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^{11}C-methionine uptake in cerebrovascular disease: A comparison with ^{18}F-FDG PET and ^{99m}Tc-HMPAO SPECT

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Objectives: Carbon-11-L-methyl-methionine (^{11}C-methionine) has been reported to be useful for evaluating brain tumors, but several other brain disorders have also shown signs of high methionine uptake. We retrospectively evaluated the significance of ^{11}C-methionine uptake in cerebrovascular diseases, and also compared our results with those for ^{18}F-FDG PET and ^{99m}Tc-HMPAO SPECT. ***Methods:*** Seven patients, including 3 patients with a cerebral hematoma and 4 patients with a cerebral infarction, were examined. All 7 patients underwent both ^{11}C-methionine PET and ^{99m}Tc-HMPAO SPECT, and 6 of them underwent ^{18}F-FDG PET. ***Results:*** A high ^{11}C-methionine uptake was observed in all 3 patients with cerebral hematoma. Increased ^{99m}Tc-HMPAO uptake was observed in 2 out of 3 patients, and all 3 patients had decreased ^{18}F-FDG uptake. Of 4 patients with a cerebral infarction, high ^{11}C-methionine uptake was observed in 3. Increased ^{99m}Tc-HMPAO uptake was also observed in one patient, whereas 3 patients had decreased ^{18}F-FDG uptake. ***Conclusions:*** We should keep in mind that high ^{11}C-methionine uptake is frequently observed in cerebrovascular diseases. CVD should therefore be included in the differential diagnosis when encounting patients with a high ^{11}C-methionine uptake.

Key words: ^{11}C-methionine, PET, cerebrovascular disease, ^{18}F-FDG, ^{99m}Tc-HMPAO

INTRODUCTION

POSITRON EMISSION TOMOGRAPHY (PET) with C-11-L-methyl-methionine (^{11}C-methionine) has been reported to be useful for evaluating brain tumors.[1–5] ^{11}C-methionine uptake was correlated with the histological grade[1] and useful for assessing tumor extent,[2] but high ^{11}C-methionine uptake has also been reported in some non-tumoral lesions, such as cerebrovascular disease (CVD),[6–9] brain abscesses[10,11] or radiation necrosis.[12] In this study we evaluated the significance of the ^{11}C-methionine uptake in CVD, while also comparing the findings with those of ^{18}F-FDG PET and ^{99m}Tc-hexamethyl-propylene amine oxime (^{99m}Tc-HMPAO) single photon emission computed tomography (SPECT) to investigate the uptake mechanisms of ^{11}C-methionine.

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MATERIALS AND METHODS

Patients

Between August 1993 and September 1997, ^{11}C-methionine PET studies were performed on 141 patients suspected of having underlying brain tumors by either CT or MRI. Seven patients were finally diagnosed to have CVD (Table 1) including cerebral hematoma (n = 3) and cerebral infarction (n = 4), including 4 males and 3 females, ranging in age from 15 to 68 yrs, with a mean age of 45 yrs. The diagnosis was made based on the clinical course in 6 out of 7 patients, and was confirmed by surgery in one patient (patient 1). A medullary venous malformation existed as an underlying disease in patient 6. ^{11}C-methionine PET was performed in the subacute phase (14 to 24 days after the last attack) in 4 patients, and in the chronic phase (34 days or more after the last attack)

Table 1 Patient data

Patient No.	Age (yr)	Sex	Location	Size (cm)	Days after stroke	CE on CT/ MRI	MET			FDG		HMPAO
							Visual	L/N ratio	Pattern	Visual	L/N ratio	Visual
Cerebral hematoma												
1	68	F	R temporal cortex	5.2 × 3.5	17	–	++	1.17	peripheral	–	0.63	–
2	15	F	L frontal cortex	1.2 × 1.0	34	+	++	1.10	peripheral	–	0.82	+
3	24	M	R temporal cortex	2.3 × 1.9	>38	–	++	1.10	peripheral	–	0.52	+
Cerebral infarction												
4	34	M	R frontal cortex	6.5 × 3.5	14	+	++	1.31	core	–	0.75	+
5	47	M	R temporal cortex	4.5 × 3.8	20	+	++	1.22	peripheral	n.d.	n.d.	–
6	67	F	R parietal white matter	4.7 × 3.4	24	+	–	0.67	–	–	0.57	–
7	60	M	L parietal white matter	6.2 × 3.8	38	+	++	1.07	core	–	0.68	–

CE = Contrast enhancement; MET = ^{11}C-Methionine, FDG = ^{18}F-FDG, HMPAO = ^{99m}Tc-HMPAO; n.d. = not done

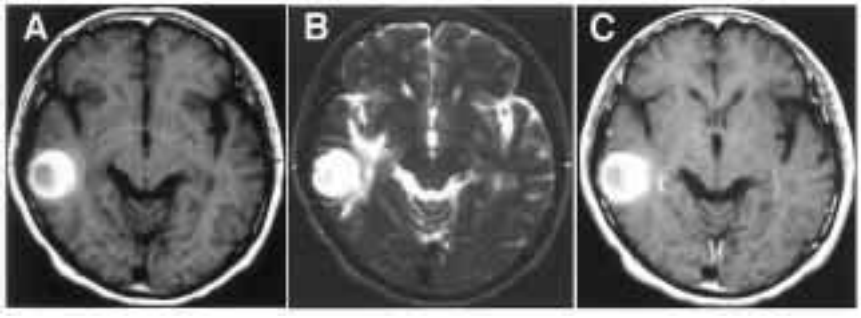

Fig. 1 Patient 1: A 68-year-old female with cerebral hematoma. Noncontrast T1- (A) and T2- (B) weighted MR images show a hyperintense hematoma in the right temporal lobe. A contrast enhanced T1-weighted image (C) shows no enhancement around the hematoma.

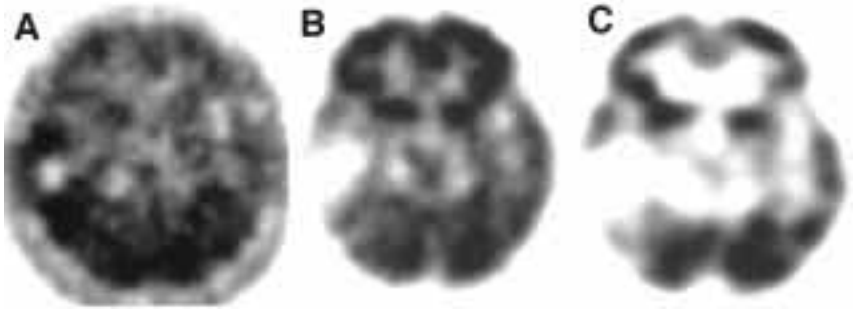

Fig. 2 Patient 1: ^{11}C-methionine PET (A) shows an increased accumulation of ^{11}C-methionine in the periphery of the hematoma. ^{18}F-FDG PET (B) shows a decreased accumulation of ^{18}F-FDG. ^{99m}Tc-HMPAO SPECT (C) shows a decreased accumulation of ^{99m}Tc-HMPAO.

in 3 patients. ^{18}F-FDG PET was performed in 6 patients and, ^{99m}Tc-HMPAO SPECT in all 7 patients. All studies were performed within a week.

Methods

All PET studies were performed with HEADTOME-III (Shimadzu Corp., Kyoto, Japan) with a spatial resolution of 8.2 mm in FWHM (full width at half maximum). Five slices, each 15 mm apart, were obtained. For ^{11}C-methionine PET, a dose of 519–755 MBq of ^{11}C-methionine was injected intravenously into the cubital vein. Emission scans were begun 14 min after the injection and data were obtained for 16 min. For the ^{18}F-FDG PET scan, a 16 min emission scan was started 20 min after the injection of 237–355 MBq of ^{18}F-FDG. In the ^{99m}Tc-HMPAO SPECT study, data were collected for 15 min, beginning 5 min after the administration of 740 MBq of ^{99m}Tc-HMPAO, by means of GCA9300A/HG (Toshiba Corp., Tokyo, Japan) with a fanbeam collimator (64 × 64 matrix). The spatial resolution was 7.4 mm in FWHM.

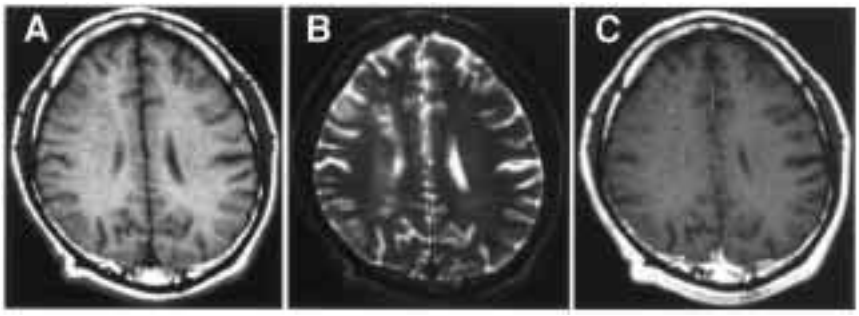

Fig. 3 Patient 2: A 34-year-old male with a cerebral infarction. A noncontrast T1-weighted MR image (A) shows a hypointense infarction and T2-weighted image (B) shows a hyperintense infarction with surrounding edema in the right frontal lobe. A contrast enhanced T1-weighted image (C) shows a spotty enhancement in the infarction after Gd-DTPA injection.

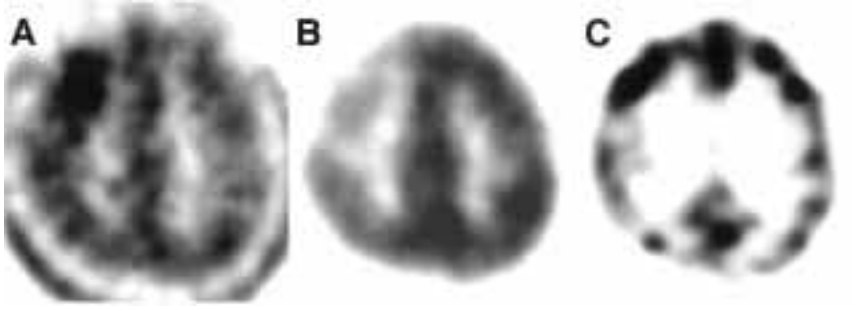

Fig. 4 Patient 2: ^{11}C-methionine PET (A) shows an increased accumulation of ^{11}C-methionine in the peripheral of hematoma. ^{18}F-FDG PET (B) shows a decreased accumulation of ^{18}F-FDG. ^{99m}Tc-HMPAO SPECT (C) shows an increased accumulation of ^{99m}Tc-HMPAO.

The PET and SPECT images were analyzed by both a visual inspection and a semiquantitative evaluation of the tracer uptake in the regions of interest. The degree of tracer uptake was visually classified into the following three groups: negative (–), clearly lower; positive (+), almost equal; intensely positive (++), clearly higher, in comparison to that observed in the gray matter contralateral to the lesion without any pathological abnormalities on MRI or CT. The tracer uptake was semiquantitatively evaluated by the lesion-to-normal ratio (L/N) which was the ratio of the average counts in the lesion to those in the contralateral normal region. We defined the regions of interest (ROIs, 15×15 mm) in the lesions, where ^{11}C-methionine showed the highest uptake on the PET images, and took the contralateral gray matter as a reference.

This study was approved by the Committee for the Clinical Application of Cyclotron Producing Radionucleoides in Kyushu University Hospital and informed consent was obtained from all patients before starting the PET study.

RESULTS

On visual inspection, high ^{11}C-methionine uptake was observed in all three patients with cerebral hematoma. ^{11}C-methionine PET showed increased uptake in the periphery of the hematoma in all cases. Mean ^{11}C-methionine uptake in the periphery of the hematoma was 1.12 ± 0.04 regarding the L/N ratio (range 1.10–1.17). On the other hand, ^{18}F-FDG PET showed decreased uptake in all 3 patients with cerebral hematoma. The ^{18}F-FDG uptake in hematoma was a 0.66 ± 0.15 L/N ratio (range 0.52–0.82). High ^{99m}Tc-HMPAO uptake was observed in 2 of 3 patients and was also seen in the periphery of the hematoma.

In 3 out of 4 patients with a cerebral infarction, high ^{11}C-methionine uptake was observed in the lesions. No accumulation of ^{11}C-methionine was observed in patient 6, whose lesion was observed only in the white matter. The mean ^{11}C-methionine uptake was a 1.07 ± 0.28 L/N ratio (range 0.67–1.31). In addition, 2 out of 4 patients had increased uptake of ^{11}C-methionine in the center of the area of infarction. ^{11}C-methionine PET showed an increased ^{11}C-methionine uptake in the periphery of the area of infarction in only 1 patient with a cerebral infarction. In patients 4, 6 and 7 the infarction was visualized as an area with low ^{18}F-FDG uptake. The ^{18}F-FDG uptake was a 0.67 ± 0.09 L/N ratio (range 0.57–0.75). ^{99m}Tc-HMPAO uptake decreased in three cases, but increased in one case (patient 4) who was in the infarct subacute phase.

Case Reports:

Patient 1. A 68-year-old female complained of headache 12 days prior to admission. A neurological examination showed dementia. MRI revealed a hyperintensity area on the T1- (Fig. 1A) and T2-weighted images (Fig. 1B) in the right temporal lobe without any Gd-DTPA enhancement (Fig. 1C). A PET scan revealed increased uptake of ^{11}C-methionine (Fig. 2A) in the periphery of the lesion and decreased uptake of ^{18}F-FDG (Fig. 2B). ^{99m}Tc-HMPAO SPECT (Fig. 2C) showed decreased uptake. The patient was finally diagnosed with a cerebral hematoma.

Patient 4. A 34-year-old male complained of headache and left hemiparesis. MRI showed a low-intensity signal on the T1-weighted image (Fig. 3A) and a high-intensity signal on the T2-weighted image (Fig. 3B) in the right frontal lobe. A contrast enhanced T1-weighted image (Fig. 3C) showed spotty enhancement. ^{11}C-methionine PET (Fig. 4A) showed increased uptake in the lesion, whereas ^{18}F-FDG PET (Fig. 4B) showed decreased uptake. ^{99m}Tc-HMPAO SPECT (Fig. 4C) showed increased uptake. The patient was diagnosed with a subacute phase cerebral infarction. The uncoupling of the glucose metabolism and perfusion indicates the occurrence of so-called "luxury perfusion."

DISCUSSION

In this study, high ^{11}C-methionine uptake was observed in patients with both cerebral hematoma and cerebral infarction in either the subacute or chronic stage, and it was more frequently observed in patients with cerebral hematoma than in those with cerebral infarction. In cerebral hematoma cases, high ^{11}C-methionine uptake was reported in all 3 patients by Dethy et al.[6] and in 3 out of 4 patients by Ogawa et al.[7] In cerebral infarction cases, it was also reported in 4 out of 12 patients by Jacobs[8] and in 1 of 2 patients by Mineura et al.[5] Our results therefore closely agree with those of these previous reports.

Although ^{11}C-methionine uptake is known to depend on amino acid transport and protein synthesis,[13,14] the mechanism of ^{11}C-methionine uptake in CVD has not yet been elucidated. In the subacute or chronic stage of cerebral hematoma, inflammatory cells infiltrate the periphery of the hematoma to absorb it, and the capsule of the hematoma is constructed of both the proliferation of fibroblasts and an increase in collagen fibers around the proliferating neovascularity.[15] Furthermore, gliosis occurs in the area immediately outside the developing capsule. These repair mechanisms are considered to increase the extent of protein synthesis, thus resulting in both increased amino acid metabolism and high ^{11}C-methionine uptake in the area surrounding the hematoma. The infiltration of inflammatory cells and gliosis is also considered to play an important role in the high ^{11}C-methionine uptake observed in cerebral infarction.[16]

Disruption of the blood brain barrier (BBB) may also contribute to the high ^{11}C-methionine uptake in both cerebral hematoma and cerebral infarction. Although BBB disruption alone does not increase the ^{11}C-methionine uptake, it does result in the leakage of ^{11}C-methionine into the extracellular space and thus enables high uptake in the cell under some conditions modifying the amino acid transport.[3] The peri-infarcted areas, which have been ischemically compromised for a certain period of time, have been reported to show signs of increased ^{11}C-methionine uptake.[8] An increase in BBB permeability was demonstrated after transient ischemia in an animal study.[17,18]

Cerebral blood flow is also considered to alter the ^{11}C-methionine uptake. In our study, 3 out of 7 patients had high ^{99m}Tc-HMPAO uptake and all 3 of these patients also had high ^{11}C-methionine uptake. Post-ischemic hyperperfusion is a well known phenomenon in the subacute phase of cerebral infarction. In cerebral hematoma, the neovascularity in the surrounding capsule may result in hyperperfusion. Increased blood flow, suggested by high ^{99m}Tc-HMPAO uptake, should modify the transport mechanism and thus result in high ^{11}C-methionine uptake.

In our study, ^{18}F-FDG PET consistently showed low ^{18}F-FDG uptake in patients with both cerebral hematoma and cerebral infarction, even in areas showing signs of high ^{11}C-methionine uptake. No correlation was seen between the ^{11}C-methionine uptake and the ^{18}F-FDG uptake. Our results are consistent with the findings reported by Heiss et al., where they reported that ischemic or hemorrhagic lesions indicated focal hypometabolism in glucose.[19] These findings also suggested that the high ^{11}C-methionine and ^{99m}Tc-HMPAO levels were not caused by neuronal activation such as that seen during an epileptic attack.

CONCLUSIONS

In conclusion, high ^{11}C-methionine uptake can be frequently observed in CVD, especially in cerebral hematomas. CVD should therefore be included in the differential diagnosis when encountering patients with high ^{11}C-methionine uptake.

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REFERENCES

1. Derlon JM, Bourdet C, Bustany P, Chatel M, Theron J, et al. [^{11}C]L-methionine uptake in gliomas. *Neurosurgery* 1989; 25: 720–728.

2. Ogawa T, Shishido F, Kanno I, Inugami A, Fujita H, et al. Cerebral glioma: evaluation with methionine PET. *Radiology* 1993; 186: 45–53.
3. Ericson K. PET studies on amino acid metabolism and protein synthesis. In: Mazoyer BM, ed. *PET Studies on Amino Acid Metabolism: Integration in clinical routine and current research in intracranial tumors*. Kluwer Academic Publishers, 1993: 215–221.
4. Sasaki M, Kuwabara Y, Yoshida T, Nakagawa M, Fukumura T, et al. A comparative study of thallium-201 SPET, carbon-11 methionine PET and fluorine-18 fluorodeoxyglucose PET for differentiation of astrocytic tumors. *Eur J Nucl Med* 1998; 25: 1261–1269.
5. Mineura K, Sasajima T, Kowada M, Ogawa T, Hatazawa J, et al. Indications for differential diagnosis of nontumor central nervous system diseases from tumors. A positron emission tomography study. *J Neuroimaging* 1997; 7: 8–15.
6. Dethy S, Goldman S, Blecic S, Luxen A, Hildebrand J, et al. Carbon-11-methionine and fluorine-18-FDG PET study in brain hematoma. *J Nucl Med* 1994; 35: 1162–1166.
7. Ogawa T, Hatazawa J, Inugami A, Murakami M, Fujita H, et al. Carbon-11-methionine PET evaluation of intracerebral hematoma: distinguishing neoplastic from non-neoplastic hematoma. *J Nucl Med* 1995; 36: 2175–2179.
8. Jacobs A. Amino acid uptake in ischemically compromised brain tissue. *Stroke* 1995; 26: 1859–1866.
9. Saito A, Kato T, Wakabayashi T, Nishino M, Ohshima M, Ito K, et al. High- and moderately high-methionine uptake demonstrated by PET in a patient with a subacute cerebral infarction. *Ann Nucl Med* 2001; 15: 387–391.
10. Dethy S, Manto M, Kentos A, Konopnicki D, Pirotte B, et al. PET findings in a brain abscess associated with a silent atrial septal defect. *Clin Neurol Neurosurg* 1995; 97: 349–353.
11. Ishii K, Ogawa T, Hatazawa J, Kanno I, Inugami A, et al. High L-methyl-[^{11}C]methionine uptake in brain abscess: a PET study. *J Comput Assist Tomogr* 1993; 17: 660–661.
12. Sasaki M, Ichiya Y, Kuwabara Y, Yoshida T, Inoue T, et al. Hyperperfusion and hypermetabolism in brain radiation necrosis. *J Nucl Med* 1996; 37: 1174–1176.
13. Bustany P, Chatel M, Derlon JM, Darcel F, Sgouropoulos F, et al. Brain tumor protein synthesis and histological grade: a study by positron emission tomography (PET) with [^{11}C]L-methionine. *J Neurol Oncol* 1986; 3: 397–404.
14. Kubota R, Kubota K, Yamada S, Tada M, Takahashi T, et al. Methionine uptake by tumor tissue: a microautoradiographic comparison with FDG. *J Nucl Med* 1995; 36: 484–492.
15. Enzmann DR, Britt RH, Lyons BE, Buxton J, Wilson D, et al. Natural history of experimental intracerebral hemorrhage: sonography, computed tomography and neuropathology. *AJNR* 1981; 2: 517–526.
16. Baron J. Positron emission tomography studies in ischemic stroke. In: Barnett H, Stein B, Mohr J, Yatsu F, eds. *STROKE*. Churchill Livingstone, 1994: 111–123.
17. Sage JI, Van Uitert RL, Duffy TE. Early changes in blood brain barrier permeability to small molecules after transient cerebral ischemia. *Stroke* 1984; 15: 46–50.
18. Yoshimine T, Hayakawa T, Kato A, Yamada K, Ushio Y, et al. Autoragiographic study of regional protein synthesis in focal cerebral ischemia with TCA wash and image subtraction techniques. *J Cereb Blood Flow Metab* 1987; 7: 387–393.
19. Heiss WD, Herholz K, Bocher-Scwarz HG, et al. PET, CT and MRI imaging in cerebrovascular disease. *J Comput Assist Tomogr* 1986; 10: 903–911.