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Paradoxical Hippocampus Perfusion in Mild-to-Moderate Alzheimer's Disease

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The purpose of this study was to clarify the changes in hippocampal perfusion in mild-to-moderate Alzheimer's disease using PET and ^{15}O-labeled water. **Methods:** Sixteen patients with probable mild-to-moderate Alzheimer's disease (age: 68.1 ± 11.3 yr; MMSE: 21.1 ± 4.5) and 10 normal volunteers (age: 65.1 ± 8.2 yr) were studied. Regional cerebral blood flow (CBF) and cerebral blood volume (CBV) were measured using ^{15}O-labeled water autoradiographic method, C^{15}O-gas inhalation technique and PET. **Results:** Although the mean CBF in the parietotemporal region was significantly lower in the patient group than in the control group, the mean CBF in the hippocampus did not show significant reduction between the two groups, both in absolute and relative values. There was no significant regional CBV difference between the two groups. Parietotemporal perfusion correlated well with cognitive scores, both in absolute and relative values, in Alzheimer's disease, but hippocampal perfusion did not correlate well. **Conclusion:** Hippocampal perfusion was preserved in mild-to-moderate Alzheimer's disease.

Key Words: PET; Alzheimer's disease; Oxygen-15-labeled water; hippocampus; cerebral blood flow

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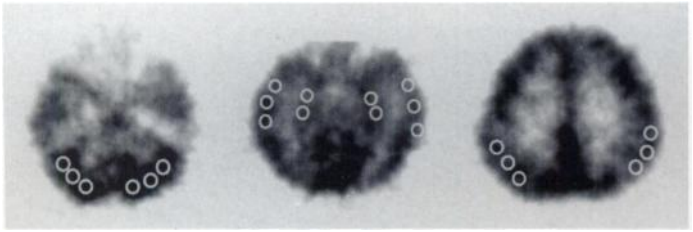

FIGURE 1. ROI settings for cerebellum, hippocampus, lateral temporal and parietal cortices on CBF images.

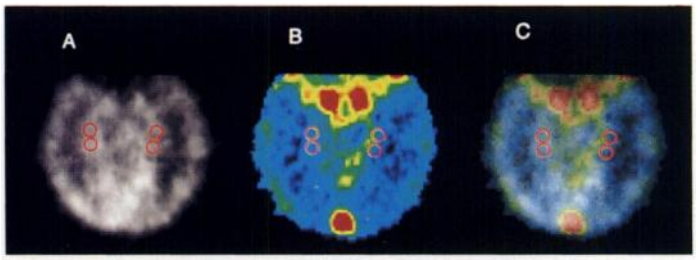

FIGURE 2. ROI settings on hippocampal longitudinal plane of a patient with Alzheimer's disease. (A) CBF image shows decreased left lateral temporal perfusion. (B) CBV image shows large vascular bed of left posterior cerebral artery. (C) Superimposed image demonstrates that distribution of left hippocampal perfusion overlaps a part of CBV distribution of the left posterior cerebral artery.

The hippocampus is essential for memory, and memory impairment is a hallmark of Alzheimer's disease. It is a major site of neuropathological changes in the early process of Alzheimer's disease (*1,2*). Studies using SPECT and ^{99m}Tc-hexamethyl propylene amine oxime (HMPAO) have shown that hippocampal perfusion is reduced in patients with memory disturbance (*3,4*). According to Ohnishi et al. (*3*), a high-resolution cerebral blood flow (CBF) SPECT system can demonstrate hippocampal perfusion. In patients with memory disturbance, hypoperfusion was noted, and they reported that the technique may be useful in assessing the extent of dementia and memory disturbance. On the contrary, Frackowiak et al. (*5*) and Powers et al. (*6*), who used PET to measure CBF in Alzheimer's disease, did not refer to the hippocampal perfusion, which was probably unclear due to the use of a low spatial resolution of the PET scanner. Recently, we reported decline in medial temporal oxygen consumption in patients with mild-to-moderate Alzheimer's disease (*7*). However, in that study we could not demonstrate significantly decreased medial temporal blood flow, though there was a significant decrease in the medial temporal oxygen consumption in Alzheimer's disease patients. Moreover, in CBF images measured with ^{15}O-labeled water or ^{15}O-labeled CO_2 in a routine PET study, we seldom have experienced decreased hippocampal perfusion in patients with mild-to-moderate Alzheimer's disease, while parietotemporal perfusion was obviously reduced. The purpose of this study was to investigate whether hippocampal perfusion in patients with mild-to-moderate Alzheimer's disease is significantly decreased or not, using PET and an autoradiographic technique with ^{15}O-labeled water.

MATERIALS AND METHODS

Subject Selection

We studied 26 subjects, including 16 patients with mild-to-moderate Alzheimer's disease (mean ± s.d.: age 68.1 ± 11.3 yr; 14 women, 2 men) and 10 sex- and age-matched healthy volunteers (mean ± s.d.: age 65.1 ± 8.2 yr; 9 women, 1 man). According to the following criteria, patients with Alzheimer's disease were selected from those who were admitted in our hospital for examination between July 1995 and September 1996. All patients were examined by both neurologists and psychiatrists and had brain MRI, MR angiography of the neck and head, EEG and standard neuropsychological examinations for more than 1 mo after admission. The inclusion criteria included:

1. National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable Alzheimer's disease (*8*).
2. No evidence of focal brain lesions on MR images except for age-related hyperintensities on T2-weighted images.
3. Functional severity mild-to-moderate: grades 0.5–2 on clinical dementia rating (CDR) (*9*).
4. Age less than 80 yr.

Exclusion criteria included:

1. Complication of other neurological diseases or poor physical conditions.
2. Presence of severe language, attention and behavioral disorders that would make a PET procedure difficult.
3. Lack of informed consent from patients and their relatives.

The mean Mini-Mental State Examination (MMSE) (*10*) score was 21.1 ± 4.5 (mean ± s.d.), and the mean Alzheimer's Disease Assessment Scale (ADAS) (*11*) score was 19.8 ± 6.1 (mean ± s.d.).

Healthy volunteers, who served as normal control subjects, had no neurological signs or significant medical antecedents and no abnormal MR findings except for age-related hyperintensities on T2-weighted images. Informed consent was obtained from all

TABLE 1
Absolute Cerebral Blood Flow (CBF) and Cerebral Blood Volume (CBV)

	R Hip	L Hip	R LT	L LT	R Par	L Par	R Cb	L Cb
CBF								
AD	42.4 ± 8.0	41.2 ± 6.7	39.3 ± 7.3*	38.6 ± 7.6*	40.8 ± 6.8†	38.3 ± 6.7†	60.7 ± 9.2	63.4 ± 9.2
NC	42.7 ± 4.4	43.5 ± 4.3	44.8 ± 5.0	43.4 ± 3.3	50.5 ± 7.9	49.3 ± 6.2	63.3 ± 8.3	63.8 ± 9.8
CBV								
AD	5.00 ± 1.37	5.26 ± 1.02	4.78 ± 0.91	4.65 ± 0.83	3.93 ± 0.67	3.93 ± 0.82	5.39 ± 1.00	5.09 ± 1.22
NC	5.19 ± 1.24	6.11 ± 2.05	4.53 ± 0.66	4.67 ± 0.58	4.09 ± 0.43	3.81 ± 0.75	6.21 ± 1.93	5.89 ± 1.69

*Significantly different from normal control values ($p < 0.05$).
†Significantly different from normal control values ($p < 0.01$).
Units: CBF = ml/100 ml/min; CBV = ml/100 ml.
Values are expressed as mean ± 1 s.d.
AD = Alzheimer's disease group; NC = normal control group; R = right; L = left; Hip = hippocampus; LT = lateral temporal; Par = parietal; Cb = cerebellum.

TABLE 2
Relative Cerebral Blood Flow (CBF) and Cerebral Blood Volume (CBV)

	R Hip	L Hip	R LT	L LT	R Par	L Par
CBF						
AD	68.8 ± 10.6	68.3 ± 8.5	63.7 ± 9.7*	62.4 ± 9.7*	66.3 ± 9.3†	62.1 ± 8.1†
NC	67.6 ± 5.2	69.0 ± 7.0	70.9 ± 6.1	68.9 ± 6.6	79.9 ± 10.9	78.0 ± 6.9
CBV						
AD	98.3 ± 29.8	104.2 ± 25.4	95.3 ± 25.3	90.9 ± 18.0	77.1 ± 14.5	76.6 ± 15.1
NC	89.5 ± 24.6	101.3 ± 25.0	78.3 ± 17.0	80.5 ± 17.0	71.5 ± 17.0	78.0 ± 11.1

*Significantly different from normal control values ($p < 0.05$).
†Significantly different from normal control values ($p < 0.01$).
Units: CBF: %, CBV: %.
Values are expressed as mean ± 1 s.d.
AD = Alzheimer's disease group; NC = normal control group; R = right; L = left; Hip = hippocampus; LT = lateral temporal; Par = parietal.

patients or their relatives and from all volunteers. The PET procedure was approved by our institution's ethical committee. Before PET scans, all subjects received MRI for diagnosis, anatomical reference and PET positioning. Detailed MRI procedures have been reported elsewhere (*12*). Immediately before the PET examination, sagittal gradient-echo images were obtained to determine the coordinates for positioning the subject's head on the PET table.

PET Procedure

PET was performed with a PET scanner (Headtome IV, Shimadzu Corp., Kyoto, Japan), which had four rings located 13 mm apart and yielded a transverse resolution of 4.5 mm FWHM (*13*). The slice thickness was 11 mm, and the slice interval was 6.5 mm when the z-motion mode was used.

The subject's head was placed horizontally on the table of the PET scanner, and the gantry and table of the PET scanner were adjusted according to the coordinates determined with the MRI so that the scans were taken parallel to the AC-PC plane. A transmission scan was performed using a $^{68}Ga/^{68}Ge$ pin source for absorption correction after each subject was positioned. PET studies were performed under resting conditions with the subject's eyes closed and ears unplugged.

CBF was measured by the $H_2{}^{15}O$ autoradiographic method (*14*). The usual amount of the tracer was 5 ml, and the dose of radioactivity of ^{15}O-labeled water was 740-1110 MBq. The scan was started at 10–20 sec after injection when the radioactivity was detected in the brain. Each position was sequentially scanned for 5 sec and repeated nine times. The total acquisition time was 90 sec. The arterial radioactivity concentration was monitored by detecting beta-rays with a plastic scintillator. The arterial blood was withdrawn at a constant rate of 5 ml/min. The dispersion was corrected by deconvolving the beta probe curve delay with a fixed dispersion time constant of 3 sec. The beta probe curve delay in comparison with the time of appearance of the radiotracer in the brain was corrected by adjusting the initial rise in radioactivity in the blood and brain. Regional CBF was calculated by using tissue radioactivity and radioactivity of the blood input function and the model equations. The blood-to-tissue partition coefficient of water was set at 1.0 for the CBF calculation (*14,15*).

The $C^{15}O$ emission scan started 2–3 min after 1-min inhalation of 2000 MBq/200 ml $C^{15}O$. Imaging took 4 min for $C^{15}O$. Arterial blood sampling also was performed three times per each scan (at the start of the scan, at the mid-point of the scan and at 30 sec before the end of the scan) to determine the radioactivity. During the examination, head stability was monitored by a laser marker. Cerebral blood volume (CBV) was calculated by the previous method (*7*).

Data Analysis

The plane CBF and CBV images parallel to the hippocampal longitudinal axis (HP scan) were reconstructed from reconstructed sagittal CBF images. Circular regions of interest (ROIs), of 10 mm in diameter, were determined on the cortical ribbon of each region on the CBF images, and the same ROIs were transferred to CBV

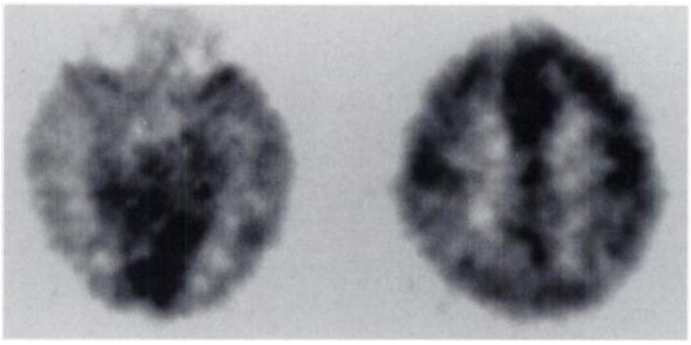

FIGURE 3. CBF images of a patient with Alzheimer's disease measured with $H_2{}^{15}O$ and PET. Patient was a 49-yr-old woman who complained of severe memory and cognitive impairment. Her MMSE score was 15. Bilateral parietal and lateral temporal blood flows were decreased, while bilateral hippocampal perfusions were preserved.

TABLE 3
Correlation Coefficients Between Test Scores and Cerebral Blood Flow in the Alzheimer's Disease Group

	Test scores	
	MMSE	ADAS
Absolute CBF		
Right hippocampus	0.152	−0.450
Left hippocampus	0.073	−0.219
Right lateral temporal	0.548*	−0.779†
Left lateral temporal	0.511*	−0.578*
Right parietal	0.585*	−0.825†
Left parietal	0.550*	−0.671†
Relative CBF		
Right hippocampus	0.037	−0.233
Left hippocampus	0.020	−0.002
Right lateral temporal	0.508*	−0.646†
Left lateral temporal	0.525*	−0.499*
Right parietal	0.509*	−0.628†
Left parietal	0.561*	−0.568*

*$p < 0.05$.
†$p < 0.01$.
CBF = cerebral blood flow, absolute and relative values; MMSE = Mini-Mental State Examination score; ADAS = Alzheimer's Disease Assessment Scale score.

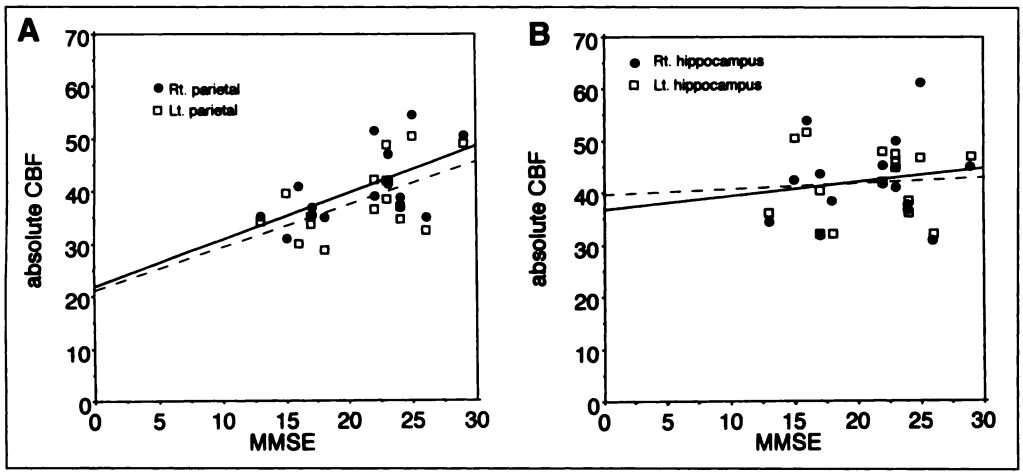

FIGURE 4. Correlation between MMSE score and absolute CBF in (A) parietal cortices and (B) hippocampus. There are good correlations between absolute CBF and MMSE scores in the (A) bilateral parietal lobes, though there are no significant correlations in the (B) bilateral hippocampus. The solid and dotted lines represent the regression lines in the right and the left regions, respectively.

images. More than two ROIs were placed on cortical regions: the ROIs for the hippocampus and lateral temporal cortices were set on the HP scan and those for the parietal lobe and the cerebellum were set on the transaxial scan (Figures. 1, 2). Regional CBF and regional CBV were expressed as absolute values (ml/100 ml/min) and relative values (%) that were calculated for the lesion-to-cerebellum ratio.

Statistical Analysis

Two-way analysis of variance (ANOVA) and posthoc Scheffé's test were performed to detect regional differences between the Alzheimer's disease and normal control groups. If there were no significant differences, we used the Student's t-test to detect each regional difference between the two groups. Pearson correlation was used to test the relationship between the regional CBF (absolute CBF and relative CBF) and cognitive function (MMSE and ADAS scores). The criterion for statistical significance was a p value <0.05.

RESULTS

Absolute and Relative CBF Value of the Two Groups

There were significant differences between the two groups both in absolute and relative CBF values ($F = 5.51$, $p = 0.027$; $F = 6.33$, $p = 0.019$). Table 1 shows the absolute value of CBF in the Alzheimer's disease group and in the normal control group. There was no significant difference in the absolute hippocampal CBF value between the two groups, though the parietal and lateral temporal absolute CBFs in the Alzheimer's disease group were significantly decreased compared with that of the normal control group. The same results were found in the relative CBF (Table 2). There was no significant difference in the hippocampal relative CBF value between the normal and the Alzheimer's disease group, though the parietal and lateral temporal relative CBF values in the Alzheimer's disease group were significantly decreased compared with those of the normal control group. The Student's t-test did not reveal significantly decreased hippocampal perfusion in the Alzheimer's disease group either in the absolute or relative CBF values.

Figure 3 shows a representative CBF image of a patient with Alzheimer's disease. The hippocampal perfusion is preserved, while parietal and lateral temporal perfusions are decreased.

In Figure 2, hippocampal CBF and CBV images of a patient with Alzheimer's disease are demonstrated. The hippocampal CBV, especially in the left side, is larger than lateral temporal CBV. In the CBF and CBV superimposed image, the distribution of the left hippocampal perfusion is overlapped with a part of the CBV distribution of the left posterior cerebral artery.

Absolute and Relative CBV Value of the Two Groups

Concerning the mean absolute and relative values of CBV, there were no significant differences in any of the regions between the Alzheimer's disease group and the normal control group (Tables 1 and 2).

Relationship Between Severity of Cognitive Disturbance and CBF Value

Table 3 shows the relationship between severity of cognitive disturbance and CBF value in the Alzheimer's disease group. There were significant correlations between the absolute/relative parietal CBF and MMSE/ADAS score (Fig. 4A). However, there was no significant correlation between the absolute/relative hippocampal CBF and MMSE/ADAS score (Fig. 4B).

DISCUSSION

The preserved hippocampal perfusion in mild-to-moderate Alzheimer's disease was observed in our study. In this study, we did not perform correction for atrophy. Quantitative assessments of the hippocampal region using MRI demonstrated hippocampal atrophy in patients with mild-to-moderate Alzheimer's disease (*7,16–18*). If there was a significant decrease in hippocampal perfusion in patients with Alzheimer's disease, the partial volume effect might be considered. However, our results demonstrated that even though partial volume effect may affect the hippocampal CBF value in patients with Alzheimer's disease, there was no significant difference in the hippocampal perfusion between the Alzheimer's disease and normal control groups. Reduced hippocampal perfusion and metabolism might be expected in Alzheimer's disease because a pathological study reported that neurofibrillary tangles accumulate preferentially in the ventromedial temporal lobe in the early stage of Alzheimer's disease and contribute to early memory impairment (*2*). Also, patients with longer duration of the disease had neurofibrillary tangles in neocortical association areas as well as in the medial temporal lobe (*2*).

There is an apparent discrepancy between our data that were obtained with PET and previously reported data that were obtained with SPECT. The SPECT studies emphasized decreased hippocampal perfusion in patients with memory disturbance including Alzheimer's disease (*3,4*). Hippocampal perfusion was reported to be a more sensitive marker than parietal hypoperfusion in diagnosing Alzheimer's disease (*3*). On the other hand, it was shown that in mild-to-moderate Alzheimer's disease, medial temporal perfusion was preserved while oxygen metabolism was decreased using PET and ^{15}O-gas steady state technique (*7*). In that study, the hippocampal perfusion in mild-to-moderate Alzheimer's disease was not decreased sig-

nificantly compared with that of normal controls, though there was a significant reduction of hippocampal volume in patients with mild-to-moderate Alzheimer's disease compared with the hippocampal volume of normal controls. This $H_2{}^{15}O$ PET study confirmed the result of preserved hippocampal perfusion in Alzheimer's disease. Moreover, our result regarding the relationship between CBF and cognitive severity is contrary to that of Ohnishi et al. (*3*). That is, in our study, parietal perfusion in Alzheimer's disease correlated well with MMSE/ADAS scores, but hippocampal perfusion did not, while in the study of Ohnishi et al. hippocampal perfusion in Alzheimer's disease correlated well with Hasegawa's dementia score, but parietal perfusion did not.

How can this paradox be explained? We consider that one of the reasons for this is the difference in spatial resolution between the SPECT and PET scanners. Because the spatial resolution of the SPECT scanner is not as good as that of PET, the SPECT image will be strongly affected by the partial volume effect, especially in the hippocampus in Alzheimer's disease, which usually has a volume loss even in the early stage. Also, an attenuation correction is not adequately done in a SPECT study, while in a PET study, attenuation correction is adequately done by the transmission scan. Because the hippocampus exists closer to the center of the field of view of the SPECT scanner than the parietal and lateral temporal cortices, the calculated data for hippocampal CBF would be affected more strongly than the data calculated for the parietal and lateral temporal CBF. Another reason could be that the SPECT tracer HMPAO may not reflect correctly the regional CBF, especially in the hippocampus. Although there are many reports (*19–21*) that HMPAO reflects CBF, these reports did not refer to the hippocampal regions, which occupy a small part of the cerebral hemisphere. Reduced accumulations of HMPAO in the hippocampus of Alzheimer's disease may be more closely related to reduced metabolic distribution than to perfusional distribution. Fortunately, our results do not question the clinical utility of HMPAO SPECT. Because the hippocampal "hypoaccumulation" of HMPAO in patients with memory impairment reflects hippocampal atrophy and may reflect metabolic reduction, HMPAO SPECT will continue to play a great role in the clinical diagnosis of Alzheimer's disease.

Some problems also exist in PET CBF images. The presence of atrophy would result in different effective partition coefficients (*22,23*), especially in the regions of Alzheimer's disease. However, this effect due to atrophy occurs not only in the hippocampus but also in the lateral temporal and parietal cortices in the Alzheimer's patients group. The partition coefficients problem would not be attributed to the regional difference in CBFs in these atrophied areas. Koeppe et al. (*24*) proposed a significant overestimation of CBF due to contaminating arterial blood volume signal. In this study, we measured CBF using a one-compartment model (*14*). Ohta et al. (*25*) reported an overestimation in CBF using $H_2{}^{15}O$ PET with a one-compartment model. They showed artifactually high blood rates in the circle of Willis in the basal cisterna, middle cerebral arteries in the Sylvian stem and posterior cerebral arteries in the ambient cisternae. There may be an overestimation of hippocampal perfusion in our study because the hippocampus is very close to the posterior cerebral artery. Our data demonstrated that hippocampal CBV tended to be larger than lateral temporal and parietal CBV in both groups, though there was no statistically significant difference in the hippocampal CBV between the two groups. If pure hippocampal CBF reduction may exceed lateral temporal and parietal CBF reduction, in spite of the complication of CBF overestimation due to contaminating arterial blood volume, there should be a significant hippocampal CBF difference between the two groups. However, in our study there was no significant hippocampal CBF difference between the two groups.

Pathophysiology of the preserved hippocampal perfusion in mild-to-moderate Alzheimer's disease should be further investigated. One possible explanation for the preserved hippocampal perfusion is that this may be attributed to a relative luxury perfusion state, which means that metabolism is affected while perfusion is still preserved in the hippocampus of mild-to-moderate Alzheimer's disease.

CONCLUSION

In Alzheimer's disease, the hippocampus would be expected to be severely affected. However, in mild-to-moderate Alzheimer's disease, hippocampal perfusion was preserved even though the parietal and lateral temporal perfusions were significantly decreased.

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Cerebral Perfusion Scanning in Treating AIDS Dementia: A Pilot Study

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Acquired immunodeficiency syndrome (AIDS) dementia complex (ADC) is a common effect of the AIDS virus. We studied the regional cerebral blood flow of patients with early ADC and its response to atevirdine mesylate. **Methods:** Ten men with early ADC, who had failed or were intolerant to zidovudine or didanosine therapy, were treated with atevirdine mesylate for 12 wk. Cerebral perfusion SPECT using ^{99m}Tc-HMPAO was performed at Week 0 and Week 12. SPECT images were analyzed qualitatively and semiquantitatively. **Results:** The cerebral perfusion abnormalities in early ADC were usually mild and characteristically involved the cortices and periventricular regions bilaterally and symmetrically. Four patients were able to complete the protocol. Three of these patients responded to atevirdine clinically, two of whom showed improvement in their Week 12 SPECT images. The other responder had an essentially unchanged image. The patient who did not respond to atevirdine showed a definite deterioration in cerebral perfusion. **Conclusion:** Cerebral perfusion SPECT is useful in detecting and assessing therapeutic responses in ADC. The preliminary results of atevirdine in treating ADC are promising and need further investigation.

Key Words: AIDS; dementia; technetium-99m-HMPAO; atevirdine
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Acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus Type 1 (HIV-1). The development of opportunistic infections, neoplasms and a progressive subcortical dementing illness, termed AIDS dementia complex (ADC) is a common effect (*1*). ADC covers three spheres of abnormality: cognitive, motor and behavioral. The cognitive features of reduced concentration, forgetfulness and slowing of intellectual processing are almost always associated with motor dysfunction ranging from slowing of fine finger movements and abnormal eye movements (inaccurate pursuit and saccades) to limb ataxia and leg weakness with, at times, bladder and bowel incontinence. Behavioral features are less common in the early phases of ADC but, as it advances, progressive apathy and social withdrawal become prominent. In the terminal stages of the disease, patients are globally demented with paraparesis and virtual mutism (*2*).

Approximately 20% of patients with AIDS have ADC to some degree, with the prevalence of ADC increasing with advancing immunodeficiency. The neuropathological features of ADC can be divided into three subsets: gliosis and white matter pallor, multinucleated-cell encephalitis and vacuolar change of spinal cord or brain. Many of these pathological abnormalities are found in the basal ganglia (*3*). Gliosis and pallor are characteristic of those patients with mild ADC, but can be found also in patients without dementia, presumably representing subclinical disease. Multinucleated-cell encephalitis is the hallmark of productive HIV-1 infection in the brain. Such changes are found characteristically in patients with moderate or severe ADC. Vacuolar change is a rare finding, the clinical correlate of which still has to be adequately defined. It is similar to the vacuolar change that may occur in the spinal cord and which has been termed "vacuolar myelopathy" (*4*). Neuronal loss is both rare and minor suggesting that ADC may be reversible.

There is reasonable evidence for the efficacy of the antiretroviral drug zidovudine (AZT) in ADC (*5–8*). However, not all patients tolerate AZT because of its myelotoxicity (*9*). Indeed, there is an association of greater toxicity with advancing stages of HIV-1 infection. In addition, some patients fail to respond to AZT or deteriorate after a period of improvement. There are conflicting data on the efficacy of didanosine (DDI) in ADC (*10,11*), but DDI also has been associated with toxicity (predominantly painful peripheral neuropathy and pancreatitis) (*12*). Consequently, patients who develop ADC while receiving AZT or in the context of intolerance to AZT have little in the way of therapy that can be offered to them.

Atevirdine mesylate, an arylpiperazine non-nucleoside reverse transcriptase inhibitor, has been shown to be effective against HIV-1 infection with studies showing equipotency to AZT (*13*). Moreover, the drug has significant central nervous system penetration (*14*) and has exhibited synergy with AZT as well as activity against AZT resistant viral strains in vitro. Furthermore, it has been shown to have lower toxicity than nucleoside analogs (*13*). As a consequence, atevirdine may be effective in the treatment of ADC.

When a variety of therapeutic choices exists for patients with ADC, a predictable and early test that also indicates the brain's response to therapy would be invaluable. Cerebral perfusion tomography (SPECT) has been shown to be frequently abnormal in patients with HIV infection even before detectable

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