Carbon-11-Methionine and Fluorine-18-FDG PET Study in Brain Hematoma

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Three patients were examined using PET with L-methyl-^{11}C-methionine (^{11}C-methionine) and 2-^{18}F-fluoro-2-deoxy-D-glucose (FDG) 20 to 32 days after the occurrence of nontumoral brain hematomas. PET revealed high uptake of ^{11}C-methionine in the area surrounding the hematoma in all three patients. In two patients, discrete spots of moderate uptake of FDG were found at the periphery of a hypometabolic area. PET studies were repeated in two patients 76 and 103 days after the bleeding, respectively, and showed a dramatic decrease in ^{11}C-methionine uptake around the hematoma. The spots of FDG uptake disappeared on the repeated late scans. We hypothesize that the subacute gliotic reaction surrounding brain hematomas is responsible for increased uptake of ^{11}C-methionine and for the presence of spots of FDG uptake. PET studies with ^{11}C-methionine and FDG performed 20 to 32 days after the initial symptom are not helpful in the differentiation between neoplastic and non-neoplastic origins of an intracerebral hemorrhage since tracer uptake at the periphery of the lesion may be increased in both.

Key Words: PET; brain hematoma; carbon-11-methionine; FDG

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Intracerebral hemorrhages have various etiologies, the most frequent being hypertensive disease with arteriolar sclerosis (*1,2*). Among other causes, primary or metastatic neoplasms are important to consider because of their specific management and prognosis (*3,4*). PET studies using ^{11}C-methionine demonstrate increased uptake of the tracer in 80% to 90% of malignant brain tumors (*5*). However, little is known concerning ^{11}C-methionine uptake in nontumoral brain lesions—information which is essential to estimate the specificity of ^{11}C-methionine uptake in brain malignancies. We report the results of PET studies in three patients with nontumoral intracerebral hemorrhage, comparing evolution of ^{11}C-methionine PET scans and FDG PET scans.

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MATERIALS AND METHODS

Patients

Three patients with an acute intracerebral hemorrhage were investigated by PET using ^{11}C-methionine and FDG on Days 20, 21 and 32, respectively (initial PET). In two patients, PET imaging was repeated on Days 76 and 103 after the hemorrhage, respectively (second PET). Patient characteristics and outcomes are summarized in Table 1. Patient 1 experienced clinical deterioration on Day 20 after the hemorrhage and CT showed an extension of the hypodense area surrounding the hematoma, a ring of contrast-enhancement and an increased mass effect. Because an underlying tumor was suspected, PET with ^{11}C-methionine and FDG were performed followed by a stereotactic biopsy. Histology of the samples revealed mononuclear perivascular infiltrates, formation of a collagen capsule with gliosis, spongiosis and microangiosclerosis in the surrounding white matter. None of the nine samples contained neoplastic cells. In Patients 2 and 3, the diagnosis of hematoma was based on initial CT results, the regression of the hyperdense area on follow-up CT performed on Days 28 and 30 after the hemorrhage, and clinical improvement. In addition, there was no evidence of systemic neoplasia in the three patients.

PET Methods

Synthesis of ^{11}C-methionine was performed using an automated synthesis system following the procedure described by Comar et al. (*6*). Radiochemical and chemical purity measured by HPLC (Ultrasphere ODS, 5 μm, 4.6 × 250 mm; eluent, 0.02 *M* NaH_2PO_4, pH 3; flow rate 1 ml/min; UV detection, 210 nm and radioactivity) was higher than 95%; enantiomeric purity determined by ligand exchange chromatography was higher than 95% (*7*). Synthesis of FDG was performed following the method described in the literature (*8*).

The PET tomograph was a CTI-Siemens 933/08-12 (Knoxville, TN). The fifteen 6.75-mm thick adjacent slices covered the entire brain. Images were corrected for attenuation using a transmission scan. A dose of 300 to 600 MBq (specific activity: 7-30 GBq/μmole) of ^{11}C-methionine was administered to the patients intravenously and a 20-min emission scan was obtained 20 min later. For the FDG scan, the dose was 200 to 300 MBq and a 20-min emission scan was obtained starting 40 min after injection. Carbon-11-methionine and FDG scans were obtained within 24 hr.

Image analysis was performed by visual inspection and by semiquantitative evaluation of tracer uptake in regions of interest (ROI). The semiquantitative uptake index was calculated as the ROI-to-Cor ratio (expressed in percent), where Cor is the mean

TABLE 1
Clinical and Computed Tomography Data

Patient no.	Age/Sex	Risk factors	Signs at admission	Hematoma on CT		Signs at discharge
				Location	Size (cm)*	
1	51/M	Hypertension and diabetes	Transcortical motor aphasia, right hemiplegia, sensory deficit	Left putamen and caudate nucleus	6.3 × 2.8	Stable aphasia, able to walk
2	79/M	Hypertension	Transcortical motor aphasia, right hemiplegia	Left putamen and internal capsule	7.3 × 3.5	Death from acute sepsis after 64 days
3	63/M	Hypertension	Transcortical sensory aphasia, right hemiparesia, vertical gaze palsy, right sensory deficit	Left thalamus and mesencephalon	1.9 × 2	Stable aphasia, total recovery of other signs

*Largest cross-sectional diameter by largest diameter perpendicular to it.

count rate in five cortical ROIs delineated in the hemisphere controlateral to the lesion.

RESULTS

CT, performed without and with contrast in Patient 1, showed spontaneously hyperdense subcortical lesions in all patients (Fig. 1C, 2C and 3C). On visual analysis, initial PET scans with ^{11}C-methionine showed increased uptake of the tracer at the periphery of the hematoma in all three patients (Fig. 1A, Fig. 2A and Fig. 3A for Patients 1, 2 and 3, respectively). In the region surrounding the hematoma, semiquantitative evaluation demonstrated a ^{11}C-methionine mean uptake index of 130%, 205% and 135% in patients 1, 2 and 3, respectively. Initial PET scans with FDG showed either discrete spots of increased uptake of the tracer next to a hypometabolic area in Patient 1 (semiquantitative uptake index = 94%, Fig. 1B) and in Patient 2 (semiquantitative uptake index = 97%, Fig. 2B) or a hypometabolic area in Patient 3 (semiquantitative uptake index = 66%). These discrete spots were found within the boundary of increased uptake of ^{11}C-methionine, either in the inner part of the hypometabolic cortical ribbon or in the medial border of the hematoma. PET scans with ^{11}C-methionine and FDG were repeated on two patients. In Patient 1, PET with ^{11}C-methionine showed a clear decrease in tracer uptake in the area of the hematoma (semiquanti-

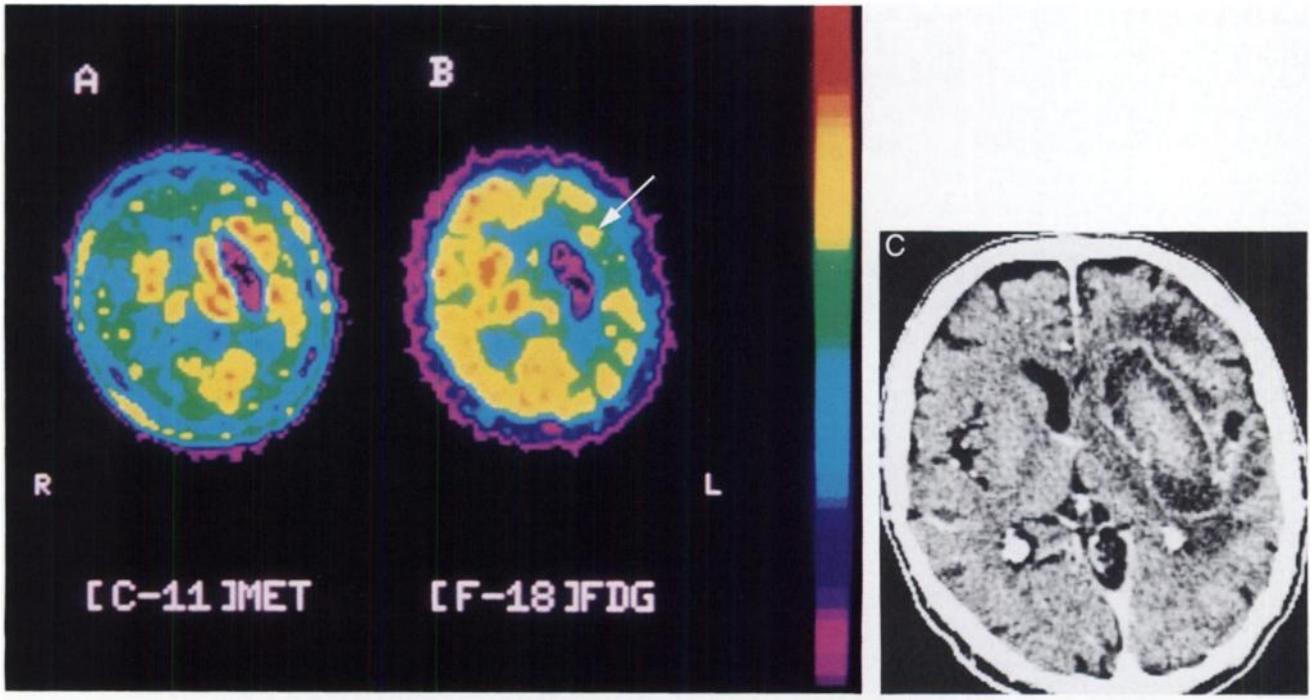

FIGURE 1. Patient 1. (A) Carbon-11-methionine PET image obtained 32 days after the hemorrhage shows high uptake of the tracer in the area surrounding the left putamino-capsular hematoma (right part of the image). (B) FDG PET image shows discrete spots of moderate uptake of the tracer next to a hypometabolic area (right part of the image). The arrow points at one spot of FDG uptake within the boundary of increased uptake of ^{11}C-methionine. (C) Contrast-enhanced CT at a level similar to the PET image shows a spontaneously hyperdense lesion surrounded by a ring-shaped zone of contrast-enhancement in the left putamino-capsular area.

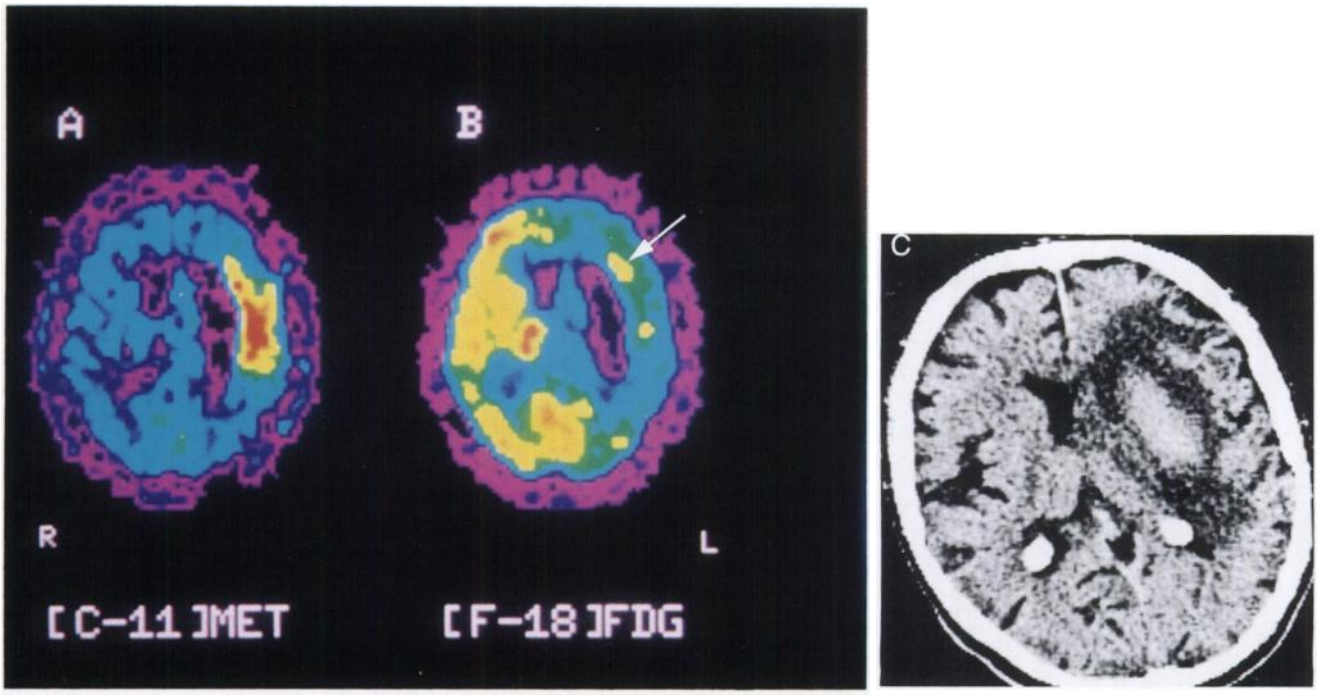

FIGURE 2. Patient 2. (A) Carbon-11-methionine PET image obtained 20 days after the hemorrhage shows high uptake of the tracer in the area surrounding the left putamino-capsular hematoma (right part of the image). (B) FDG PET image shows discrete spots of moderate uptake of the tracer next to a hypometabolic area (right part of the image). The arrow points at one spot of FDG uptake within the boundary of increased uptake of ^{11}C-methionine. (C) CT at a level similar to the PET image shows a spontaneously hyperdense lesion in the left putamino-capsular area.

tative uptake index = 110%) but an increased uptake in thalamus and lenticular nucleus on the same side compared to the contralateral basal ganglia. The semiquantitative uptake indices were 151% and 159% on the left and 118% and 137% on the right in the thalamus and the lenticular nucleus, respectively. PET with FDG demonstrated disappearance of spots of higher tracer uptake giving place to an homogeneous hypometabolic area (semiquantitative uptake index = 76%). In Patient 3, PET with ^{11}C-methionine showed disappearance of the increased uptake in the area of the hematoma (semiquantitative uptake index = 59%, Fig. 3B) and PET with FDG, previously hypometabolic in the area of the hematoma, remained almost unchanged (semiquantitative uptake index = 49%).

DISCUSSION

In all three patients, PET with ^{11}C-methionine, performed within 1 mo following the hemorrhage, demonstrated high uptake of tracer in the area surrounding brain hematoma while the second PET obtained in two patients showed dramatic reduction or disappearance of the uptake. The first PET with FDG showed discrete spots of moderate uptake at the periphery of the lesion in two patients, and the second PET showed disappearance of these spots.

Two physiological mechanisms may explain the high uptake of ^{11}C-methionine. Pathological studies in animals and in humans have revealed a collagen capsule formation with mononuclear perivascular infiltrates and gliotic reaction at the periphery of a brain hematoma, starting 2 to 3 wk after the bleeding (*9,10*). These pathological changes were also found in the biopsy performed in Patient 1, 32 days after the occurrence of the hemorrhage. The uptake of ^{11}C-methionine is related to the protein synthesis rate which is increased in inflammatory cells or proliferating glial cells (*11*). Therefore, the high uptake of ^{11}C-methionine observed in our patients may be related to the cellular reaction surrounding the hematoma.

Disruption of the blood-brain barrier (BBB) may also contribute to the high uptake of ^{11}C-methionine surrounding a brain hematoma as suggested in tumors and in irradiated brain areas (*5,12*). Indeed, in Patient 1, CT with contrast showed disruption of the BBB at the time of the first PET.

In comparison to the ^{11}C-methionine studies, the increased uptake of FDG around the hematoma was either limited to discrete spots in two patients or absent in one. These spots were bordering the hematoma inside the limits of the area of increased uptake of ^{11}C-methionine, therefore, we did not consider that these spots of FDG could correspond to normal metabolic activity in displaced cortical or sub-cortical structures. As for ^{11}C-methionine uptake, these spots of FDG may be related to tissular-proliferative reaction. An autoradiographic study has demonstrated that macrophages and young granulation tissue with fibroblastes contribute to the increase of FDG uptake in tumors (*13*).

The uptake of ^{11}C-methionine was increased on the second PET scan in the thalamus and putamen of one patient.

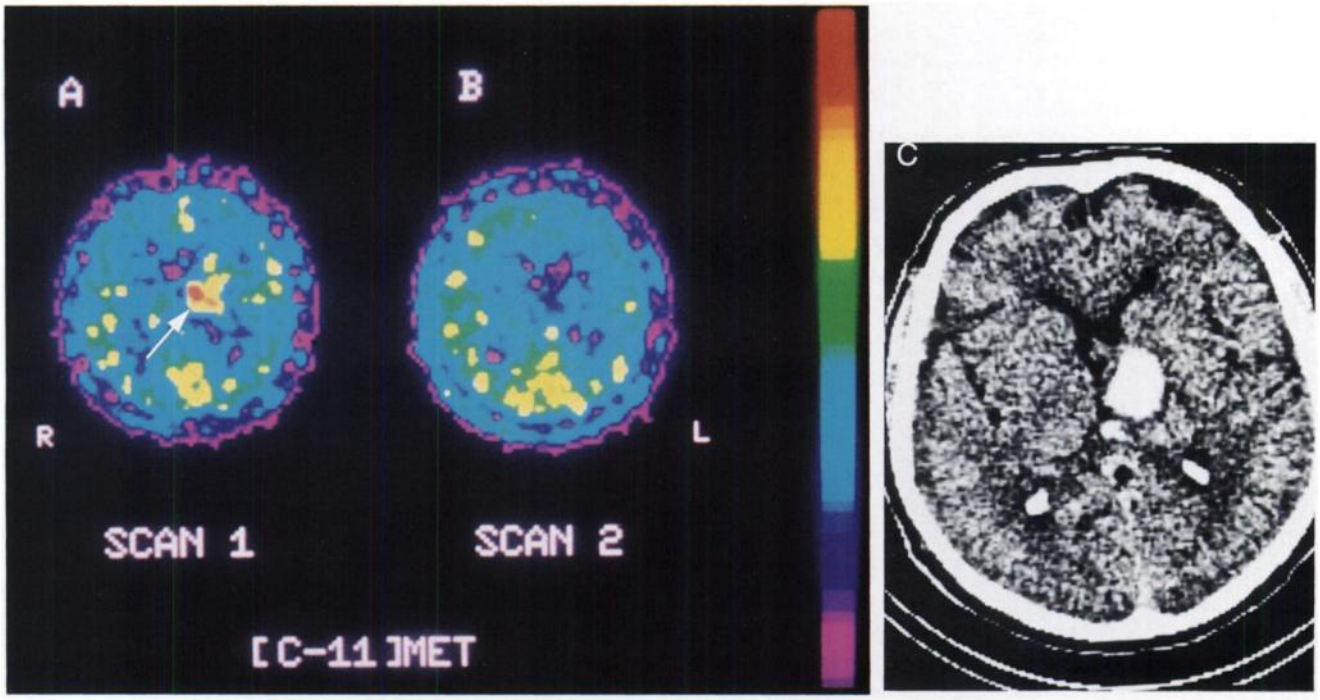

FIGURE 3. Patient 3. (A) Carbon-11-methionine PET image obtained 21 days after the hemorrhage shows high uptake of the tracer in the area of the left thalamic hematoma (right part of the image, arrow). (B) Carbon-11-methionine PET image obtained 76 days after the hemorrhage shows disappearance of increased uptake in the area of the hematoma (right part of the image). (C) CT at a level similar to the PET image shows a spontaneously hyperdense lesion in the left thalamus.

This unexpected observation may be related to a high protein synthesis rate in response to axonal lesions. Such high-protein synthesis rates revealed by labeled amino-acid uptake have been demonstrated in the hypoglossal nucleus after sectioning of the twelfth nerve in adult rats (*14*). Since this observation was made in one patient only, it should be confirmed before concluding that PET with labeled amino acid markers might help in tracing neural reaction to axonal injury in human.

PET with ^{11}C-methionine has been successfully applied to grading and delineation of gliomas (*12,15*). However, information concerning uptake of ^{11}C-methionine in nontumoral lesions is scarce. Increased uptake of ^{11}C-methionine has occasionally been seen in necrotic areas secondary to radiation therapy of brain tumors (*16*). An experimental study has indicated that ^{11}C-labeled leucine, another protein precursor, is unable to differentiate brain abscess from brain tumor (*17*) and the authors have recently described in one patient a high ^{11}C-methionine uptake in a brain abscess (*18*). Hemorrhage in a primary or metastatic neoplasm is not rare. Metastases from germ cells and melanoma are hemorrhagic in 59% and 31% of the cases, respectively (*4*) and hemorrhage in glioblastomas and oligodendrogliomas is not uncommon (*3*). Occurrence of hemorrhage in neoplastic brain lesions dramatically modifies their radiological aspect, often delaying the accurate diagnosis until resorption of the hematoma is completed. Our results indicate that PET with ^{11}C-methionine, performed 20 to 32 days after the clinical onset, is not helpful in the differentiation between neoplastic and nonneoplastic causes of an intracerebral hemorrhage since tracer uptake at the periphery of the lesion may be elevated in both. Presence of occasional spots of increased uptake of FDG around some hematomas indicates that PET studies with this tracer may be equally misleading in attempts to differentiate neoplastic from spontaneous intracerebral hemorrhage. Follow-up PET in two patients in this study suggests that increased ^{11}C-methionine and FDG uptakes are not persistent several months after a spontaneous hemorrhage; such a persistent tracer uptake could therefore indicate underlying neoplasia.

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