

High- and moderately high-methionine uptake demonstrated by PET in a patient with a subacute cerebral infarction

Atsuko NAGANO-SAITO,*** Takashi KATO,* Toshihiko WAKABAYASHI,*** Masanari NISHINO,** Motonori OHSHIMA,**** Kengo ITO,*** Tsuneo ISHIGUCHI,** Masanori TADOKORO,** Takeo ISHIGAKI,** Yuji ABE* and Masahiko BUNDO****

**Department of Biofunctional Research, National Institute for Longevity Sciences*

***Department of Radiology and ***Department of Neurosurgery, Nagoya University School of Medicine*

*****Department of Pharmacy, Nagoya University Hospital*

In patients with cerebral tumors, high accumulations of L-methyl- ^{11}C -methionine (^{11}C -Met) have been reported in some cases of cerebral ischemic disease, but no high accumulations of ^{11}C -Met in areas where only transient arterial occlusions are most likely to occur have been reported. Herein we present a case of a high accumulation of ^{11}C -Met in an area of frontal interhemispheric cerebral infarction and a moderately high accumulation with an unclear margin in a distant frontal convexity area. A craniotomy revealed a subacute stage of cerebral infarction in the interhemispheric lesion, and an ischemic change in the distant convexity area. Sixteen months after onset, CT scans demonstrated an infarction area in the interhemispheric lesion only, and no atrophic changes were observed in the distant convexity area indicating that no serious tissue damage had occurred.

Key words: positron emission tomography, L-methyl- ^{11}C -methionine, transient artery occlusion, cerebral infarction

CASE REPORT

A 41-year-old man presented himself with a mild dysarthria and a mild headache of one day's duration. Three days after the onset, CT scans were performed. A plain CT showed a low density region at the left frontal interhemispheric cortex, which included the left anterior cingulate gyrus and the anterior genu of the corpus callosum. In addition, an enhanced CT showed a small enhanced area in the latter region (Fig. 1). On day 12, in the left frontal interhemispheric area, MRI indicated a low signal intensity with a small area of high signal intensity on a T1-weighted image, high signal intensity on a T2-weighted image, and Gd-DTPA enhancement was observed widely on a T1-weighted image (Fig. 2). In the left frontal

convexity area, including both the middle frontal gyrus and inferior frontal gyrus, the fissures were obscure on the T1-weighted image, and faint high signal intensity was observed on the T2-weighted image. It was also noted that a slightly enhanced area in the middle frontal gyrus might exist on the T1-weighted image with Gd-DTPA enhancement (Fig. 2). On day 17, PET with L-methyl- ^{11}C -methionine (^{11}C -Met) as a tracer was performed with a Headtome IV (Shimadzu Corporation, Kyoto, Japan). Scanning began at the initiation of tracer injection and the dynamic data included 8 timed frames (2×8 min). A static image was obtained from 23 min to 37 min after tracer injection. The static image showed a high accumulation in the well-enhanced area that was observed in the enhanced MRI. A moderately high accumulation of ^{11}C -Met with unclear margins was also observed in a distant frontal convexity area, and which was widely dispersed throughout the area where obscure signal changes were noted in the MRI (Fig. 3). Regions of interest were put on the center of the high uptake area, and on the center of the moderately high uptake area corresponding to the left middle frontal gyrus (Fig. 3). The dynamic data indicate

Received January 9, 2001, revision accepted May 11, 2001.

For reprint contact: Atsuko Nagano-Saito, M.D., Department of Biofunctional Research, National Institute for Longevity Sciences, 36-3, Gengo, Morioka-cho, Obu, Aichi 474-8522, JAPAN.

E-mail: anagano@sannet.ne.jp or saito@nils.go.jp

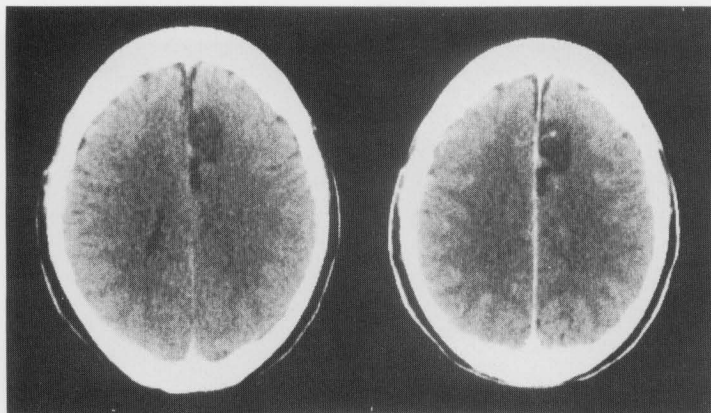


Fig. 1 CT scans on day 3. A plain CT (left) shows a low density area at the left frontal interhemispheric cortex. An enhanced CT (right) shows a partial enhanced area.

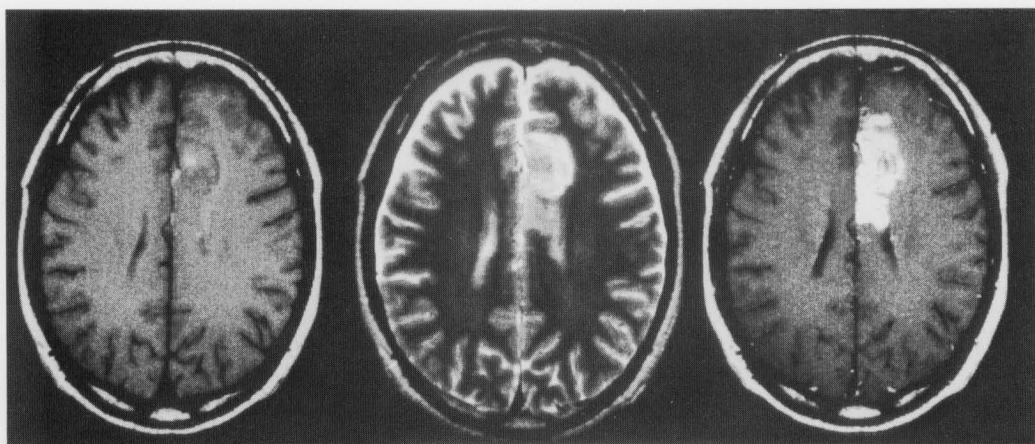


Fig. 2 MRI on day 12. A low intensity signal in the left frontal interhemispheric cortex and an obscurity of the fissures of the left frontal convexity cortex are observed on a T1-weighted image (left). A high intensity signal on a T2-weighted image (middle), and a high intensity signal on a T1-weighted image with Gd-DTPA enhancement (right) are also observed in the left interhemispheric cortex. A faintly high signal intensity was observed in the left frontal convexity cortex on the T2-weighted image (middle).

that the difference in the uptake of ^{11}C -Met in the very early phase (0 to 5 min) led to the difference in the accumulation of ^{11}C -Met in the static phase, and no lasting increase in the accumulation of ^{11}C -Met, which is a pattern for tumoral uptake, was observed (Fig. 4). The standard uptake value (SUV) and the tumor to normal tissue ratio (TNT ratio) were calculated. The SUV was calculated by (regional activity) \times (weight of patient)/(injected dose) \times (cross calibration factor). The TNT ratio was calculated by the regional activity divided by the activity of the mirror region. The SUVs were 2.32 and 1.61, and the TNT ratios were 2.10 and 1.51, for the high accumulation and the moderately high accumulation areas, respectively. Digital subtraction angiography (DSA) projection on day 19 showed no tumor staining. A left internal carotid arteriogram revealed an occluded pericallosal artery with a dilated collateral artery and collateral development from the middle cerebral artery. A

left vertebral arteriogram showed the growth of leptomeningeal vessels from the posterior cerebral artery (Fig. 5). An electrocardiogram (ECG) indicated no heart disease.

From these data, a cerebral infarction was suspected, but because of the finding with ^{11}C -Met PET, the patient's age, the absence of heart disease, and the frontal cortex lesion involvement of both the frontal and middle cerebral artery regions, a brain tumor remained a possibility. Accordingly, a craniotomy was performed on day 27. A yellowish change was observed on the surface of the left frontal convexity area. This kind of observation is commonly seen after an inflammatory or ischemic process. A histopathological examination of the region of high ^{11}C -Met accumulation revealed degenerating glia cells, gliosis, and angiogenesis surrounded by fat granular cells, which indicated the phagocytosis of myelin by microglia (Fig. 6). These findings are consistent with the subacute

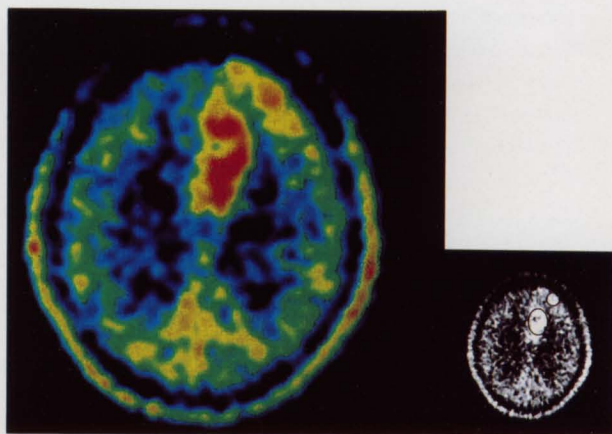


Fig. 3 A static image of PET with ^{11}C -Met on day 17. High accumulation of ^{11}C -Met is observed in at the region of where the MRI enhancement well-enhanced area. A moderately high accumulation of ^{11}C -Met with an unclear margin is observed at the distant frontal cortex. Regions of interest are shown in the right lower figure.

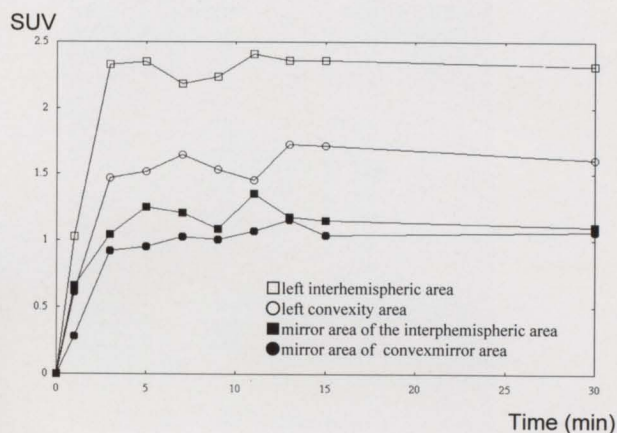


Fig. 4 The dynamic data of ^{11}C -Met uptake. A transverse axis indicates the middle time of the dynamic scan after the injection of ^{11}C -Met. The vertical axis indicates the calculated SUV with decay correction. The open square indicates the area of the high accumulation area, and the open circle indicates the area of the moderately high accumulation area. The closed square and circle correspond those areas on the contralateral sides of the mirror areas.

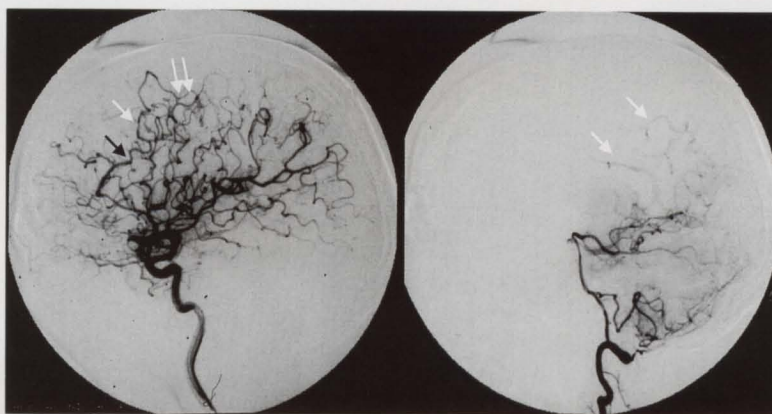
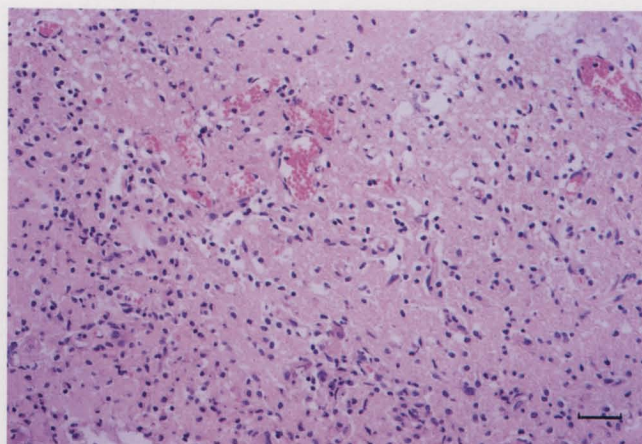


Fig. 5 DSA projections on day 19. A left internal carotid arteriogram, lateral view (left), shows an occluded pericallosal artery (black arrow) with a dilated collateral artery (white arrow) and collateral development from the middle cerebral artery (white double arrows). A left vertebral arteriogram, lateral view (right), shows the growth of leptomeningeal anastomoses from the posterior cerebral artery (white arrows). No tumor staining is observed.

Fig. 6 A histological examination at the region of high accumulation of ^{11}C -Met accumulation reveals a degenerating glia cells, gliosis, and angiogenesis surrounded by fat granular cells, which indicates the phagocytosis of myelin by microglia. The scale bar in the right corner indicates 100 μm . (Hematoxylin-Eosin)



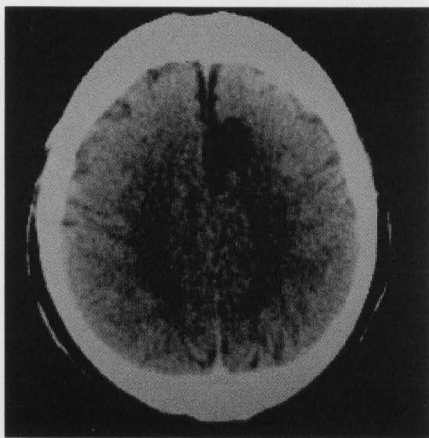


Fig. 7 CT at sixteen months after onset. Infarction area is observed only at the left frontal interhemispheric area. No atrophic changes is observed at the left frontal convexity area.

stage of cerebral infarction in the interhemispheric area. Sixteen months after onset, CT scans showed an infarction area in the interhemispheric region only, and no atrophic changes in the distant convexity area (Fig. 7).

DISCUSSION

PET with ^{11}C -Met as a tracer is clinically useful for evaluating cerebral gliomas, especially in assessing the extent of the tumors.^{1,2} The presence of necrosis in anaplastic areas of the tumors significantly reduced the uptake of ^{11}C -Met,³ but the grade of tumor malignancies also can be assessed with ^{11}C -Met.^{2,4,5} The advantage of ^{11}C -Met in discriminating between tumorous and non-tumorous lesions has also been reported,^{2,6,7} but in cases of acute or subacute stages of brain infarctions,^{8,9} brain abscesses,¹⁰ areas surrounding the hematomas in subacute stages,¹⁰ delayed cerebral radionecrosis,¹² and cerebritis,^{9,13} high accumulations of ^{11}C -Met have been reported.

Here we present a patient with regions of high and moderately high accumulations of ^{11}C -Met in an infarction site and in the area where a transient arterial occlusion probably occurred, respectively. Retrospectively, it may be true that, at the onset of the dysarthria, embolisms occurred in both the left frontal and middle cerebral artery branches, and that the occlusion (except in the left pericallosal artery) improved immediately. Alternatively, it is possible that an embolism occurred only in the left frontal cerebral artery branches, and the lesion in the middle cerebral artery distribution occurred as a consequence of a hemodynamic ischemia. The frontal cortical hypoperfusion, particularly in the anterior opercular and medial frontal regions, plays an important role in the development of pure dysarthria,¹⁴ and the dysarthria in our case can be accounted for by the infarction in the interhemispheric area. The frontal convexity area vascularized by both the anterior and middle frontal cerebral

arteries might have been exposed to only transient ischemia, and the disruption of the blood-brain barrier visible on MRI might be limited to a small area. Nevertheless, the high and moderately high accumulation of ^{11}C -Met were dispersed more widely than in the obviously enhanced area on MRI. In addition, the TNT ratios were higher than 1.2 as the threshold between the tumor and nontumor regions⁷ in both the high and moderately high accumulation areas, so a craniotomy was performed.

Recent murine studies have revealed the mechanism of tissue accumulation for ^{11}C -Met. The accumulation of ^{11}C -Met reflects the active transport of amino acids rather than the rate of protein synthesis.¹⁵ In a study of tumors, ^{14}C -Met uptake occurs within the tumors mostly by viable cancer cells, but partly by granulation tissue, macrophages, and necrotic debris.¹⁶ The disruption of the blood-brain barrier may also contribute to the accumulation of ^{11}C -Met.^{8,9}

In cases of transient ischemia, the expression of c-fos protein has been reported both adjacent to and distant from the ischemic territory in the early stage.¹⁷ In addition, the induction of hsp70 mRNA at the margins of the infarct, and the diffuse induction of c-fos, junB, and c-jun mRNA in all regions of the cortex outside the infarct in early stages has been reported.¹⁸ The induction of these mRNAs indicates a certain degree of cellular damage. Recent observations in both humans and animals suggest that selective neuronal necrosis is the consequence of either a short-term arterial occlusion or a permanent occlusion accompanied by ischemia of moderate severity.¹⁹ Lin et al. reported two patterns of subacute and chronic ischemic injury.²⁰ The first pattern consists of a mild-to-moderate ischemic neuronal injury appearing at 1–2 weeks, associated with an astrocytic and microglial proliferation lasting for several weeks. The second pattern consists of a more severe ischemic neuronal injury, associated with focal astrocytosis and microglial proliferation occurring in a spatial relationship to abnormal blood vessels. Kondo et al. reported an astroglial and ferritin-immunopositive microglial reaction without neuronal death or atrophy at 8 weeks after transient ischemia.²¹

In our case, in addition to the high accumulation of ^{11}C -Met in the region of the cerebral infarction, a moderately high accumulation with unclear margins was observed in a distant area where transient arterial occlusion probably occurred. The area with a high accumulation of ^{11}C -Met was substantially enhanced on a T1-weighted image with Gd-DTPA enhancement, and indicated a disruption of the blood-brain barrier. The histopathological findings indicated gliosis and angiogenesis. In the area with a moderately high accumulation of ^{11}C -Met, the disruption of the blood-brain-barrier was limited, and the presence of a yellowish change, as evident upon craniotomy, is a common finding after ischemic change. The area with a high accumulation of ^{11}C -Met may correspond to the region

with severe ischemic neuronal injury. The area with a moderately high accumulation of ^{11}C -Met may correspond to the region with mild-to-moderate ischemic neuronal injury, where inflammatory reactions occurred subsequent to non-lethal ischemia with the preservation of the brain tissue framework. The high and moderately high accumulation of ^{11}C -Met may correspond mainly to the disruption of the blood-brain-barrier and the active transport of amino acids reflecting gliosis and angiogenesis, respectively.

We reported a case of high and moderately high accumulations of ^{11}C -Met in a cerebral infarction and as well as in an area where transient arterial occlusion probably occurred.

ACKNOWLEDGMENT

The authors thank Dr. Masataka Tajima, Tajima Clinic, for allowing using the CT films.

REFERENCES

- Ogawa T, Shishido F, Kanno I, Inugami A, Fujita H, Murakami M, et al. Cerebral glioma: Evaluation with methionine PET. *Radiology* 1993; 186: 45–53.
- Moskwin M, von Holst H, Rergström M, Collins VP, Eriksson L, Johnström P, et al. Positron emission tomography with ^{11}C -methionine and computed tomography of intracranial tumors compared with histopathologic examination of multiple biopsies. *Acta Radiologica* 1987; 28: 673–681.
- Goldman S, Levovoe M, Pirotte B, Brucher JM, Wikler D, Damhaut P, et al. Regional methionine and glucose uptake in high-grade gliomas: a comparative study on PET-guided stereotactic biopsy. *J Nucl Med* 1997; 38: 1459–1462.
- Derlon JM, Petit-Taboue MC, Chapon F, Beaudouin V, Noel MH, Creveuil C, et al. The *in vivo* metabolic pattern of low-grade brain gliomas: a positron emission tomographic study using ^{18}F -fluorodeoxyglucose and ^{11}C -L-methyl methionine. *Neurosurgery* 1997; 40: 287–288.
- Kaschten B, Stevenaert A, Sadzot B, Deprez M, Degeldre C, Del Fiore G, et al. Preoperative evaluation of 54 gliomas by PET with fluorine-18-fluorodeoxyglucose and/or carbon-11-methionine. *J Nucl Med* 1998; 39: 778–785.
- Ericson K, von Holst H, Moskwin M, Bergström M, Lindqvist M, Noren G, et al. Positron emission tomography of cavernous hemangiomas of the brain. *Acta Radiologica Diagnosis* 1986; 27: 379–383.
- Suzuki A, Mineura K, Sasashima T, Kowada M, Ogawa T, Hatazawa J, et al. Sequential analysis of the integrated images of PET, CT and MR in malignant brain tumors before and after radiotherapy. *No to Shinkei—Brain & Nerve* 1996; 48: 449–457.
- Jacobs A. Amino acid uptake in ischemically compromised brain tissue. *Stroke* 1995; 26: 1859–1866.
- Mineura K, Sasajima T, Kowada M, Ogawa T, Hatazawa J, Uemura K. Indications for differential diagnosis of nontumor central nervous system diseases from tumors. *J Neuroimaging* 1997; 7: 8–15.
- Ishii K, Ogawa T, Hatazawa J, Kanno I, Inugami A, Shimosegawa E, et al. High L-methyl- ^{11}C methionine uptake in brain abscess: A PET study. *J Comput Assist Tomogr* 1993; 17: 660–661.
- Dethy S, Goldman S, Bleic S, Luxen A, Levivier M, Hildebrand J. Carbon-11-methionine and fluorine-18-FDG PET study in brain hematoma. *J Nucl Med* 1994; 35: 1162–1166.
- Tashima T, Morioka T, Nishio S, Hachisuga S, Fukui M, Sasaki M. Delayed cerebral radionecrosis with high uptake of ^{11}C -methionine on positron emission tomography and ^{201}Tl -chloride on single-photon emission computed tomography. *Neuroradiology* 1998; 40: 435–438.
- Ochi H, Yamada T, Hara H, Yoshimura T, Iwaki T, Nagashima K, et al. A case of progressive multifocal leukoencephalopathy with methionine uptake demonstrated by PET. *Clin Neurol* 1996; 36: 858–863.
- Okuda B, Kawabata K, Tachibana H, Sugita M. Cerebral blood flow in pure dysarthria: role of frontal cortical hypoperfusion. *Stroke* 1999; 30: 109–113.
- Ishiwata K, Kubota K, Murakami M, Kubota R, Sasaki T, Ishii S, et al. Re-evaluation of amino acid PET studies: Can the protein synthesis rates in brain and tumor tissues be measured *in vivo*? *J Nucl Med* 1993; 34: 1936–1943.
- Kubota R, Kubota K, Yamada S, Tada M, Takahashi T, Iwata R, et al. Methionine uptake by tumor tissue: A microautoradiographic comparison with FDG. *J Nucl Med* 1995; 36: 484–492.
- Uemura Y, Kowall NW, Moskowitz MA. Focal ischemia in rats causes time-dependent expression of c-fos protein immunoreactivity in widespread regions of ipsilateral cortex. *Brain Research* 1991; 552: 99–105.
- Kinouchi H, Sharp FR, Chan PH, Koisinaho J, Sagar SM, Yoshimoto T. Induction of c-fos, junB, c-jun, and hsp70 mRNA in cortex, thalamus, basal ganglia, and hippocampus following middle cerebral artery occlusion. *J Cereb Blood Flow Metab* 1994; 14: 808–817.
- Garcia JH, Lassen NA, Weiller C, Sperling B, Nakagawara J. Ischemic stroke and incomplete infarction. *Stroke* 1996; 27 (4): 761–765.
- Lin B, Ginsberg MD, Busto R, Dietrich WD. Sequential analysis of subacute and chronic neuronal, astrocytic and microglial alterations after transient global ischemia in rats. *Acta Neuropathol* 1998; 95: 511–523.
- Kondo Y, Ogawa N, Asanuma M, Ota Z, Mori A. Regional differences in late-onset iron deposition, ferritin, transferrin, astrocyte proliferation, and microglial activation after transient forebrain ischemia in rat brain. *J Cereb Blood Flow Metab* 1995; 14: 216–226.