (2.5)
13	55, F	14	L	R	HS	1.0	I	P (250), Z (300)	Unchanged
14	23, M	11	L	R	HS, FCD	2.4	I	P (200), B (90), M (15)	Unchanged
15	20, F	6	R	L	HS	1.0	I	C (400), P (200)	Unchanged

HS = hippocampal sclerosis, FCD = forcal cortical dysplasia. AEDs = antiepileptic drugs, C = carbamazepine, V = valproate, P = phenytoin, B = phenobarbital, Z = zonisamide, N = clonazepam, M = clobazam, G = gabapentin, D = diazepam, A = acetazolamide. The doses of AEDs are indicated in parentheses.

Table 2 Demographic and clinical data

	Side of resection		
	Dominant side ($n=7$)	Non-dominant side ($n=8$)	
Males/females	2/5	3/5	$P=0.57$, NS[b]
Education (year)	13.9 (1.5)	13.4 (1.9)	$P=0.60$, NS[c]
Preoperative IQ	77.9 (8.9)	99.1 (9.8)	$P<0.005$[c]
Duration of the disease (year)	18.9 (7.1)	16.1 (11.2)	$P=0.56$, NS[c]
Age at surgery (year)	27.6 (5.7)	28.4 (12.9)	$P=0.88$, NS[c]
Postoperative interval (year)	2.7 (1.6)	2.5 (1.4)	$P=0.79$, NS[c]
Seizure free patients[a]	5 (71%)	8 (100%)	$P=0.20$, NS[b]

The cells contain the number of patients (for gender and postoperative seizure status) or group means (with standard deviation in parentheses).
a Engel outcome class I
b Fisher's exact test
c t-test, NS = not significant.

This study was approved by the Ethics Committee of the Kyoto University Graduate School of Medicine, and written informed consent was obtained from all patients (Tables 1 and 2).

Surgical procedures and outcome

The language-dominant hemisphere was determined pre-surgically by the Wada test. In one patient, the right hemisphere was language-dominant; as she was to undergo surgery on the left hemisphere, she was classified into the non-dominant MTLE group. In patients with dominant-side MTLE, the basal temporal language area was defined using long-term subdural electrodes (Usui *et al.*, 2003). All patients underwent SAH by a combined subtemporal, transventricular, transchoroidal fissure approach. When the temporal horn was opened from the basal surface of the temporal lobe, the basal temporal language area was preserved and a transsulcal approach was used as much as possible to avoid damage to the surrounding cortices. The details of the surgical procedure are provided elsewhere (Miyamoto *et al.*, 2004; Mikuni *et al.*, 2006). Intraoperative electrocorticograms were performed and additional corticotomies were conducted in the small, potentially epileptogenic areas adjacent to the hippocampus. In all patients, hippocampal sclerosis was confirmed by pathological examination.

At the postoperative evaluation, 13 of the 15 patients were seizure-free following subtemporal SAH. The overall seizure-free ratio (Engel class I) was 87% (95% confidence interval 62–96%). This is comparable with the seizure-free rates achieved using other surgical procedures for patients with MTLE with MRI-defined hippocampal sclerosis; freedom from disabling seizures has been reported in 66–89% of patients 2–3 years after a non-subtemporal SAH or anterior temporal lobectomy (Wieser *et al.*, 2003; Paglioli *et al.*, 2004; Janszky *et al.*, 2005; Paglioli *et al.*, 2006).

Image data acquisition

Preoperative and postoperative FDG-PET scans were performed using a PET scanner (Advance, General Electric Medical Systems, Milwaukee, WI, USA). [^{18}F]-FDG at 370 MBq (10 mCi) was injected intravenously

into patients who had been fasting for at least 4 h. Then, 40 min after the administration of the radiotracer, 35 slices of brain-emission images were acquired over a 20-min period. The patients were studied in an awake, resting state, with their eyes closed and their ears unplugged in a dimly lit environment. Although EEG was not performed during the FDG-PET study, ictal studies were unlikely, because no abnormal behaviours were observed, and patients did not report any subjective manifestations of seizures during the examination. Emission images were reconstructed into a 128×128 matrix image with a pixel size of 1.95×1.95 mm^2 and a slice thickness of 4.25 mm. All reconstructed images were corrected for attenuation using ^{68}Ge–^{68}Ga transmission scans performed before the actual scan.

To increase the accuracy of the spatial normalization in the postoperative FDG-PET images when performing voxel-wise analysis using mask images for the surgically resected region, three-dimensional anatomical MRI images were obtained on the same day as the postoperative FDG-PET scanning. The scans were performed using a 3 T MRI scanner (Trio, Siemens, Erlangen, Germany) with the following sequence: magnetization-prepared rapid-acquisition gradient-echo sequence, repetition time (TR)/echo time (TE) = 2000/4.38; matrix size, 240×256; field of view, 24 cm; slice thickness, 1.0 mm.

FDG-PET data analyses

In order to increase the statistical power of the group analyses, the FDG-PET images from the patients with right MTLE were flipped horizontally so that the epileptogenic zone was lateralized to the left side in all of the images. The voxel-wise analysis of the FDG-PET images was performed using SPM5 (Wellcome Department of Imaging Neuroscience, UCL, London, UK).

The preoperative FDG-PET images were spatially normalized to fit to the standard FDG-PET template using affine and nonlinear warping. In the presence of a focal brain lesion, automated methods for spatial normalization are liable to cause inappropriate image distortion due to the abnormal signal within the lesion, particularly during nonlinear transformation; furthermore, cost-function masking provides better and more reliable matching to the standard template (Brett *et al.*, 2001). Thus, we used cost-function masking with a mask image for the surgically resected lesion when normalizing the postoperative FDG-PET images. The procedure was as follows. The surgically resected region was defined in the anatomical postoperative MRI of each individual using MRIcron (http://www.sph.sc.edu/comd/rorden/mricron/), as shown in Fig. 1B. This mask image was modified with a value of 0 within the resected region and a value of 1 elsewhere (Fig. 1C). The mask image was smoothed and expanded using a Gaussian filter of a full-width at a half maximum (FWHM) of 8 mm with a 0.1% threshold border. This resulted in the expansion of 9.6 mm of the masked area (Fig. 1D). Then, the anatomical MRI was co-registered onto the postoperative FDG-PET image of each individual using the mutual information algorithm implemented in SPM5, and the transformation matrix was adjusted to the expanded mask image of the same subject. The result was used for the cost-function masking during the spatial normalization of the postoperative FDG-PET image of each individual. Note that this process does not imply that the areas under the mask remained untransformed, but rather that a continuation of the solution for the unmasked portion of the image was applied to the masked regions.

The spatially normalized images were smoothed with an isotropic Gaussian kernel with 16 mm FWHM to increase the signal-to-noise ratio and to account for normal inter-individual variation in macroanatomy. To remove the effects of global activity, each voxel count was normalized to the total count of the whole brain using proportional scaling (Van Bogaert *et al.*, 2000).

A paired *t*-test was used for the voxel-wise group comparison of the FDG-PET images before and after surgery. We investigated brain regions showing increases and decreases in glucose metabolism after surgery, at a height threshold of $P = 0.01$ corrected for multiple comparisons using the false discovery rate (FDR) algorithm and an extent threshold of 100 voxels (Genovese *et al.*, 2002). Regional glucose hypometabolism adjacent to the surgically resected region—due to deafferentiation or the partial volume effect—could reduce the global count in the postoperative FDG-PET images. This might result in the overestimation of increases and the underestimation of decreases in postoperative regional glucose metabolism. To minimize this effect, we first confirmed the region of the brain showing a postoperative decrease in glucose metabolism, which was located in a restricted area adjacent to the resected region (Fig. 2). This area was expanded as described above and used as an explicit mask in the group-comparison analysis. Again, each voxel count was normalized to the total count by masking this area, and the second analysis was conducted to find the brain regions that showed either an increase or a decrease in glucose metabolism.

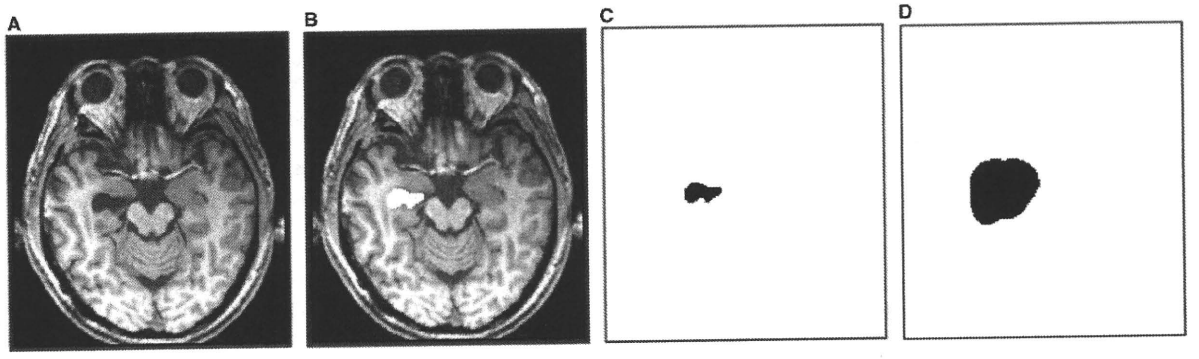

Fig. 1 Process of constructing the cost-function masking images for the spatial normalization of the postoperative FDG-PET images in a representative case. (**A**) A postoperative anatomical MRI of each individual was obtained. (**B**) The surgically resected region was defined manually. (**C**) The mask image was made with the value of 0 within the resected region and 1 elsewhere. (**D**) The mask image was expanded using a Gaussian filter of 8 mm FWHM with a 0.1% threshold border and then was coregistered onto the postoperative FDG-PET image of each individual.

For visualization, the significant clusters were projected onto a surface-rendered anatomical template provided by SPM5. The spatial coordinates of the local maxima from the *t*-statistics were used to identify the corresponding brain areas according to the atlas of Talairach and Tournoux (Talairach and Tournoux, 1988). The non-linear transformation of the Montreal Neurological Institute (MNI) coordinates to the Talairach coordinates was performed using appropriate converter software (mni2tal.m; http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml).

Neuropsychological tests

Preoperative general intelligence was assessed using the Japanese version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R). Preoperative and postoperative memory function was evaluated using the Wechsler Memory Scale-Revised (WMS-R). Postoperative WMS-R testing and the FDG-PET scanning were conducted within a 1-week interval. The memory scores were evaluated in each of four domains: verbal memory, visual memory, delayed recall and attention/concentration.

Statistical analyses

A two-sample *t*-test and Fisher's exact test were used for the statistical analyses of the clinical features. To evaluate the effect of surgery on memory function at the group level, we evaluated the changes in the WMS-R memory scores using a repeated-measures analysis of variance (ANOVA), with time (before or after surgery) as the within-subject variable, and group (MTLE in the dominant or non-dominant hemisphere) as the between-group variable. To assess the change in memory function at the individual level, we counted the number of patients showing an increase or a decrease of 1 SD or more of the preoperative scores on each memory variable in WMS-R. We used SPSS 16.0J for Windows for these statistical analyses.

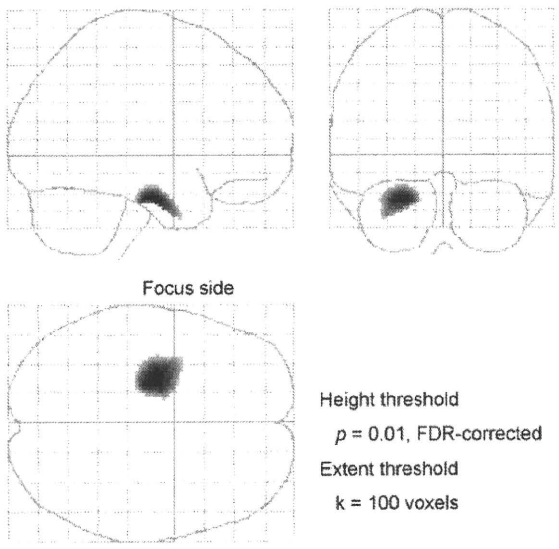

Fig. 2 Three-dimensional orthogonal projection of the areas showing a significant decrease in glucose metabolism after subtemporal SAH. The analysis was conducted without an explicit mask at a height threshold of $P=0.01$, FDR-corrected, and an extent threshold of 100 voxels. Focus side: side of the epileptogenic focus.

Results

FDG-PET

The postoperative glucose metabolism decreased only in the mesial temporal lobe ipsilateral to the resection, in regions such as the parahippocampul gyrus and the area immediately adjacent to the resected hippocampus (Fig. 2 and Table 3). When we reanalysed the data using this region as an explicit mask, no additional areas were detected that showed decreased glucose metabolism. The group comparison using the explicit mask revealed that postoperative glucose metabolism increased in the middle and inferior frontal gyri [Brodmann area (BA) 9, 46, 44 and 45], the dorsomedial and ventromedial frontal gyri (BA 8, 10, 9, 6 and 11), the posterior part of the superior temporal gyrus (BA 22/42) and the temporal pole (BA 38) ipsilateral to the resection, and bilaterally in the inferior parietal lobules (BA 7/40) (Fig. 3 and Table 4). Even in the analysis conducted without the explicit mask, no increase in glucose metabolism was detected adjacent to the surgically resected region.

Neuropsychological tests

In both the dominant and non-dominant MTLE groups, there was a trend towards postoperative improvement in all domains of memory function. For verbal memory, delayed recall and attention/concentration, the repeated-measures ANOVA demonstrated significant effects of time of testing ($P<0.005$ for verbal memory and delayed recall; $P<0.05$ for attention/concentration), but did not show a time × group interaction ($P=0.94$ for verbal memory; $P=0.94$ for overall delayed recall; $P=0.77$ for attention/concentration). For visual memory, there was no significant effect of time of testing ($P=0.09$) and no time × group interaction ($P=0.98$) (Fig. 4). At the individual level analyses, postoperative improvement was more frequent in the dominant side MTLE group for delayed recall and in the non-dominant side MTLE group for attention/concentration, although it did not reach significance (Table 5).

Discussion

This study had three main findings related to the change in human cerebral function after the selective removal of the epileptogenic region in the mesial temporal lobe using a subtemporal

Table 3 Brain regions showing significant decrease in glucose metabolism after subtemporal amygdalohippocampectomy. $P<0.01$, FDR-corrected; without an explicit mask

Brain region	Side	Coordinate of the peak			T-value
		x	y	z	
Hippocampus	I	−24	−15	−19	14.07
Parahippocampal gyrus	I	−30	−7	−23	12.10

I = ipsilateral side to the focus.

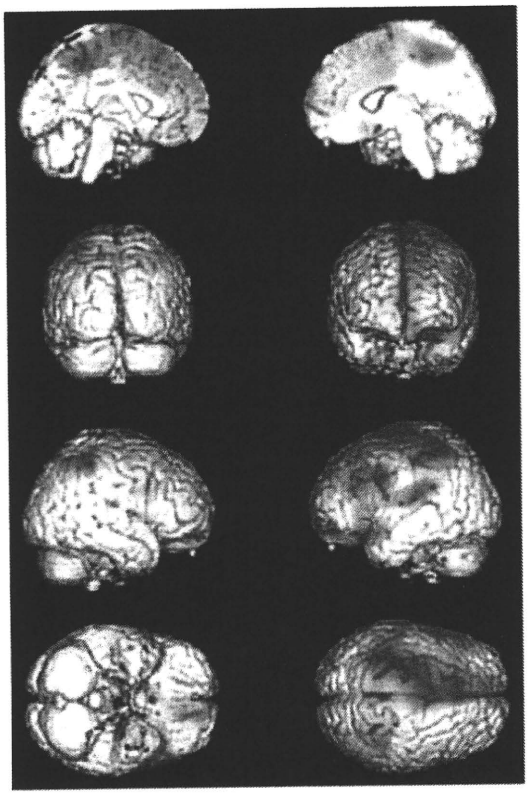

Fig. 3 Brain regions showing a significant increase (red) and decrease (blue) in glucose metabolism after subtemporal SAH. The epileptogenic zone was lateralized to the left side. Note that the results of the group-comparison analysis without an explicit mask are displayed for decrease in glucose metabolism, because when the data were reanalysed with an explicit mask no additional brain regions were detected. Height threshold was set at $P = 0.05$, FDR-corrected for display purposes. Even at the lower statistical threshold, the postoperative decrease in glucose metabolism was limited to the mesial temporal area adjacent to the resected region. $n = 13$; paired t-test; extent threshold of 100 voxels.

approach: first, compared to the preoperative state, glucose metabolism increased in many extratemporal regions as well as in the remnant temporal lobe; second, the postoperative decrease in glucose metabolism was limited to the area around the resected region and third, memory function improved regardless of the resected side.

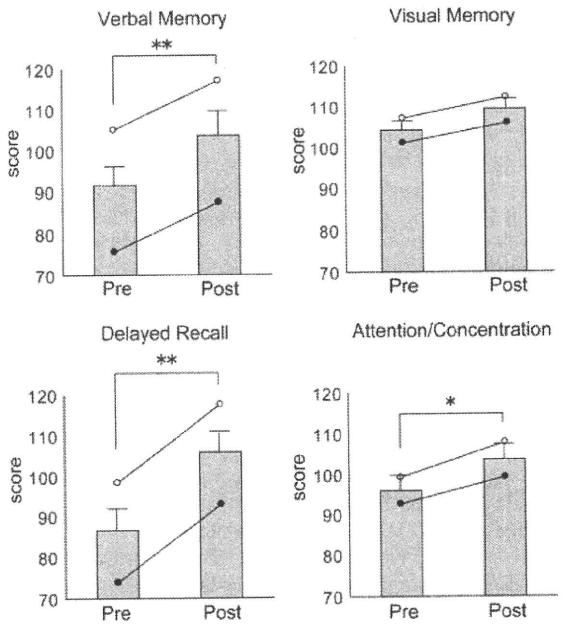

Fig. 4 Bar charts illustrating the mean WMS-R scores of all patients for verbal memory, visual memory, delayed recall and attention/concentration at preoperative and postoperative evaluation. Error bars show SEM. Solid circles and open circles indicate the mean scores of patients with language-dominant side and language-non-dominant side MTLE, respectively. The postoperative scores were significantly higher in verbal memory, overall (verbal + visual) delayed recall and attention/concentration ($^{**}p < 0.005$, $^{*}p < 0.05$), but there was no time × group interaction in any of the domains.

Table 4 Brain regions showing significant increase in glucose metabolism after subtemporal amygdalohippocampectomy. $P < 0.01$, FDR-corrected; with an explicit mask

Brain region	Brodmann area (BA)	Side	Coordinate of the peak			T-value
			x	y	z	
Middle and inferior frontal gyri	[9/46/44/45]	I	−61	11	27	10.76
		I	−57	23	25	5.58
		I	−59	22	4	6.58
Superior temporal gyrus	[22/42]	I	−55	−26	20	7.75
Inferior parietal lobule	[7/40]	I	−30	−46	50	7.25
		C	24	−52	47	7.70
Dorsomedial frontal gyrus	[8/10/9/6]	I	−2	32	57	7.15
Temporal pole	[38]	I	−53	13	−16	5.87
Ventromedial frontal gyrus	[11]	I	−6	34	−12	5.06
		I	−8	50	−13	4.68
Orbitofrontal gyrus	[11]	I	−18	48	−19	4.52

I = ipsilateral side to the focus, C = contralateral side to the focus.

Table 5 Individual changes in memory scores after subtemporal SAH

Memory variable	Dominant side (n=7)		Non-dominant side (n= 8)	
	Gain	Loss	Gain	Loss
Verbal	3	0	3	0
Visual	2	1	2	0
Delayed (verbal + visual)	5	0	3	0
Attention/Concentration	1	0	4	1

Cells provide the number of patients showing an increase or a decrease of one standard deviation or more of the preoperative scores on each memory variable in WMS-R.

Increased glucose metabolism in the projection areas

Animal studies have shown that cortical hypometabolism in remote brain regions is not present when the putative neural pathway from the epileptic focus is destroyed before the epileptic focus is produced (Bruehl *et al.*, 1998). Thus, the transmission of the epileptic activity via the neural connections from the focus is thought to suppress cerebral glucose metabolism in regions remote from the epileptic focus. Although such clear evidence has not been found in human studies, the combination of FDG-PET and EEG in humans has revealed that both clinical and subclinical epileptic activity coincides with interictal glucose hypometabolism outside the focus region (Merlet *et al.*, 1996; Chassoux *et al.*, 2004).

In the present study, glucose metabolism increased compared to the preoperative state in many extratemporal areas in the frontal and parietal lobes. These particular areas are thought to receive direct projections from the area adjacent to the resected mesial temporal region. The projection fibres from the parahippocampal gyrus to the frontal lobe consist of two pathways: the ventral limbic pathway and the dorsal limbic pathway (Petrides and Pandya, 2002). The ventral pathway includes two groups of fibres: the caudal pathway, which enters the extreme capsule and terminates in the dorsolateral prefrontal cortex (BA 9, 46); and the rostral pathway, which runs through the uncinate fasciculus towards the ventromedial prefrontal cortex (BA 10, 11). By contrast, the dorsal limbic pathway runs as a part of the cingulum bundle, with branches to the dorsomedial frontal regions, and directs its fibres towards the frontal pole (Mori *et al.*, 2005). Another contingent of parahippocampal efferent fibres projects to the inferior parietal lobule (Van Hoesen, 1982). In addition, the anterior region of the inferior temporal cortex (area TE) and the posterior region of the inferior temporal cortex (area TEO) in macaque monkeys connect with the inferior frontal gyrus, including the homologue of BA 45, and these areas also project to the inferior parietal lobule (Ungerleider *et al.*, 1989; Webster *et al.*, 1994). Among these areas, the prefrontal region was shown to be a major route of seizure propagation from the mesial temporal focus in a depth EEG study (Lieb *et al.*, 1991). Particularly, the dorsolateral prefrontal cortex is the region in which interictal glucose hypometabolism was detected in association with high seizure-frequency and the same region showed ictal hyperperfusion in patients with MTLE (Van Paesschen *et al.*, 2003; Takaya *et al.*, 2006). The present results indicate that a decrease in the epileptic activity emanating from the seizure focus in the mesial temporal lobe improved interictal cerebral glucose metabolism in a wide range of projection areas.

The topography of the improved glucose metabolism in the affected temporal lobe is another point of interest in the present study. The cerebral glucose metabolism increased as compared to the preoperative state in areas in the remnant temporal lobe distant from the resected epileptogenic lesion, such as the superior temporal gyrus and the temporal pole. These areas have reciprocal connections to the parahippocampal gyrus (Van Hoesen, 1982). However, glucose metabolism remained unchanged in the other areas around the mesial temporal region. FDG-PET and diffusion MRI studies have shown that functional abnormalities extend to a wide area around the epileptogenic region in the temporal lobe in patients with intractable MTLE (Arnold *et al.*, 1996; Chassoux *et al.*, 2004; Concha *et al.*, 2005). The two-hit hypothesis has been proposed to explain the generating mechanism of MTLE, in which a combination of inherent pre-existing abnormalities in the temporal lobe, due to genetic factors or developmental abnormalities, and precipitating events, such as prolonged febrile seizures, eventually cause an epileptogenic lesion in the hippocampus (Velisek and Moshe, 2003; Wieser, 2004; Love, 2005). According to this hypothesis, pre-existing abnormalities in the affected temporal lobe remain even after the epileptogenic lesion is selectively removed and seizures cease. In fact, a recent diffusion MRI study revealed that the abnormal integrity of the axonal microenvironment persisted even after the cessation of epileptic activity in the major limbic white-matter pathways such as the fornix and cingulum adjacent to the mesial temporal lobe (Concha *et al.*, 2007). The present findings suggest that functional abnormalities in the cortex around the hippocampus also remain after the selective removal of the epileptogenic region in MTLE.

AEDs cause a variable degree of reduction in global glucose metabolism, but no consistent region-specific cortical effects have been noted (Theodore *et al.*, 1986*a*, *b*, 1989; Gaillard *et al.*, 1996). In the present study, the dose or number of AEDs remained unchanged or decreased postoperatively in all but two patients, which we assume would increase the postoperative global glucose metabolism in each patient. To control for this, we normalized the value of each voxel to the global mean in each scan. This method is thought to remove the effects of the inter-scan variation in global counts on the patterns of regional glucose metabolism. However, in the present study, it is probable that there was an underestimation of the increase and an overestimation of the decrease in postoperative regional glucose metabolism. Thus, the brain regions showing a postoperative improvement in glucose metabolism are likely to be more extensive.

Decreased glucose metabolism is limited to the mesial temporal region

In the present study, while a broadly distributed improvement in glucose metabolism was seen, the postoperative decrease in glucose metabolism was limited to the mesial temporal area adjacent to the resected region. After anterior temporal lobectomy, glucose

metabolism decreased widely in remote areas such as the basal ganglia, thalamus, fusiform gyrus, lingual gyrus and posterior insular cortex (Joo *et al.*, 2005*b*). These metabolic changes are assumed to be the result of deafferentiation following the resection of anterior temporal structures. A study using a region-of-interest method reported decreased glucose metabolism in the ipsilateral temporal pole after trans-sylvian SAH (Dupont *et al.*, 2001). This could be attributed to the disconnection of the fibre tracts that project to the temporal pole through the deep white matter of the temporal lobe, such as the uncinate fasciculus or the lateral cholinergic pathway from the nucleus basalis of Meynert (Selden *et al.*, 1998; Ikeda *et al.*, 2005; Helmstaedter *et al.*, 2008). In the present study, the sparing of these dense bundles by the subtemporal approach might have led to the preservation of glucose metabolism in the remote projection areas of the brain. However, FDG-PET analyses are substantially different between the two studies. Thus, a direct comparison of the two surgical procedures (trans-sylvian SAH versus subtemporal SAH) using the same FDG-PET analyses is expected to yield conclusions.

Improved memory function

The postoperative decline in verbal memory impairs cognitive performance in patients with MTLE. Verbal memory function after anterior temporal lobectomy or trans-sylvian SAH deteriorates at the group level in patients with dominant-side MTLE, whereas it tends to improve in patients with non-dominant-side MTLE (Novelly *et al.*, 1984; Lee *et al.*, 2002; Morino *et al.*, 2006). In the present study, an improvement in verbal memory was observed regardless of the resected side. Previous studies have reported that subtemporal SAH might spare verbal memory decline in patients with dominant-side MTLE (Mikuni *et al.*, 2006; Hori *et al.*, 2007). Preservation of the basal temporal language area resulted in improved verbal memory 1 year after the operation, even when the AED dosage remained unchanged (Mikuni *et al.*, 2006). The present study also shows a long-lasting improvement in verbal memory following subtemporal SAH.

Although functional neuroimaging studies have emphasized the contribution of frontal and mesial temporal regions to memory, a study using recordings of microelectrodes placed on the human cortex revealed that the inferior lateral and basal temporal cortices were involved in verbal memory tasks (Ojemann *et al.*, 2002). In fact, a broader resection of the inferior or basal temporal gyri of the language-dominant hemisphere was associated with postoperative decline in the verbal delayed recall score in patients with MTLE (Joo *et al.*, 2005*a*). The basal temporal language area is located between 10 mm and 75 mm posterior to the temporal tip, and is important in processing verbal information (Lüders *et al.*, 1991; Schaffler *et al.*, 1996). In the Japanese language, this area has been associated with the processing of both *kanji* (Japanese morphograms) and *kana* words (Japanese syllabograms) (Nakamura *et al.*, 2000; Usui *et al.*, 2003, 2005). In the present study, the seizure activity ceased in the language-dominant side of the temporal lobe following surgical treatment in which the basal temporal language area and the fibre tracts passing through the temporal stem were preserved. This could result in the improvement of verbal memory processing in patients with dominant-side MTLE.

An alternative explanation for the memory improvement observed in the present study is simply the non-specific improvement of cerebral function resulting from decreased seizure frequency and AED intake. A long-term follow-up study in temporal lobe epilepsy has shown that good seizure control after surgery is an important factor for improved cognitive function (Helmstaedter *et al.*, 2003). In the present study, this was corroborated by the improvement in multiple WMS-R domains, including verbal memory, delayed recall and attention/concentration, and these improvements were present regardless of the resected side. In addition, the dominant side MTLE group in the present study consisted of relatively young adult patients with the borderline impaired range of mean IQ and verbal memory scores. Age of surgery and preoperative cognitive function are associated with postoperative cognitive outcome (Helmstaedter *et al.*, 2002; Rausch *et al.*, 2003; Gleissner *et al.*, 2005; Baxendale *et al.*, 2006). A longitudinal study with a larger number of patients that evaluates the multivariate effects on neuropsychological results and the specific brain regions that contribute to cognitive improvement is now warranted.

Conclusion

Subtemporal SAH preserving the basal temporal language area in patients with intractable MTLE improved cerebral glucose metabolism in the extratemporal projection areas and the remote regions of the remnant temporal lobe, and improved memory function. In addition, the postoperative decrease in glucose metabolism was restricted to the mesial temporal region. This implies that the brain regions with postoperative functional impairments can be minimized by the use of subtemporal SAH in patients with intractable MTLE with hippocampal sclerosis.

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Amygdalar enlargement in patients with temporal lobe epilepsy

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ABSTRACT

Objective The purpose of the study was to clarify the significance of amygdalar enlargement (AE) in patients with temporal lobe epilepsy (TLE) detected by MRI.

Methods 11 TLE patients (eight men, mean age 45.3 (SD 18.2) years) with AE treated at Kyoto University Hospital were studied. Clinical history, ictal semiology, EEG, fluorodeoxyglucose–positron emission tomography (FDG-PET), interictal single photon emission CT (SPECT) and MRI were investigated. Amygdalar volume measured by 3 T MRI and its laterality index (LI) were compared with the three other groups: normal controls, patients with partial epilepsy of non-TLE and mesial TLE with hippocampal sclerosis (HS).

Results Average age of onset was 39.8 years (SD 19.5). Eight had complex partial seizures and three had generalised seizures. Epileptiform discharges were found in the temporal area ipsilateral to the AE by EEG. Interictal FDG–PET/SPECT revealed regional hypometabolism or hypoperfusion in the ipsilateral temporal area. MRI showed AE on the right in five patients, on the left in five and bilateral in one, all without apparent HS. Ten of 11 patients were diagnosed as unilateral TLE ipsilateral to the AE by neurophysiological and neuroimaging methods. Enlarged amygdalae showed iso- to slightly high intensity in FLAIR images without enhancement. Unilateral AE was not seen in the other three groups for amygdalar volume and LI ($p<0.05$).

Discussion AE is most likely a subtype of TLE without ipsilateral HS. This possibility of AE should be considered in TLE patients if there is no apparent HS.

INTRODUCTION

Mesial temporal lobe epilepsy (MTLE) with hippocampal sclerosis (HS) is a well defined epileptic syndrome. The amygdala, which is a part of the limbic system, may play an important role in the epileptogenicity of patients with MTLE with HS.[1–3] In neurophysiological studies using intracerebral recordings, 5% of MTLE patients had seizure onset in the amygdala.[4] In previously reported imaging studies, isolated unilateral amygdala damage determined by either reduced volume or prolonged T2 relaxation time was observed in 8% of MTLE patients.[5] Therefore, the amygdala may not only be involved and affected in MTLE but may also be regarded as an independent cause of MTLE. The amygdala is decreased in volume by at least 20% in 19% of temporal lobe epilepsy (TLE) patients.[6] Recently, amygdalar enlargement (AE) was observed in 4% of intractable TLE patients.[7] Accounting for laterality of the amygdala,[8] AE could be an epileptogenic focus. However, a role for the amygdala as a focus of epilepsy has not been explicitly established, unlike hippocampal epilepsy.

The main purpose of this study was to clarify the clinical significance of AE in patients with TLE detected by MRI. The occurrences of AE were compared with other partial epilepsies such as non-TLE and typical MTLE with HS as well as with normal controls. One of the patients (Patient 2) was shown previously as a case report.[9]

METHODS

Subjects

Subjects were 11 MTLE patients with AE (mean age 45.3 (SD 18.2) years) treated at Kyoto University Hospital from 2003 to 2007 (AE group). MTLE with AE was diagnosed by the presence of complex partial seizures (CPSs) and by 1.5 T MRI and conventional scalp EEG, as described below. MRI indicated AE in all patients, as determined by the assessment and agreement of two neurologists. The volume of the amygdala was finally measured by 3 T MRI, as described below. Patients in whom there was a high suspicion of tumorous disease where the enlarged amygdala apparently compressed the adjacent tissue or showed clear intensity changes in T2 weighed or FLAIR images were excluded. Patients with dual pathologies were also excluded from the study. Routine EEG in 10 patients indicated focal epileptiform discharges predominantly in the temporal area ipsilateral to the AE. Fluorodeoxyglucose–positron emission tomography (FDG-PET) or single photon emission CT (SPECT) was also performed to support the clinical diagnosis. Localisation of the epileptogenic focus was determined by taking into account clinical semiology, EEG, conventional neuroimaging studies such as 1.5 T MRI, and FDG-PET/SPECT. Time from the first seizure to the date of the present study was at least 1 year.

As a comparison for amygdala volume, 17 focal epilepsy patients who had focal epileptiform discharges except for the temporal area without structural lesion by 1.5 T MRI (non-TLE group, mean 27.1 (SD, 11.6) years), 15 MTLE patients with HS by 1.5 T MRI (MTLE+HS group, mean 29.7 (SD 13.9) years) and 14 healthy volunteers (normal group, mean 30.1 (SD 8.3) years) were also recruited from the subjects who underwent 3 T MR imaging study during the same period. The former two groups (ie, non-TLE group and MTLE+HS group) had 3 T MRI for volume analysis of the amygdala.

3 T MRI acquisition

For the eight patients with AE, as determined by conventional 1.5 T MRI, an MRI study was also performed with a 3 T MR scanner (Magnetom Trio; Siemens, Erlargen, Germany) with magnetisation prepared rapid acquisition gradient echo (MPRAGE) sequences (repetition time (TR) 2000; echo time (TE) 4.4; time interval (TI) 990 ms; flip angle 8°; matrix 256×256; field of view 24 cm; 208 slices; slice thickness 1 mm; voxel size 0.9375×0.9375×1 mm; no interslice gap; signal averaging). Figure 1 shows a representative image of AE by 3 T MRI. All patients provided informed consent prior to 3 T MRI examination. Similarly, 17 patients from the non-TLE group, 15 patients from the MTLE+HS group and 14 normal volunteers underwent a 3 T MR imaging study during the same period.

Amygdalar volumetry

We measured amygdalar volume by counting the number of voxels in a manually outlined volume of interest (VOI) on the MPRAGE images based on Cavalieri's method. VOI was manually drawn on the three dimensional MPRAGE image using MRICro (V.1.39, Roden, 2005). The amygdala was traced by a single rater (TM) using the method described in a previous study and also based on an atlas based approach.[10 11] An example of a VOI is shown in figure 2. Anatomical borders were adopted from previous studies.[8 12–14] Adjacent structures such as the putamen, hippocampus and parahippocampal gyrus were carefully excluded.

Statistical analysis of amygdalar enlargement

Amygdalar volumes were statistically analysed by paired t tests to determine the laterality between the normal and abnormal sides for each patients (AE, non-TLE and MTLE+HS) and also analysed between the larger and smaller sides for the normal group. We also compared the laterality between the AE group, non-TLE group, MTLE+HS group and normal controls by volume and laterality index (LI=(larger side−smaller side)/(larger side+smaller side)). These analyses were performed using SPSS 14.0 (SPSS Inc. 2005).

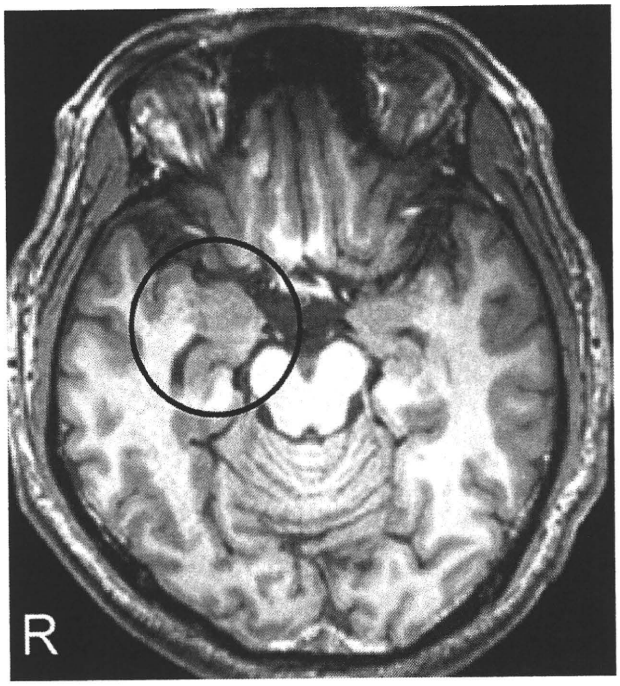

Figure 1 Axial T1 weighed MRI in patient No 9. Open circle indicates a representative image of right amygdalar enlargement. The intensity of the amygdala does not show laterality. No abnormal lesions were found in areas adjacent to the amygdala.

RESULTS

Clinical profiles of 11 patients

Patients included eight men and three women with an averaged seizure onset age of 39.8 years (SD 19.5). Two out of 11 patients had febrile seizures, eight had CPS and three had generalised tonic–clonic seizures. Two patients (patient Nos 2 and 9) felt anger and one patient (patient No 10) felt anxiety as their habitual psychic auras. Seizure frequency was at least once per month in 10 of 11 patients. Only one patient (patient No 3) had seizures once a year. Routine EEG in 10 patients indicated focal epileptiform discharges predominantly in the temporal area ipsilateral to the AE. For 10 patients, interictal FDG-PET/SPECT showed regional glucose hypometabolism or decreased regional cerebral blood flow in the ipsilateral temporal lobe. By 1.5 T MRI, AE was detected on the right in five patients, on the left in five and was bilateral in one. The enlarged amygdala showed iso- to slightly high intensity in 1.5 T FLAIR images but no enhancement by gadolinium. Mild HS ipsilateral to the enlarged amygdala was suspected in only one patient. Epileptogenic foci were ipsilateral to the AE in 10 patients with unilateral AE. One patient with bilateral AE (patient No 10) showed no laterality (table 1).

Valproic acid (mean dose 800 mg/day) was used in five patients and sufficient seizure control was obtained in four patients. Carbamazepine (CBZ) (mean dose 317 mg/day) was later given to nine patients, and eight patients became seizure free or showed a dramatic improvement in seizure occurrence.

Among 11 patients, one (patient No 1) had intractable seizures and underwent selective amygdalohippocampectomy and partial resection of the adjacent temporal lobe cortex guided by intraoperative electrocorticogram.[15] His seizures subsequently decreased (Engel's class II). A pathological study indicated hippocampal gliosis compatible with TLE and partial dysplasia in the right temporal tip. Only non-specific gliosis was found in the amygdala. Patient No 11 also underwent lesionectomy of the enlarged amygdala and became free from seizures after surgery (Engel's class I). A pathological study also indicated focal cortical dysplasia with mild gliosis in the left amygdala.

Follow-up 1.5 T or 3 T MRIs were performed in five patients (patient Nos 2, 5, 7, 8 and 9) 2–5 years after the first MRI. None showed further increased volume of the abnormal amygdala (no change in two and slight improvement in three).

Results of 3 T MRI amygdalar volumetry

Table 2 shows the amygdalar volumes of eight patients in the AE group determined by 3 T MRI. On the side of the AE with seizure focus, amygdalar volume ranged from 1333.3 mm^3 to 2011.8 mm^3 (mean 1700.1 (SD 285.0) mm^3). On the contralateral side, amygdalar volume was smaller and ranged from 957.8 mm^3 to 1658.5 mm^3 (mean, 1189.1 (SD 227.4) mm^3). There was a significant difference between the two sides ($p<0.05$, figure 3). In the non-TLE group (17 patients), amygdalar volume on the ipsilateral side to the seizure focus ranged from 773.2 mm^3 to 1270.6 mm^3 (mean 1028.4 (SD 158.1) mm^3) and that of the contralateral side ranged from 782.0 mm^3 to 1448.2 mm^3 (mean 1093.2 (SD 174.3) mm^3). There was a significant difference between the two sides ($p<0.01$, figure 3),

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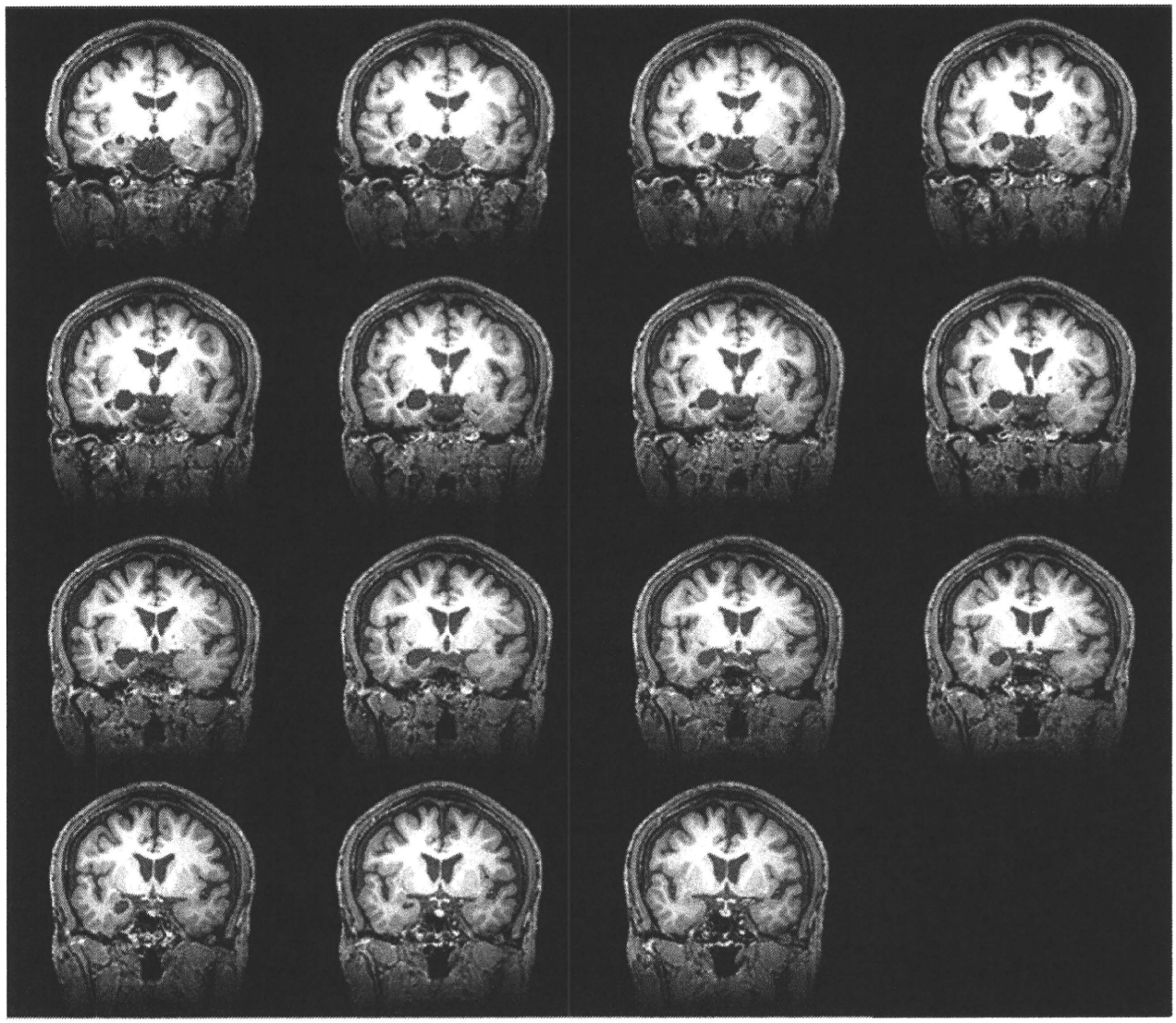

Figure 2 Volume of interests (VOIs) in the amygdala (patient No 2). VOIs are indicated in red. Hippocampal head and basal ganglia are excluded.

being smaller on the focus side. In the MTLE+HS group (15 patients), the amygdalar volume on the ipsilateral side to the seizure focus ranged from 778.5 mm^3 to 1293.6 mm^3 (mean 1060.4 (SD 150.9) mm^3) and that of the contralateral side ranged from 859.7 mm^3 to 1343.1 mm^3 (mean 1122.4 (SD 157.4) mm^3). There was a significant difference between the two sides ($p<0.01$, figure 3). Namely, both non-TLE and MTLE+HS groups showed a smaller amygdalar volume on the focus side in contrast with the AE group.

In normal subjects (14 patients), the left amygdalar volume ranged from 941.3 mm^3 to 1433.2 mm^3 (mean 1140.0 (SD 154.5) mm^3) and the right ranged from 998.4 mm^3 to 1342.2 mm^3 (mean 1152.6 (SD 108.4) mm^3). There was no significant difference between the two sides (not shown in figure 3). When they were grouped into smaller and larger sides, the smaller side ranged from 941.3 mm^3 to 1342.2 mm^3 (mean 1105.5 (SD 117.6) mm^3) while the larger side ranged from 998.4 mm^3 to 1433.2 mm^3 (mean 1187.7 (SD 134.9) mm^3). There was a significant difference between the two sides ($p<0.01$, figure 3).

Amygdalar volume of the affected side among the three patient groups and larger side in the normal group was compared, and it was the significantly largest in the AE group (one way ANOVA with post hoc test, $p<0.01$, figure 3).

When normal subjects were grouped into left and right sides (not shown in figure 3), there was no significant difference between the unaffected side of the AE group and either left or right side in normal subjects (not shown in figure 3). There was a significant difference between the affected side of the AE group and both the left and right sides in normal subjects ($p<0.05$, not shown in figure 3).

Among the three groups, except for the AE group, the affected side of MTLE+HS was significantly smaller than the larger side of the normal group ($p<0.05$, figure 3). There was no significant difference between the affected side of non-TLE and MTLE+HS (figure 3).

In terms of LI, LI of the AE group (0.176 ± 0.107) was significantly larger than that of the non-TLE group (0.036 ± 0.034), MTLE+HS group (0.028 ± 0.026) and normal controls (0.035 ± 0.025) (one way ANOVA with post hoc test, $p<0.05$, figure 4).

Table 1 Clinical profiles of the 11 patients

Patient No	Age at scan (years)*	Gender	Onset age	FS	Seizure type	EEG	Imaging studies†	Current medication and dosage‡	Seizure frequency§
1	21	M	9	–	CPS	R	R	VPA 1400, ZNS 225, CLB 5, CBZ 800	2/month
2	63	M	46	–	CPS	R	R	***CBZ 250***	Free
3	25	M	15	–	GTC	L	L	VPA 400, ***CBZ 400***	Free
4	24	F	19	–	CPS	L	L	PB 90, ***CBZ 200***	Free
5	57	M	49	–	CPS	L	L	VPA 600, ***CBZ 200***	Free
6	41	M	40	+	CPS	R	Not done	***CBZ 600***	2/year
7	32	F	32	+	GTC	L	L	VPA 800, ***CBZ 350***	Free
8	63	M	61	–	CPS	R	R	***CBZ 400***	Free
9	45	M	44	–	GTC	R	R	VPA 800, ***CBZ 200***	Free
10	74	F	72	–	CPS	R	Bilateral	***CBZ 50***	Free
11	53	M	51	–	CPS	L	L	***CBZ 200***, DZP 4	Free

*Patient age at the time of 1.5 or 3 T MRI examination. Mean age was 45.3 years (SD 18.2).
†Imaging studies consisted of interictal SPECT (single photon emission CT) and FDG-PET (fluorodeoxyglucose–positron emission CT).
‡Current medication is shown. Note that CBZ monotherapy or polytherapy with a relatively low dose of CBZ (written in ***bold, italic body***) improved seizure control.
§Seizure frequency after drug administration.
CBZ, carbamazepine; CLB, clobazam; CPS, complex partial seizure; DZP, diazepam; FS, febrile seizures; GTC, generalised tonic-clonic seizure; L, left; PB, phenobarbital; R, right; VPA, valproic acid; ZNS, zonisamide.

DISCUSSION

Amygdalar enlargement as a cause of TLE

MTLE is regarded as surgically remediable focal epilepsy characterised by hippocampal atrophy and sclerosis as the epileptogenic area. However, it has remained poorly understood how important the amygdalar body is in patients with MTLE or whether the amygdalar body per se plays a sole role in epileptogenicity.[2 3] The results of this study, in conjunction with previous electrophysiological and radiological studies, indicate that AE may function as an epileptogenic focus in subgroups of TLE patients.[9 16] AE was observed bilaterally in 16–18% of epilepsy patients with psychosis.[17] In contrast, significant amygdalar atrophy was seen in TLE patients with ictal fear[18] or affective aggression.[19] In previous studies,[20] the amygdaloid body was severely altered in TLE patients without HS and was smaller in volume compared with those analysed in the present study.

Concordant with a previous study, amygdalar volumes were smaller in the affected side of MTLE+HS and non-TLE patients in the context of conventional amygdalar sclerosis. In the present study: (1) we defined the clinical features of patients with TLE and AE and (2) we found that no AE was observed in patients with MTLE and HS, those with unilateral partial epilepsies other than TLE or in normal groups. Additionally, when we grouped normal data into larger and smaller sides of amygdala body, AE was significantly larger than in normal subjects. The AE group also showed a significantly larger LI among the other three groups. Namely, AE seems to be a specific phenomenon which can be observed in a certain subgroup of TLE patients. Moreover, we may consider a certain population of MTLE to have an epileptogenic focus in the amygdala, especially when the amygdala is enlarged.

Table 2 Comparison of amygdalar volume among the four groups

	Affected side (mm^3)	Unaffected side (mm^3)
AE (n=8)	1700.2±285.0	1189.1±227.4
Non-TLE (n=17)	1028.4±158.1	1093.2±174.3
MTLE+HS (n=15)	1060.8±150.9	1122.4±157.4
Normal (n=14)	**Larger side (mm^3)**	**Smaller side (mm^3)**
	1187.7±134.9	1105.5±117.6
	Left (mm^3)	**Right (mm^3)**
	1140.6±154.5	1152.6±108.4

Values are mean±SD.
Each of the four groups have been defined in the methods section.
Affected side means the AE side and seizure focus, and unaffected side means contralateral side of seizure focus.
Data for normal subjects are shown in two ways: the smaller versus larger sides and left versus right side. Smaller versus larger side in normal data is compared with unaffected versus affected sides in the patient groups, respectively. Left versus right side in normal is also compared with unaffected versus affected side as well as with affected versus unaffected side in the patient groups. Details are described in the results section.
AE, amygdalar enlargement; HS, hippocampal sclerosis; L, left; MTLE, mesial temporal lobe epilepsy; R, right.

Since we did not have direct recording from the amygdala by means of depth electrodes and as we did not have ictal SPECT, we could not definitively prove that the enlarged amygdala was epilpeptogenic. This needs further evaluation by means of more direct documentation such as invasive recording, if possible. As patients with AE and complex partial seizures are very rare in number, it might be difficult to obtain this in most institutes. We believe that it is worthwhile to extract and characterise this particular group of patients with AE and complex partial seizures among TLE patients, and this study could contribute in this regard. We need to pay attention not only to the degree of atrophy of the hippocampus but also to unilateral AE in TLE patients.

AE has not been fully recognised and documented from a surgical point of view because the hippocampus is typically considered to harbour epileptogenic foci rather than the amygdala. A pathological study of the amygdala in MTLE revealed neuronal loss and dendritic alterations.[21] With regard to the aetiologies of AE in the present study, there are several possibilities, such as neurodevelopmental abnormalities (ie, focal cortical dysplasia), very benign tumour (ie, hamartoma or low grade glioma)[22] or inflammatory process. Most of our patients developed symptoms in adulthood and there was no gadolinium enhancement by MRI and no significantly high signal changes in FLAIR images.

Recently, autoimmune processes in the development of partial epilepsies associated with anti-N-methyl-D-aspartate receptor antibody, anti-voltage gated potassium channel antibody, anti-glutamic acid decarboxylase antibody and other autoimmune antibodies have been raised as chronic epilepsies, and some of them reportedly showed a self-limited course.[23 24] As none of our patients showed increased regional glucose metabolism in the mesial temporal area, it is unlikely that a very active

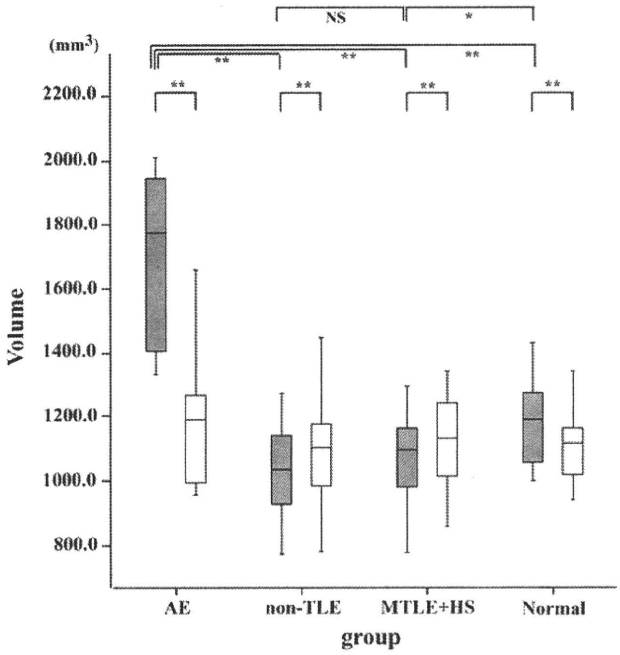

Figure 3 Comparison of amygdalar volumes in epilepsy patients (AE, non-TLE and MTLE+HS) and normal subjects (Normal). Closed boxes indicate the focus side volume in the patient groups and the larger side in normal subjects. Open boxes indicate the contralateral side to the epilepsy focus in the patient groups and the smaller side in normal subjects. The amygdalar volume is significantly larger on the ipsilateral side to the focus in AE ($p<0.01$) and it is the largest among the four groups. In non-TLE and MTLE+HS groups, the focus side shows the significantly smaller amygdalar volume, as opposed to the AE groups ($p<0.01$). The larger side volume in normal controls is also significantly smaller than the focus side in the AE group ($p<0.01$). *$p<0.05$, **$p<0.01$. Medians in each group appear as bars. AE, patients with amygdalar enlargement; non-TLE, patients with partial epilepsies other than temporal lobe epilepsy (TLE); MTLE+HS, patients with mesial TLE with hippocampal sclerosis.

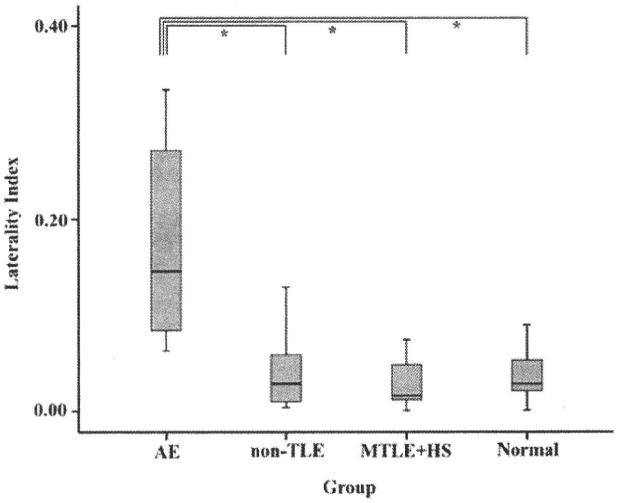

Figure 4 Comparison of laterality index (LI) in epilepsy patients (AE, non-TLE and MTLE+HS) and normal subjects (normal). LI is significantly larger in AE but not in the other three groups. Medians in each group appear as bars. AE, patients with amygdalar enlargement; non-TLE, patients with partial epilepsies other than temporal lobe epilepsy (TLE); MTLE+HS, patients with mesial TLE with hippocampal sclerosis.

inflammatory process was present at the time of investigation in our patients. However, the possibility that chronic, long lasting inflammatory processes with or without a self-limited course occurred could not be completely excluded.

Two patients (patient Nos 1 and 11) in our study underwent epilepsy surgery and showed non-specific gliosis and focal cortical dysplasia in the amygdala. Radiological and pathological findings were concordant, not showing features in the amygdala suggestive of tumour in patient Nos 1 and 11. Furthermore, repeated MRI examination in the five patients in the present study showed no increase in volume of the amygdala but no change in two and slight improvement in three. Therefore, these results suggest that AE patients in the present study could still be heterogenous in aetiology but being commonly benign in nature, as discussed above.

Overall clinical features of patients with AE

With regards to ictal semiology, three patients with AE in this study showed generalised tonic–clonic seizures without aura, similar to idiopathic generalised epilepsy. It seems distinct from typical MTLE, given that the amygdala might cause direct propagation to the thalamus through direct neuronal connections. Three other patients had ictal symptoms of anger and anxiety, which may be produced by direct amygdala activation. A previous study indicated that female patients with depression had significant AE on both sides.[25] However, only one patient (patient No 10) with bilateral AE and CPS in the present study was in a depressive state. Thus the main finding of this study could not be attributed to depression.

Only one patient (patient No 1) had intractable seizures and thus underwent surgery. Nine patients were free from seizures after antiepileptic drug administration, in particular after administration of a low dose of CBZ. Carbamazepine may have an effect on other antiepileptic drugs with higher concentrations, or CBZ itself may be effective against AE associated seizures, and thus further accumulation is needed. We should consider the presence of AE in TLE patients when they do not present with hippocampal sclerosis or atrophy. Future studies may reveal more patients who present with 'TLE and AE'.

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Competing interests None.

Ethics approval This study was conducted with the approval of the Kyoto University Graduate School and Faculty of Medicine, Ethics Committee (Approval No. 463).

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症例報告

けいれん様不随意運動の発現に基底核の関与が示唆された convulsive syncope の1例

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福山　秀直[2)]　池田　昭夫[1)*]　高橋　良輔[1)]

要旨：起立時にけいれん様不随意運動と軽度の意識減損を呈する症例で症状出現時の脳波および脳血流 SPECT による脳血流変化を検討した．患者は純粋自律神経不全の 74 歳男性．「起立時にけいれんがおこる」との主訴で来院した．臥位から座位や立位になって約1分後より，起立性低血圧にともなう意識減損と両上下肢（右優位）と体幹のけいれん様不随意運動が 10～30 秒程度持続した．不随意運動出現時には，脳波はびまん性に徐波化し，脳血流 SPECT では臥位安静時にくらべて左基底核，両側前頭葉および右小脳半球の血流低下をみとめた．本症例におけるけいれん様不随意運動の発現に関して，基底核の機能低下が関与している可能性が示唆された．

（臨床神経 2011;51:338-344）
Key words：convulsive syncope，脳波，脳血流SPECT，起立性低血圧

はじめに

起立性低血圧などによる血行力学的脳虚血状態による失神またはその前段階と考えられる立ちくらみや軽度の意識減損（presyncope）[1)2)]にともなって，時にけいれんや不随意運動をみとめることがある．前者はとくに convulsive syncope と呼ばれ，てんかん発作との鑑別が重要である[3)]が，その病態生理についてはよくわかっていない．後者に関しては，これまで可逆性の虚血が原因と推定される limb shaking[4)-10)]やその他の不随意運動[11)-13)]を呈する患者で，脳血管撮影や脳血流 SPECT によって非発作時における潜在的脳虚血部位を示した報告はあるが，発作時の局所的脳血流変化を明らかにしたものは少ない．今回，私たちは，立位や座位負荷によってけいれん様の不随意運動が右上肢優位に出現する患者において症状出現時と非出現時の脳血流 SPECT と脳波の変化を検討し，その病態について考察した．

症　例

症例：74 歳，男性

主訴：起立時に気が遠くなり，けいれんのような不随意運動がおこる

既往歴：特記すべき事はない．

家族歴：父が悪性腫瘍，母が悪性腫瘍（ともに詳細不明），姉が肺結核．兄が患者と同様の起立性低血圧の症状がある．

現病歴：軽度の慢性閉塞性肺疾患にて近医通院加療中であった．2005 年5月頃から起立時に立ちくらみが出現し，よく転倒するようになったため，前医神経内科にて入院精査された．安静臥位での血中カテコラミンが低値で，head up tilt 試験で起立性低血圧をみとめ，ノルアドレナリン試験などにて脱神経過敏性を示したことから純粋自律神経不全（pure autonomic failure：PAF）と診断された．ドロキシドパ，メチル硫酸アメジニウムが開始されたが，依然として起立時に気が遠くなる感じがし，しばしば転倒した．2006 年3月から起立時に右上下肢に優位のけいれん様不随意運動が出現するようになった．意識は軽度減損するが完全に消失することはなく，けいれん様不随意運動がおこっていることを本人は自覚していた．同年6月に当科に入院した．

入院時現症：身長 159.5cm，体重 38.3kg，体温 36.3℃．血圧，脈拍は臥位で 108/62mmHg（68 回/分），立位2分後で 67/40 mmHg（70 回/分），胸部，腹部に異常所見なし．

神経学的所見：意識清明．脳神経に異常なく，麻痺や感覚障害もみとめなかった．筋強剛や振戦，小刻み歩行といったパーキンソニズムはみとめなかった．継ぎ足歩行をさせると軽度動揺するが転倒はしなかった．四肢の失調もみとめなかった．

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（受付日：2010 年 11 月 6 日）

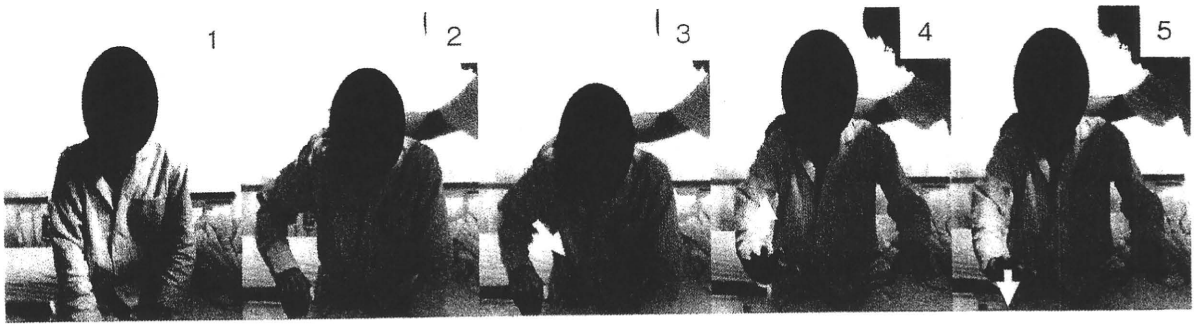

Fig. 1　Convulsive movements.
Immediately after sitting up on the bed from the supine position, no involuntary movements were observed (1). Approximately 60 seconds later, shaking movements of the trunk and the bilateral limbs appeared (2-3). When the patient was instructed to raise and stretch his arms and keep them in the air, flapping like movements of the hands appeared (4-5). The movements were prominent on the right side. During the involuntary movements, he experienced lightheadedness, but he was oriented and able to respond to our instructions. The symptoms lasted for approximately 30 seconds while he was sitting.

臥位から座位や立位になると，約1分後に体幹，両上下肢のとくに近位部に律動的なミオクローヌス様の粗大な不随意運動が右側上肢優位に出現した(Fig. 1)．患者は意識が遠のく感じを訴え，やや応答が鈍くなるが，見当識はかろうじて保たれており，簡単な口頭指示にはしたがうことができた．更にこの状態でBarre肢位を取らせると，上肢は上腕が軽度外転し，手関節で羽ばたくような1Hz程度の半律動的な不随意運動に変化した．この不随意運動は，右側で振幅がより大きく，左右の運動は同期していなかった．発作は坐位のまま数10～30秒持続した後に停止し意識も回復した．その後は歩行してもふたたび座位や臥位からおき上がらなければ症状が出現することは無かった．

入院時検査所見：血算は正常範囲で貧血はみとめなかった．一般血清生化学検査でも特記すべき異常はなく電解質も正常範囲であった．安静臥位時の血中カテコラミンはドロキシドパ内服中止後3日目の朝でadrenalin 5.0pg/ml以下，noradrenalin 299pg/ml，dopamine 24pg/mlであった．尿中のカテコラミン代謝産物は，尿中メタネフリン0.07mg/day，尿中ノルメタネフリン0.60mg/dayであり，いずれも正常範囲であった．MIBG心筋シンチではいちじるしい集積低下をみとめた．

発作時ビデオ—脳波記録：安静閉眼覚醒時の脳波には特記すべき異常はなかった(Fig. 2A)．座位負荷50秒後から2～3 Hzの左右差なく，前頭部で最大の全般性徐波が出現し，60秒後からは不随意運動が出現して約15秒間持続した．全般性徐波は不随意運動が出現している間持続し，心電図には不随意運動によると考えられる筋電図の混入がみとめられた(Fig. 2B)．aborted spikeを示唆するような律動性発射ではなく，またてんかん発作を示唆する進展様式もみとめなかった．さらに発作間欠期にも明らかなてんかん性放電はみとめなかった．

発作時SPECT：症状出現時の血流分布変化をしらべる目的で，split dose法[14]をもちいて臥位安静時と座位後の症状出現時でそれぞれ^{99m}Tc-ECD (ethylcysteinate dimmer) SPECTを施行した．この方法は2条件下の脳血流イメージが1日でえられる利点がある．撮像時には，まず臥位安静時に^{99m}Tc-ECDを静注して1回目のSPECT撮像をおこない，続けて患者を座位にして右上肢の不随意運動が出現した時点でもう一度^{99m}Tc-ECDを静注し2回目のSPECT撮像をおこなった(Fig. 3)．画像解析時に，2回目の撮像画像から半減期補正をおこなった1回目の撮像画像を差分することで，座位時負荷時の脳血流分布画像を作成した．その後，それぞれのボクセルのカウントを全脳の平均カウントで除してカウントの標準化をおこなうことで，両画像の直接比較ができるようにした(Fig. 4上段，中段)．更に臥位の血流分布画像から座位の血流分布画像を差分して，血流低下の程度を示す画像を作成した(Fig. 4下段)．その結果，安静臥位時と比較して，座位負荷時には，左基底核（尾状核），両側前頭葉および両側小脳半球（右＞左）で血流低下がみとめられた．

頭部MRIおよびCT血管撮影：頭部MRI T_2強調画像にて軽度の白質の高信号域をみとめたが年齢相応と考えた(Fig. 5A)．CT血管撮影では，右中大脳動脈全体の軽微な狭小化がうたがわれたが，臨床上問題となると考えられるような高度な狭窄はみとめなかった（Fig. 5B)．

入院後の経過：症状出現時の脳波所見よりてんかん性のけいれん発作ではなく，起立性低血圧によるconvulsive syncopeと診断した．入院後も日常生活での通常の起床により症状が出現するため，急激な姿勢変化を避けるなど生活指導をおこなった．ドロキシドパの増量，ミドドリンの追加などをおこなったが症状の変化はみとめなかった．その後，フルドロコルチゾンを追加投与し，起床時にゆっくりした姿勢変化をおこなうようにするなどして，発作の出現頻度は減少して，退院となった．

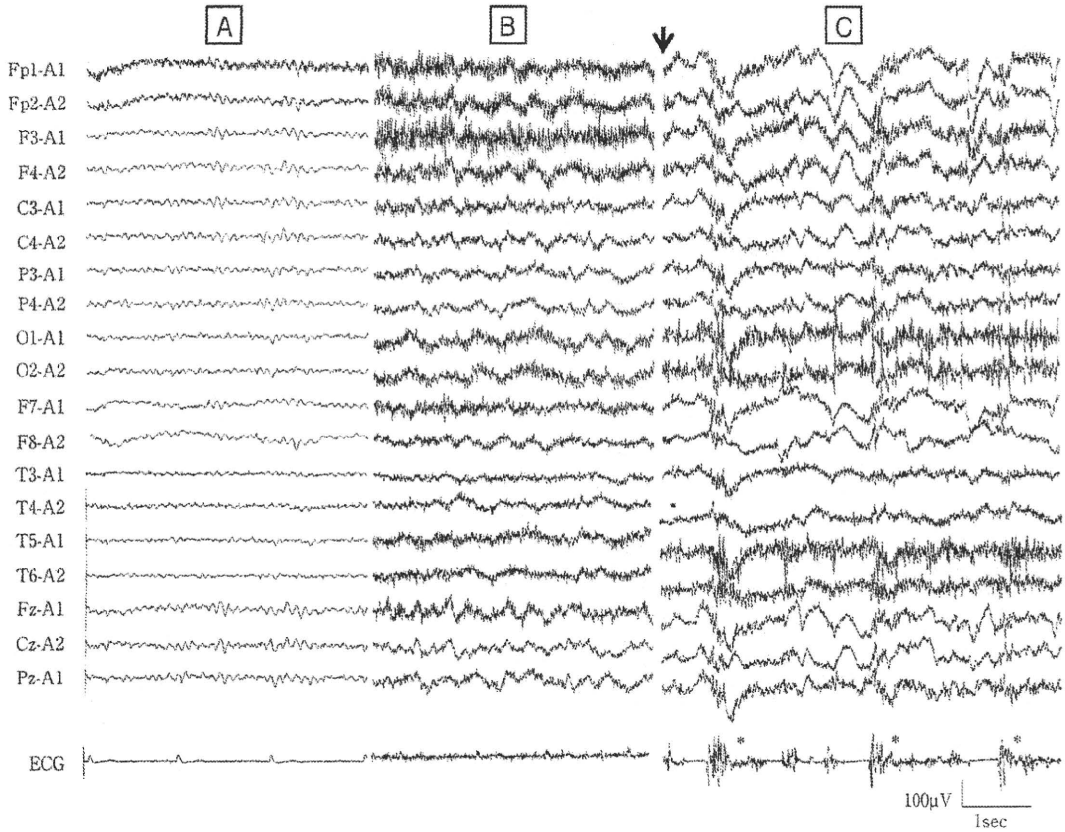

Fig. 2　Electroencephalography (EEG).

A: EEG (awake on the supine position with no symptoms): No clear abnormality was observed in this recording.

B: EEG (after sitting up and before the occurrence of convulsive syncope): The EEG showed generalized slows (2-3Hz) 50 sec after taking the sitting position.

C: EEG (after sitting up and the occurrence of convulsive syncope): The EEG started showing rather continuous high amplitude, generalized semirhythmic slows (2-3Hz), maximum in the bilateral frontal areas, 60 sec after taking the sitting position. Once the symptoms occurred, the electrocardiogram (ECG) also recorded electromyogram (EMG) artifacts of the involuntary movements (*). Note that an arrow indicates the onset of the intermittent convulsion like symptoms.

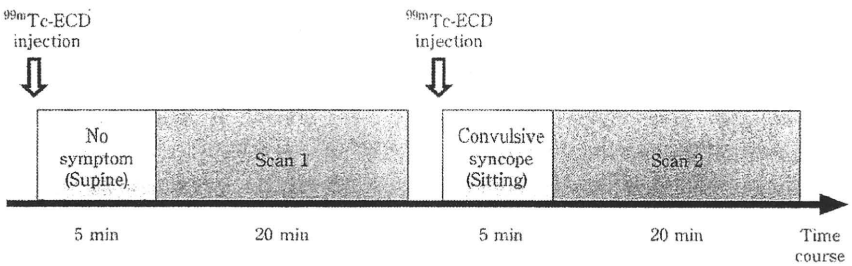

Fig. 3　The protocol of split dose ^{99m}Tc-ethylcysteinate dimmer single photon emission computed tomography (^{99m}Tc-ECD SPECT).

The patient underwent 2 consecutive SPECT scans in the same day. The first injection of ^{99m}Tc-ECD was done when the patient was at rest in the supine position. Five minutes after the injection, the patient was scanned for 20 minutes. After the first scan, the second injection of ^{99m}Tc-ECD was done when the patient sat up and the convulsive syncope appeared.

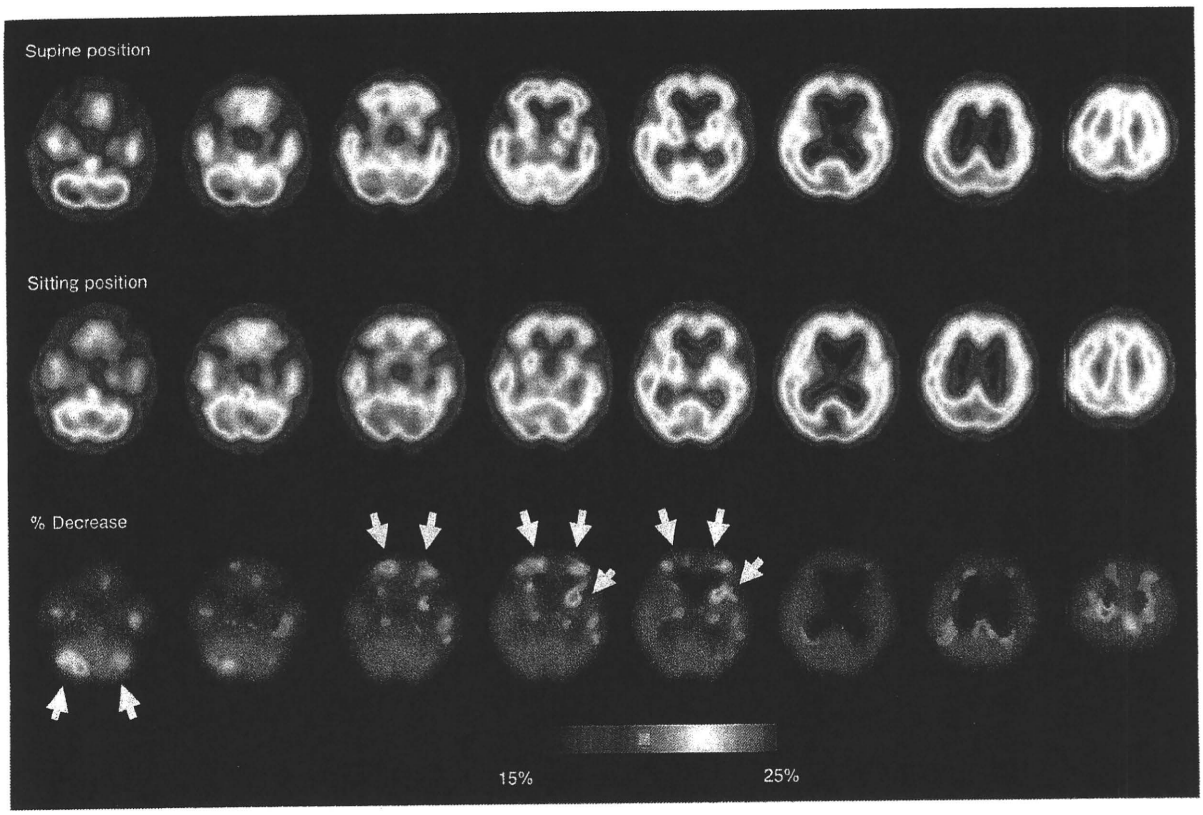

Fig. 4 ^{99m}Tc-ECD SPECT images.
Two cerebral blood flow images were obtained when the patient was at rest in the supine position (top) and then when convulsive syncope developed by sitting up from the supine position (middle). Note that the latter images were coregistered onto the former images, and, to remove the effects of global activity, each voxel count was normalized to the mean count of the whole brain using proportional scaling. The latter were then subtracted from the former, and the degree of % decrease in blood flow was displayed (bottom). During convulsive syncope, a significant decrease in blood flow was clear in the anterior part of the left basal ganglia (caudate), the bilateral frontal cortices, and the bilateral cerebellar hemispheres more on the right.

考　察

本患者は起立性低血圧が誘因となって，軽度の意識減損と左右非対称性のけいれん様不随意運動を呈した．不随意運動は常に臥位から座位や立位を取った後に誘発されており，症状出現時の脳波ではてんかん性放電をともなわないことから，てんかん発作ではなく，一過性脳低灌流に関連した軽度の意識減損にともなうけいれん様不随意運動（convulsive syncope）と診断した．臥位から立位になる時点で症状は出現するものの，一旦停止した後は歩行をしても症状がおこることはなく，一過性に起立性低血圧による脳低灌流をきたすものの，時間とともに代償されたためと考えられた．このような症例においては，抗けいれん薬は無効で，原因となる起立性低血圧などの血行動態の改善を目的とした治療をおこなう必要がある．そのため，てんかん発作との鑑別が重要であり，Grubb らはいわゆる convulsive syncope との鑑別に，isoproterenol を併用した head-up tilt 試験が診断に有用としている[5]．本症例では薬剤負荷をおこなうことなく，日常生活における姿勢変化で頻繁にけいれん様不随意運動が誘発され，不随意運動発現時の SPECT の結果，左基底核の相対的血流低下が検出され，病態との関連が示唆された．

血行力学的一過性脳虚血による不随意運動については，内頸動脈の高度狭窄にともなう limb shaking がこれまで比較的多く報告されている．Yanagihara らは頸動脈の狭窄病変を有する反復する hand shaking や jerk をみとめた 12 例を報告した[4]．これらの症例では歩行や起立，頸部の屈曲などの誘因で症状が出現していること，脳波上は症状出現時に徐波化をみとめるのみでてんかん性の異常をみとめないこと，いわゆる jacksonian march のような進展様式を示さないことなどから，これらの症状は内頸動脈の高度狭窄による大脳半球の局所血流低下によりおこるもので，てんかん性の異常によるものではないとしている．

一過性脳虚血による不随意運動の病態生理については，報

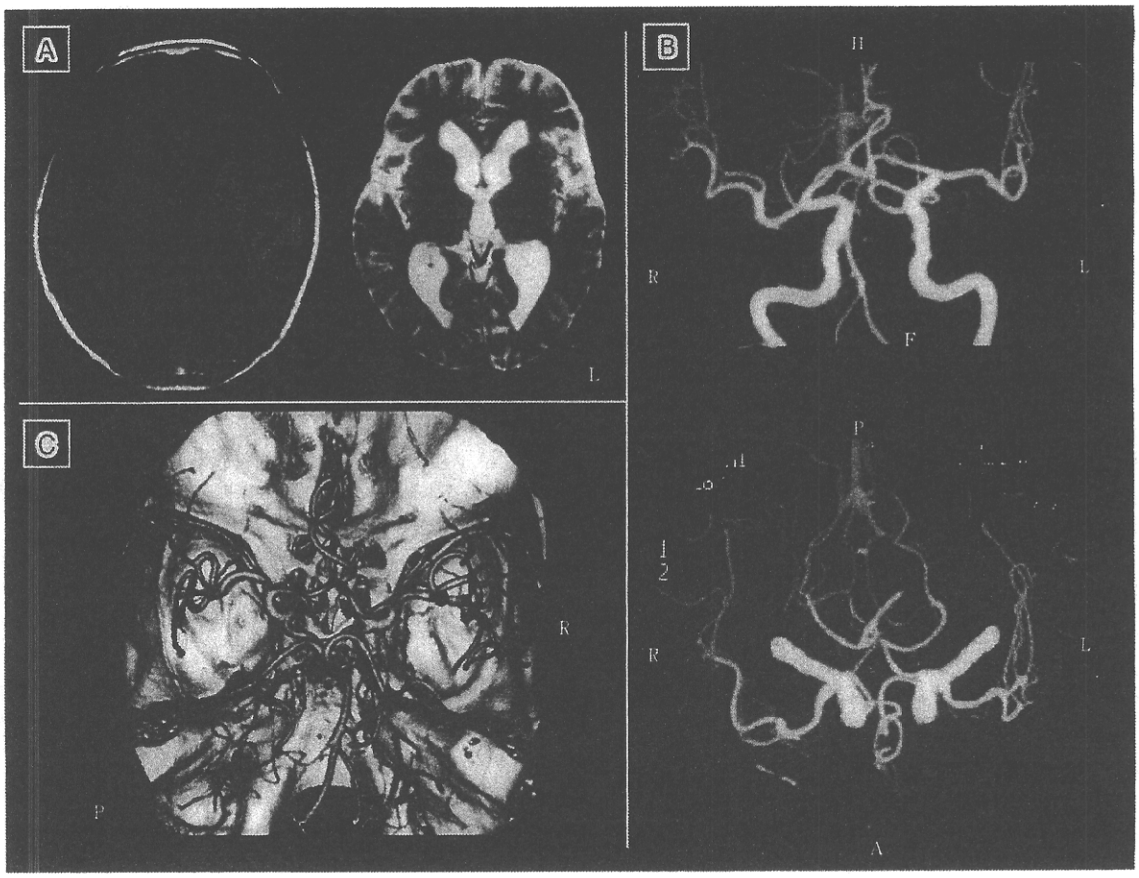

Fig. 5　Magnetic resonance imaging (MRI) and computed tomography (CT) angiography.
A: T_1 (left) (Axial, 1.5T; TR 436ms, TE 11ms) and T_2 (right) (Axial, 1.5T; 3310ms, TE 80ms) weighted image showed no remarkable lesion.
B, C: CT angiography showed that the right middle cerebral artery was slightly narrower than the left. But there was no severe stenosis.

告数が多くないことに加え，症例によってことなる不随意運動を呈することから，十分に明らかにはなっていない．比較的多い limb shaking を呈するものについては，$Xe^{[3][5][6]}$や ^{99m}Tc-hexamethylpropylene amine oxime（HMPAO）[7][8]，^{99m}Tc-ECD[9]をもちいた脳血流 SPECT より脳血流を評価した報告があり，dorsofrontal region をはじめとする anterior circulation の血流低下が報告されている．しかし，これらの報告の多くは不随意運動出現中の血行動態の変化をしらべたものは少なく，二酸化炭素[6]，降圧剤[6]，acetazolamide[7]~[9]負荷によって潜在的脳虚血部位を明らかにしたものであり，負荷によっても発作は誘発されていない．Han らは左下肢の limb shaking を示す前大脳動脈の狭窄例において，症状発現時に右前頭葉内側面の血流上昇をみとめたとしている[9]．一方で，和田らは安静時と立位負荷後の不随意運動出現時で ^{99m}Tc-HMPAO SPECT を撮影したが，明らかな差異はみとめなかったと報告している[8]．ただしこの症例では，不随意運動が左右対称性であったため，SPECT 画像の視察的比較では，左右対称性の血流低下が存在したとしても，その検出が難しかったのかもしれない．

もやもや病の患者においては，過換気などの虚血負荷時に，一過性の麻痺や，limb shaking[11][12]，chorea[11]や hemichorea[13]を呈することがある．本病態における一過性の chorea の出現機構は以下に示すように，本例と類似するものと判断される．もやもや病では過呼吸負荷で徐波化した脳波が一旦正常化したあとに1~2分以内に再度徐波化する現象がみられ（再徐波化）[16][17]，この状況で一過性麻痺や chorea などの臨床症状が出現する[17]．すなわち一過性麻痺は過呼吸にともなう大脳皮質の虚血，chorea は大脳基底核の虚血が示唆されている．前者の機序は過呼吸による皮質の虚血で容易に説明されるが，後者の機序は炭酸ガス反応性を有する脳表の血管とそれを有さない異常なもやもや血管のアンバランスにより脳深部から脳表への血流の逸脱がおこり，その結果脳深部の虚血が生じ徐波化や不随意運動などの脳深部由来の症状が出現するとされている[17]．これは本例での脳波の徐波化，基底核領域の血流低下に類似する病態が示唆される．Im らも，もやもや病における不随意運動には基底核と大脳皮質の不均衡が関与してい