Annals of Nuclear Medicine Vol. 21, No. 2, 109–113, 2007

Crossed cerebellar diaschisis: a positron emission tomography study with L-[methyl-^{11}C]methionine and 2-deoxy-2-[^{18}F]fluoro-D-glucose

Katsufumi KAJIMOTO,* Naohiko OKU,* Yasuyuki KIMURA,* Hiroki KATO,* Makiko RAI TANAKA,* Yasukazu KANAI,* Kazuo KITAGAWA,** Motohiko MARUNO,*** Toshiki YOSHIMINE,*** Masatsugu HORI** and Jun HATAZAWA*

*Department of Nuclear Medicine and Tracer Kinetics, Osaka University Graduate School of Medicine
**Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine
***Department of Neurosurgery, Osaka University Graduate School of Medicine

Objective: Crossed cerebellar diaschisis (CCD) is defined as a depression of blood flow and oxidative metabolism of glucose in the cerebellum contralateral to a supratentorial brain lesion, as detected with positron emission tomography (PET) and single photon emission computed tomography. We examined whether L-[methyl-^{11}C]methionine (MET) uptake is affected in CCD. ***Methods:*** In 12 patients with a unilateral supratentorial brain tumor, we evaluated the uptake of 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) and MET in the cerebellar hemispheres by means of PET. Asymmetry index (AI) was defined as a difference in the average count between the ipsilateral and contralateral cerebellar hemispheres divided by the average count in both cerebellar hemispheres. Patients with AI of FDG PET more than 0.1 and those with AI equal to 0.1 or less than 0.1 were classified as CCD-positive and CCD-negative, respectively. ***Results:*** Six patients were CCD-positive and others were CCD-negative in the FDG PET study. Between CCD-positive and CCD-negative patients, mean AI of MET was not significantly different (0.017 ± 0.023 and 0.014 ± 0.039, respectively). ***Conclusions:*** Different from glucose metabolism, cerebellar MET uptake was not affected in CCD. The present study may indicate that cerebellar MET uptake is independent of suppression of cerebellar neuronal activity.

Key words: crossed cerebellar diaschisis, 2-deoxy-2-[^{18}F]fluoro-D-glucose, L-[methyl-^{11}C]methionine, positron emission tomography

INTRODUCTION

POSITRON EMISSION TOMOGRAPHY (PET) studies have shown a depression of brain energy metabolism and blood flow in the cerebellar hemisphere contralateral to the side of supratentorial lesions.[1] This phenomenon, defined as crossed cerebellar diaschisis (CCD), has often been observed in patients with stroke,[1] supratentorial brain tumors,[2] head injury,[3] and epilepsy[4] as a result of interruption of the cortico-ponto-cerebellar pathway. A recent experimental study demonstrated that CCD is associated with a pronounced decrease in the Purkinje cell spiking activity.[5] Although the hemodynamics, energy metabolisms, and their relationships in CCD have been extensively studied,[6,7] little is known about the amino acid uptake in CCD.

L-[Methyl-^{11}C]methionine (MET) has been used as a tracer for PET studies of amino acid metabolism.[8] The administered MET is transported through the blood-brain barrier via the neutral amino acid transport system. In the brain, MET is transformed to methionyl-tRNA, which is a precursor for protein synthesis. The MET is also transformed to *S*-adenosyl-L-methionine, a major methyl donor for many biochemical reactions. The labeling of $-^{11}CH_3$ is transferred to various methyl acceptors. The relative rate of methionine flux into the transmethylation

Received September 28, 2006, revision accepted December 4, 2006.

For reprint contact: Jun Hatazawa, M.D., Ph.D., Department of Nuclear Medicine and Tracer Kinetics, Osaka University Graduate School of Medicine, D9, 2–2 Yamadaoka, Suita, Osaka 565–0871, JAPAN.

E-mail: hatazawa@tracer.med.osaka-u.ac.jp

Table 1 Clinical data of patients

Patient	Age, years/ Sex	Location of Tumor	Diagnosis	Asymmetry Index in FDG PET	Asymmetry Index in MET PET	Interval between FDG PET and MET PET, days
1	34/M	Lt frontal	Glioblastoma	0.164	0.007	1*
2	63/M	Rt frontoparietal	Glioblastoma	0.113	0.040	3
3	64/M	Rt temporoparietal	Glioblastoma	0.289	0.042	3*
4	67/M	Rt frontal	Glioblastoma	0.140	–0.021	16*
5	75/M	Rt temporoparietal	Glioblastoma	0.113	0.011	1*
6	46/F	Lt frontal	Glioblastoma	0.235	0.021	9
7	42/M	Lt frontoparietal	Glioblastoma	0.079	0.022	17*
8	55/M	Lt temporal	Glioblastoma	0.034	0.041	3*
9	63/M	Lt occipital	Glioblastoma	0.062	–0.035	4
10	69/M	Rt frontoparietal	Glioblastoma	0.068	–0.034	4
11	33/F	Rt temporal	Oligodendroglioma	0.076	0.055	4
12	46/F	Rt parietal	Glioblastoma	0.023	0.038	22*

*: FDG PET is followed by MET PET

cycle is estimated to be 10% of the rate of methionine incorporation into brain proteins, so that the MET is mainly directed towards protein synthesis.[9]

In the present study, we studied the uptake of MET and 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) in CCD in patients with brain tumors by means of PET, in order to clarify whether MET uptake is affected by neuronal deactivation in CCD.

MATERIALS AND METHODS

Subjects

Among the consecutive patients with brain tumors who underwent both FDG and MET PET between September 2004 and August 2005, we selected 12 patients who met the following criteria: (1) had a unilateral supratentorial brain tumor confirmed on MRI; (2) had no structural abnormality in the cerebellum or brain stem on MRI; (3) normal angiographic findings in the vertebrobasilar system, as determined by the use of either conventional or MR angiography. The patients ranged in age from 33 to 75 years (56.6 ± 14.3 years, mean ± 1SD) and consisted of 3 females and 9 males. All patients underwent the FDG and MET PET at an interval ranging from 1 to 22 days (7.3 ± 7.1 days); there were no symptomatic changes in any of the patients during this interval period. The patients were receiving no specific treatments that could potentially have affected the brain metabolism during this interval. The Ethics Committee of the Osaka University Hospital approved of the present study, and informed consent was obtained from all of the patients after providing them with a detailed explanation of the purpose of the study and the scanning procedure.

PET protocol

The PET scans were performed using a Headtome V PET scanner (Shimadzu, Kyoto, Japan) with retractable septa. All studies were performed in the stationary mode with septa in, which allowed acquisition of 63 contiguous transverse slices with a spatial resolution of 3.7 mm full-width at half-maximum (FWHM) in the transaxial direction and 5 mm in the axial direction. The patient's head was fixed in place with a head holder and was positioned with light beams to obtain transaxial slices parallel to the orbitomeatal line. The patients were required to fast for at least 6 hours before the PET scanning, and images were acquired with the patient resting in the supine position, with their eyes closed. Corrections for absorption were performed with attenuation measured in a transmission scan using a retractable rotating rod source. FDG and MET were administered intravenously at the dose of 370 MBq and 555–740 MBq, respectively. Regional emission images of the brain were obtained for 10 min, beginning 40 min after the FDG injection and 20 min after the MET injection. Scan data were reconstructed with an ordered-subset expectation maximization algorithm (12 iterations with 4 ordered subsets).

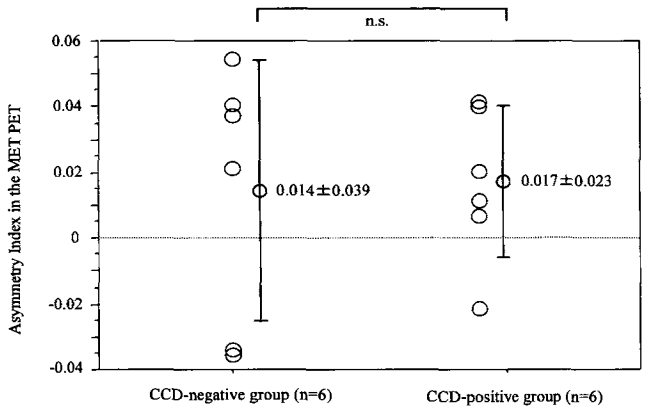

Fig. 1 Comparison of the asymmetry index in the MET PET between CCD-negative and CCD-positive groups. The mean asymmetry index in the CCD-positive group was 0.017 ± 0.023, which was not significantly different from that in the CCD-negative group (0.014 ± 0.039).

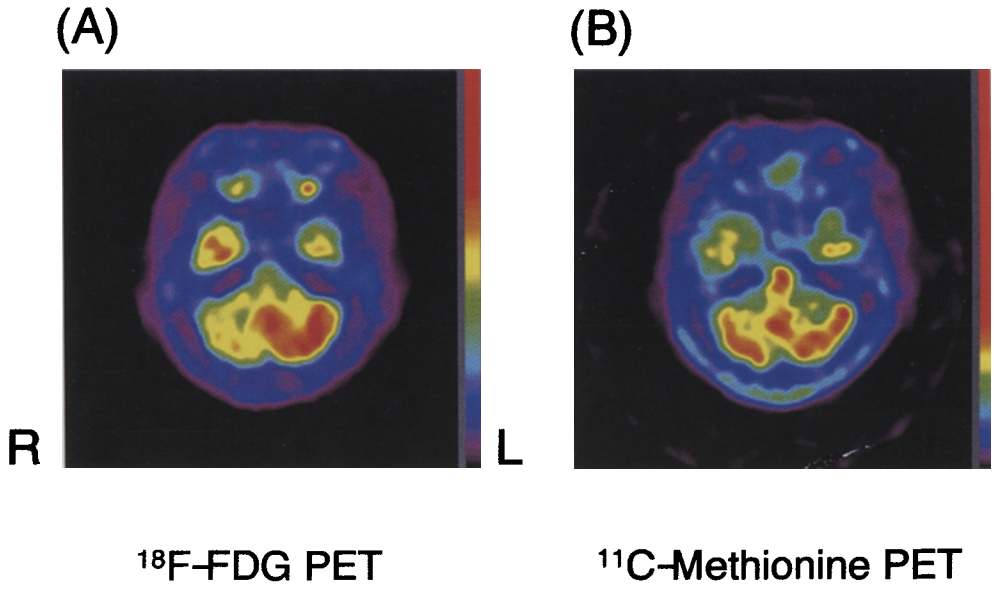

Fig. 2 The FDG and MET images in a CCD-positive patient with brain tumor located in the left frontal lobe. (A) The FDG PET image shows a significant decrease in the FDG uptake in the right cerebellar hemisphere as compared with that in the left cerebellar hemisphere. The asymmetry index was 0.235. (B) The MET PET image shows little decrease in the MET uptake in the right cerebellar hemisphere as compared with that in the left cerebellar hemisphere. The asymmetry index was 0.021.

Data analysis

We analyzed the tomographic images corresponding to the level of the cerebellum. We selected the slice that most satisfactorily depicted the cerebellar hemisphere for the analysis. First, in the FDG PET images, we placed symmetrically 2 circular regions of interest (ROIs), 32 mm in diameter each, over the cerebellar hemispheres. These ROIs were then copied on to the MET PET images. The mean counts for each cerebellar hemisphere were then obtained. From the mean counts, we calculated the asymmetry index for the cerebellum according to the following formula: an asymmetry index (AI) = (the mean cerebellar count in the ipsilateral hemisphere minus the mean cerebellar count in the contralateral hemisphere)/(the average count in both cerebellar hemispheres). In the FDG PET analysis, patients with AI of higher than 0.1 were defined as a CCD-positive group, and those with AI equal to or less than 0.1 were defined as a CCD-negative group.[10–13] The individuals conducting the cerebellar analysis were blinded to the findings on the supuratentorial images and clinical details of the patients.

Statistical analysis

The mean AIs in the MET PET were compared between the CCD-positive and CCD-negative groups. The statistical significance of the results was analyzed using an unpaired Student's *t* test. A p value of less than 0.05 was considered to be significant. Data were analyzed using Stat View version 5.0 (SAS Institute Inc).

RESULTS

The pathological diagnosis and location of brain tumor, cerebellar asymmetry indices for FDG and MET, and time interval between FDG and MET study are summarized in Table 1.

Of the 12 patients with unilateral supratentorial brain tumor, six were classified as CCD-positive (mean AI ± 1SD = 0.176 ± 0.072) and the remaining 6 as CCD-negative group (0.057 ± 0.023) in the FDG PET. Figure 1 shows the comparison of the AI in the MET PET between the CCD-negative and CCD-positive groups. The mean AI in the MET PET was 0.017 ± 0.023 in the CCD-positive group and 0.014 ± 0.039 in the CCD-negative group, the difference not being statistically significant. Figure 2 shows the FDG and MET PET images from one patient with CCD.

DISCUSSION

The present study demonstrated the absence of decrease in MET uptake in CCD in supratentorial brain tumor patients. The results may indicate that the MET uptake is not affected by a suppression of neuronal activity in the cerebellum.

Local glucose consumption in the central nervous system is tightly coupled with the frequency of electrical stimuli[14,15] and the magnitude of physiological stimuli.[16] Recently, a 50% decrease in Purkinje cell spiking activity in association with CCD was demonstrated in rats with

focal neocortical ischemia.[5] Therefore, the decreased FDG uptake in the present CCD-positive patients suggests a decrease in the excitatory input to the cerebellar hemisphere contralateral to the side of supratentorial brain tumors.

Several experimental studies have addressed the relationship between neuronal activity and brain uptake of amino acids. Previous experimental studies indicated that neurons synthesize proteins at a higher rate than do glial cells.[17] Therefore, MET uptake may reflect neuronal rather than glial activity. Kennedy et al. studied the brain ^{11}C-leucine uptake after monocular deprivation in the monkey at 2 and 25 days of age.[18] In chronic monocular deprivation experiments from 2 to 25 days, the laminae of the lateral geniculate bodies innervated by the occluded eye showed a local decrease in the ^{11}C-leucine uptake. However, no other parts of the visual system showed any evidence of local changes in the pattern. Acute monocular deprivation for 3 hours did not alter the ^{11}C-leucine uptake even in the laminae of the lateral geniculate bodies. They speculated that the rate of amino acid uptake, unlike glucose utilization, does not reflect the level of functional activity. The present observation of the absence of any significant changes in the MET uptake in patients with CCD was consistent with their speculation.

In diseased brains, a decrease in cerebral glucose metabolism is often observed in PET studies. However, it is difficult to distinguish between hypometabolism due to neuronal deactivation and that due to neuronal loss. Lajtha et al. proposed that neuronal loss could be evaluated by determining the local rate of protein synthesis using MET PET.[19] When cerebral glucose utilization is reduced in certain pathologic conditions, MET PET may be useful for discriminating between functional deactivation (normal MET and decreased FDG) and neuronal loss (decreased MET and FDG). Salmon et al. demonstrated a decrease in the temporoparietal glucose metabolism in Alzheimer's disease patients in spite of normal MET uptake,[20] indicating that glucose hypometabolism may precede neuronal loss in the early stage of Alzheimer's disease. Nakagawa et al. reported normal or even higher uptake of the MET associated with decreased FDG uptake in the brain areas adjacent to those affected by cerebral infarction or hematoma,[21] indicating that cerebrovascular lesions may induce neuronal deactivation in the surrounding brain. Normal MET uptake associated with decreased FDG found in the CCD may be another example of structurally normal but functionally depressed state in the brain.

In conclusion, the MET uptake is not decreased in CCD. Cerebellar MET uptake may be independent of suppression of cerebellar neuronal activity. The MET PET combined with FDG PET may reveal whether brain hypometabolism of glucose is due to functional suppression or neuronal loss in pathological states.

REFERENCES

1. Baron JC, Bousser MG, Comar D, Castaigne P. "Crossed cerebellar diaschisis" in human supratentorial brain infarction. *Trans Am Neurol Assoc* 1980; 105: 459–461.
2. Patronas NJ, Di Chiro G, Smith BH, De La Paz R, Brooks RA, Milam HL, et al. Depressed cerebellar glucose metabolism in supratentorial tumors. *Brain Res* 1984; 291: 93–101.
3. Alavi A, Mirot A, Newberg A, Alves W, Gosfield T, Berlin J, et al. Fluorine-18-FDG evaluation of crossed cerebellar diaschisis in head injury. *J Nucl Med* 1997; 38: 1717–1720.
4. Stubgen JP. Crossed cerebellar diaschisis related to recurrent focal seizures. *Epilepsia* 1995; 36: 316–318.
5. Gold L, Lauritzen M. Neuronal deactivation explains decreased cerebellar blood flow in response to focal cerebral ischemia or suppressed neocortical function. *Proc Natl Acad Sci USA* 2002; 99: 7699–7704.
6. Yamauchi H, Fukuyama H, Kimura J. Hemodynamic and metabolic changes in crossed cerebellar hypoperfusion. *Stroke* 1992; 23: 855–860.
7. Ito H, Kanno I, Shimosegawa E, Tamura H, Okane K, Hatazawa J. Hemodynamic changes during neural deactivation in human brain: a positron emission tomography study of crossed cerebellar diaschisis. *Ann Nucl Med* 2002; 16: 249–254.
8. Comar D, Cartron JC, Maziere M, Marazano C. Labelling and metabolism of methionine-methyl-^{11}C. *Eur J Nucl Med* 1976; 1: 11–14.
9. Grange E, Gharib A, Lepetit P, Guillard J, Sarda N, Bobilliier P. Brain protein synthesis in the conscious rat using L-[^{35}S]methionine relationship of methionine specific activity between plasma and precursor compartment and evaluation of methionine metabolic pathways. *J Neurochem* 1992; 59: 1437–1443.
10. Shamoto H, Chugani HT. Glucose metabolism in the human cerebellum: an analysis of crossed cerebellar diaschisis in children with unilateral cerebral injury. *J Child Neurol* 1997; 12: 407–414.
11. Meneghetti G, Vorstrup S, Mickey B, Lindewald H, Lassen NA. Crossed cerebellar diaschisis in ischemic stroke: a study of regional cerebral blood flow by ^{133}Xe inhalation and single photon emission computerized tomography. *J Cereb Blood Flow Metab* 1984; 4: 235–240.
12. Niimura K, Chugani DC, Muzik O, Chugani HT. Cerebellar reorganization following cortical injury in humans: effects of lesion size and age. *Neurology* 1999; 52: 792–797.
13. Kim SE, Choi CW, Chung JK, Roth JH, Lee MC, Koh CS. Crossed cerebellar diaschisis in cerebral infarction: technetium-99m-HMPAO SPECT and MRI. *J Nucl Med* 1997; 38: 14–19.
14. Sokoloff L. Relation between physiological function and energy metabolism in the central nervous system. *J Neurochem* 1977; 29: 13–26.
15. Yarowsky P, Kadekaro M, Sokoloff L. Frequency-dependent activation of glucose utilization in the superior cervical sympathetic trunk. *Proc Natl Acad Sci USA* 1983; 80: 4179–4183.
16. Kennedy C, Miyaoka M, Suda S, Macko K, Jarvis C, Mishkin M, et al. Local metabolic responses in brain accompanying motor activity. *Trans Am Neurol Assoc* 1980; 105: 13–17.

17. Shahbazian FM, Jacobs M, Lajtha A. Regional and cellular differences in rat brain protein synthesis *in vivo* and in slices during development. *Int J Devel Neurosci* 1986; 4: 209–215.
18. Kennedy C, Suda S, Smith CB, Miyaoka M, Ito M, Sokoloff L. Changes in protein synthesis underlying functional plasticity in immature monkey visual system. *Proc Natl Acad Sci USA* 1981; 78: 3950–3953.
19. Lajtha A, Dunlop D, Banay-Schwarts M. Cerebral protein turnover: aspects and problems. In *PET studies on amino acid Metabolism and protein synthesis* (Mazoyer BM, Heiss WD, Comar D, eds), Dordrecht Kluwer Academic Publishers, 1993: 1–17.
20. Salmon E, Gregorire MC, Delfiore G, Lemaire C, Degueldre C, Frank G, et al. Combined study of cerebral glucose metabolism and [^{11}C]methionine accumulation in probable Alzheimer's disease using positron emission tomography. *J Cereb Blood Flow Metab* 1996; 16: 399–408.
21. Nakagawa M, Kuwabara Y, Sasaki M, Koga H, Chen T, Kaneko K, et al. ^{11}C-methionine uptake in cerebrovacular disease: A comparison with ^{18}F-FDG PET and ^{99m}Tc-HMPAO SPECT. *Ann Nucl Med* 2002; 16: 207–211.