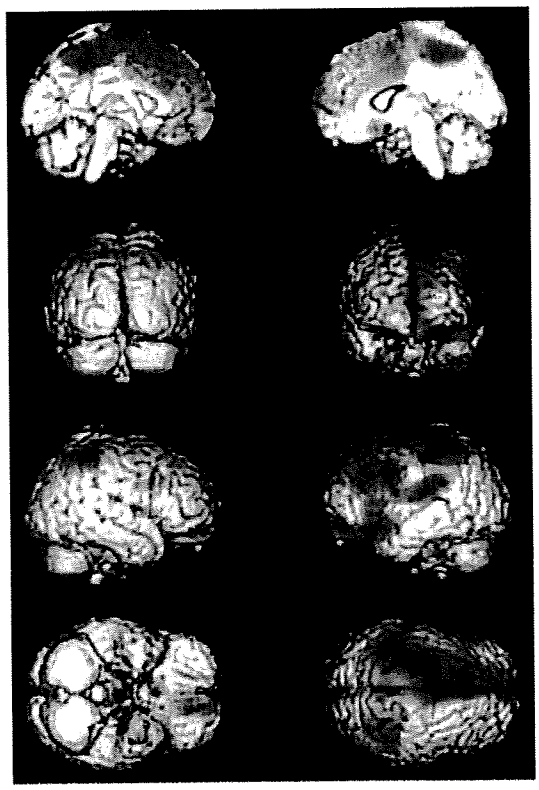

Fig. 3 Brain regions showing a significant increase (red) and decrease (blue) in glucose metabolism after subtemporal SAH. The epileptogenic zone was lateralized to the left side. Note that the results of the group-comparison analysis without an explicit mask are displayed for decrease in glucose metabolism, 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.

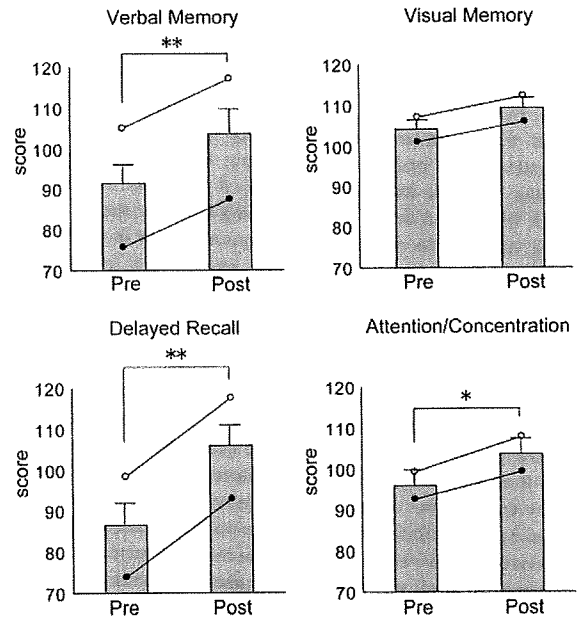

Fig. 4 Bar charts illustrating the mean WMS-R scores of all patients for verbal memory, visual memory, delayed recall and attention/concentration at preoperative and postoperative evaluation. Error bars show SEM. Solid circles and open circles indicate the mean scores of patients with language-dominant 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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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Reversible Alcohol-related Dementia: A Five-year Follow-up Study Using FDG-PET and Neuropsychological Tests

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Abstract

Objective As the pathophysiology of alcohol-related dementia (ARD) is unclear, we examined a patient with reversible ARD using neuropsychological tests and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET).

Methods Design: A five-year follow-up case study with neuropsychological tests and FDG-PET. Setting: Kyoto University Hospital.

Patients A 42-year-old patient who was unable to perform his office duties because of slowly progressive amnesia with executive dysfunction.

Results The initial evaluation with neuropsychological tests showed severe verbal memory disturbance. The patient did not discuss his excessive alcohol consumption in the initial history-taking session and thiamine deficiency was absent; therefore, early-stage Alzheimer's disease was suspected. Later, the patient revealed prior excessive alcohol intake and his cognitive function improved markedly after a period of abstinence. Retrospective analysis of initial FDG-PET images using a voxel-wise statistical method revealed glucose hypometabolism in the diencephalon and basal forebrain. Follow-up for 5 years after the initial evaluation showed improved cognitive function and recovery of glucose metabolism in the two brain regions.

Conclusion Hypofunction in the diencephalon and basal forebrain was associated with cognitive decline in our patient. This case may provide evidence for the etiopathic brain regions in reversible type ARD.

Key words: alchohol related dementia, Wernicke-Korsakoff syndrome, FDG-PET, Alzheimer disease, diencephalon, basal forebrain

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Introduction

The Wernicke-Korsakoff syndrome (WKS) is a representative alcohol-induced memory disturbance characterized by neuropathological changes in the diencephalon, including the anterior part of the thalamus, and the mammillary body caused by thiamine deficiency (1). The most characteristic neuropsychological feature of WKS is marked memory deficits, while the other intellectual abilities are relatively preserved (2, 3). An ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) study of WKS showed regional glucose hypometabolism in the diencephalic grey matter, which is consistent with the underlying neuropathology. Glucose hypometabolism was also found in the medial temporal lobe and retrosplenium, which is interpreted as secondary metabolic effects within the diencephalic-limbic memory circuits (4).

Alcohol-related dementia (ARD) has been broadly defined as alcohol-induced dementia in the Diagnostic and Statistical Manual of Mental Disorders IV- Text Revision (DSM-IV-TR). ARD has been reported as the organic brain syndrome induced by alcohol abuse, which results in severe cognitive impairment, including executive dysfunction and lack of

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Table 1. Results of Neuropsychological Assessments

Battery	On admission	3 weeks after admission	5 years after discharge
Mini-Mental State Examination	30 (full marks)	ND	30
WAIS-R			
VIQ	100	ND	130
PIQ	107	ND	137
FIQ	104	ND	137
Geriatric Depression Scale	15 (full marks)	,ND	0
Miyake's Verbal Memory Test			
Associated paired-word test	9–10–10	ND	10–10–10
Nonassociated paired-word test	1–4–4	6–7–6	8–10–10

WAIS-R: Wechsler Adult Intelligence Scale-Revised ; VIQ: verbal intelligence quotient; PIQ: performance intelligence quotient; FIQ: full-scale intelligence quotient; ND: not done

emotional control, in addition to memory disturbance (5). Although the pathophysiology of WKS has been relatively well studied, the neural basis of ARD remains unclear. Two concepts have been proposed for ARD: 1) ARD is a variant of WKS and is associated with thiamine deficiency-induced dysfunction in the diencephalon (6) and 2) ARD originates from the disturbance impairment of the cholinergic system, including projection fibers from the nucleus basalis of Meynert or the dorsal brainstem (7-12). Functional neuroimaging techniques such as PET have been expected to elucidate the neural substrate of ARD (13).

Here, we describe a series of neuropsychological and FDG-PET studies over 5 years for a 42-year-old male office worker with dementia resulting from excessive alcohol intake for several years. To the best of our knowledge, there has been no report showing that regional cerebral glucose hypometabolism improves with the amelioration of neuropsychological impairment in a patient with ARD. We discuss the possible neural basis of reversible ARD.

Case Report

A 42-year-old man was admitted to hospital for the evaluation of his slowly progressive impairment in recent memory. He reported that he had been suffering from daily stress at work and forgetfulness for a few years. He complained that he had difficulty in concentrating and thinking and lacked motivation, although he did not report appetite loss or sleep disturbance. For 6 months before admission, his supervisor had recognized that his memory disturbance was becoming worse. Although he made notes to remember some things, he often forgot to write them down. He lost his way home once. He often lost his temper, but sometimes could not remember the reason for his behavior. He gradually became unable to do his work. He had no history of neurological or psychiatric illness. Since he had not revealed a history of excessive alcohol intake, an early stage of Alzheimer's disease was initially suspected, and he was admitted to the hospital for the evaluation of dementia.

On admission, he showed mild cognitive decline and impairment in emotional control and concentration. He appeared to be apathic. In his general and neurological examination, extraocular movements were full and truncal or limb ataxia was not noted. He was slightly disoriented, and his recent memory was definitely disturbed, while his remote memory was relatively preserved. Neuropsychological batteries on admission showed an immediate verbal memory decline. The geriatric depression scale (GDS) revealed the worst possible score (15 points), which indicated that he was in a depressive state (see Neuropsychological Assessment in Results). Blood tests revealed a slight elevation of the levels of aspartate and alanine aminotransferases and triglycerides, thereby suggesting fatty liver. Serum thiamine level (37 ng/mL) was within the normal range (20-50 ng/mL), while serum vitamin B_{12} level was 323 pg/mL(normal range, 249-938 pg/mL). Serological tests for syphilis were negative, and thyroid function was normal. The finding of brain magnetic resonance imaging was unremarkable. Electroencephalography showed generalized intermittent irregular slow waves (theta range). His memory and emotional control improved gradually after admission to hospital. The score of Miyake's Verbal Memory Test improved at 3 weeks after admission as compared to those performed on admission (Table 1). Since his motivation did not improve despite the recovery of memory function, a low dose of an antidepressant (25 mg/day of maprotiline hydrochloride) was started.

One year after discharge, he confessed that he had a history of daily excessive alcohol intake for several years prior to admission. He had consumed 2 drinks/day for several years and 6 drinks/day for 1 year prior to admission (1 drink equals 12 g of pure ethanol; National Institute on Alcohol Abuse and Alcoholism recommends alcohol consumption of $\leq$2 drinks/day for people of similar age) (1, 14). He had abstained from alcohol since admission to hospital, although he had shown no symptoms of withdrawal during hospitalization. This information confirmed the final diagnosis as a reversible type of ARD. To elucidate the pathophysiology of this unique condition, we conducted a follow-up study with FDG-PET and neuropsychological tests for 5

years after hospitalization. At present, the patient is working in a middle management position with no problems at work.

Methods

Neuropsychological tests

The Japanese edition of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) was used for the assessment of intelligence. Miyake's Paired-associated Word Learning Test for Verbal Memory was used as the verbal memory test. In this test, the subject is requested to memorize 10 pairs of either associated or non-associated nouns and immediately recollect the paired word. This procedure is repeated 3 times with a time interval. The results are expressed as the number of words recalled accurately in each procedure (15, 16). The Japanese version of the Geriatric Depression Scale (GDS) was used as the depression scale, although the patient's age was younger than the target age group considered for this scale (17). The Mini-Mental State Examination (MMSE) was used for a simple intelligence scale.

Image data acquisition and analyses

FDG-PET was performed using a General Electric Advance PET scanner (General Electric Medical Systems, Milwaukee, WI, USA). A 370 MBq (10 mCi) of [^{18}F]-FDG was injected intravenously into the patient. Forty minutes after administration of the radiotracer, 35 slices of brain emission images were acquired over a 20-min period. The emission images were reconstructed using an iterative reconstruction method. All reconstructed images were corrected for attenuation by using ^{68}Ge-^{68}Ga transmission scans.

In voxel-wise analyses using SPM2 software (Wellcome Department of Imaging Neuroscience, UCL, London, UK), spatially normalized images were smoothed with an isotopic Gaussian Kernel set at 16-mm full-width at half-maximum (FWHM). To remove the effect of the global count, the count of each voxel was normalized to the total count of the brain by using proportional scaling. The FDG-PET image of the patient was compared with those of 12 age-matched controls (mean age, 37.3 ± 12.9 years) by using t statistics. We investigated hypometabolic brain areas for the patient as compared with control subjects. The regions were considered to be significant at a height threshold of p=0.01, uncorrected for multiple comparison (Z score=2.34), and an extent threshold of 50 voxels. For visualization, significant clusters were projected onto a surface-rendered anatomical template provided by SPM2. The spatial coordinates of the local maxima from the statistical analysis were used to identify the corresponding brain areas according to the atlas of Talairach and Tournoux (18). The nonlinear transformation of the Montreal Neurological Institute (MNI) coordinates into the Talairach coordinates was performed using appropriate converter software (mni2tal.m; http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml).

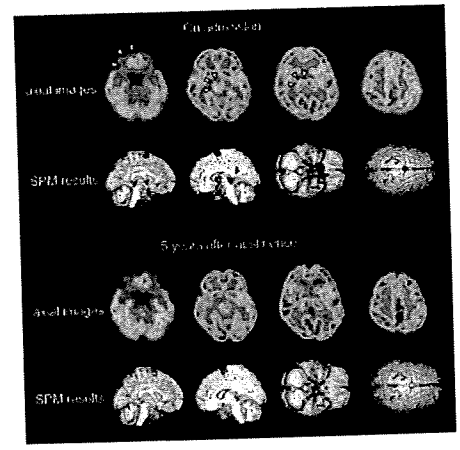

Figure 1. This figure shows axial images of FDG-PET and the results of the voxel-wise statistical comparison with healthy subjects (n=12) by using SPM2 (height threshold, z>2.34, p<0.01; extent threshold>50 voxels). FDG-PET on admission showed glucose hypometabolism in the right diencephalon, including the anterior thalamus and the bilateral basal forebrains more on the right side (white arrow heads). The SPM results clarified that cerebral glucose hypometabolism improved at 5 years after abstinence in the right diencephalon and bilateral basal forebrains and temporal poles.

Results

Neuropsychological assessments

As shown in Table 1, a trend of amelioration was found in all neuropsychological batteries. Among these batteries, the score of the nonassociated paired-word test in Miyake's Verbal Memory Test was markedly improved at 5 years after discharge. The depression scale score at 5 years after discharge also showed complete amelioration as compared to that at admission.

FDG-PET analyses by SPM2

As shown in Fig. 1 and Table 2, the voxel-based statistical analysis using SPM2 for the first FDG-PET revealed glucose hypometabolism in the right diencephalon, including the anterior thalamus; the bilateral basal forebrains, temporal poles and supplementary motor areas (SMAs); the dorsal brainstem. The subsequent FDG-PET analysis at 5 years after discharge revealed improvement in cerebral glucose metabolism in the right diencephalon and the bilateral basal forebrains and temporal poles.

Although glucose hypometabolism was still detected to some extent in the temporal pole, SMA and dorsal basal brain stem, magnetic resonance imaging showed no anatomical abnormalities in such regions.

Table 2. Brain Regions of Our Patient Showing a Significant Decrease in Glucose Metabolism in FDG-PET Study on Admission and 5 Years after Abstinence as Compared with Those of the Healthy Subjects

Brain region	Side	Talairach coordinates of the peak			Z score
		x	y	z	
On admission					
Diencephalon	R	12	−2	6	3.94
Temporal pole	L	−24	18	−29	3.91
Orbitofrontal gyrus	R	10	10	−24	3.19
Retrosplenium	R	32	−44	21	3.34
SMA	L	−2	3	64	2.85
Dorsal brain stem	−	8	−27	5	2.84
5 years after abstinence					
Temporal pole	L	−24	18	−29	3.14
SMA	L	8	−27	5	2.93
Dorsal brain stem	−	8	−27	5	2.66

R: right; L: left, SMA: supplementary motor cortex

Discussion

Etiopathic brain regions for tentative cognitive decline

The patient had no evidence of alcohol dependency throughout the clinical course, although the patient had a history of excessive alcohol drinking. We consider the patient did not have acute abstinent syndrome, which was originates from not only alcohol but also from drugs, because our patient did not have abstinent syndrome during the hospitalization, and the patient's MMSE score was full. We also consider that acute brain syndrome, like black out, due to excessive alcohol drinking, or caused by repetitive toxicity, might was not seen in the patient, throughout this patient's hospitalization.

In the present patient, cerebral glucose hypometabolism was initially detected in the diencephalon and basal forebrain. Five years of abstinence resulted in improvement in cerebral glucose metabolism in these regions and cognitive function. This might suggest that the tentative hypofunction in these 2 brain regions was ascribed to the reversible nature of cognitive dysfunction in our patient.

The diencephalon and basal forebrain have been associated with amnesic diseases such as WKS or Alzheimer's disease. In WKS, neuropathological changes occur in the memory circuit in the diencephalons such as the anterior nuclei of the thalami, the mammillary bodies, and mammillothalamic tracts (19-22). A more recent FDG-PET study revealed that glucose metabolism is decreased in these brain regions (4). Thus, both the structural and functional changes in the diencephalons are ascribed to the irreversible nature of cognitive decline in WKS (1).

Cognitive impairment in WKS is also ascribed to the cholinergic pathway from the basal forebrain, as in the case of Alzheimer's disease (23). Thiamine is thought to play a role in the cholinergic synaptic transmission and axonal conduction, and an excessive alcohol intake can result in thiamine deficiency (5). In our patient, the cholinergic neurons in the basal forebrain might be impaired tentatively because of either direct toxicity of excessive alcohol or a rapid decrease in thiamine concentration in the blood, although the thiamine concentration was within the normal range.

Although ARD might represent a heterogeneous disease concept, including a variant of WKS, the present case might provide a clue to elucidate the etiopathic brain regions in the reversible type of ARD. It remains to be studied whether the irreversible type of ARD results from the same lesions as those observed in our patient.

Furthermore, regarding the recovery ability of this patient, another important factor for the recovery of cognitive abilities might be cognitive plasticity adaptation after brain damage due to excessive drinking, especially for relatively young patients as in the present case. In the future, it will be necessary to elucidate the mechanism of this plasticity, as few studies have considered this point (24).

Clinical implication

The initial symptoms in the present case included amnesia, slight disorientation, and impairment of emotional control and concentration. These symptoms are compatible with the early stage of Alzheimer's disease according to DSM-IV-TR. While Alzheimer's disease is irreversible, cognitive function in the present patient showed gradual improvement after cessation of alcohol intake on hospitalization. Therefore, we finally diagnosed his illness as ARD.

The proportion of depressive patients among alcoholics is approximately 2 times higher than that among healthy population (25). In the present patient, a complication of depression was also suspected based on the lack of motivation and low GDS score in the initial evaluation. However, his mem-

ory function had already improved at 3 weeks after abstinence when the antidepressant had not yet been administered. In addition, the topography of changes in glucose hypometabolism in our patient differed from those in patients with depression. In patients with depression, glucose hypometabolism in the prefrontal cortices is common, and these areas are associated with neuropsychological impairment (26, 27). The patient had no history of psychiatric disease, including depression, apathy, alcohol dependence, and drug abuse before this alcohol excessive drinking history. Thus, we consider that depression was unlikely the main cause of cognitive decline in our patient, although it might have played a partial role in the recovery from executive dysfunction in his daily life after discharge.

In summary, we report a case of reversible ARD without thiamine deficiency that mimiced Alzheimer's disease. Detailed medical history taking is necessary for the early diagnosis and intervention of this disease. FDG-PET might also facilitate early diagnosis of this disease.

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