



Title	11C-Methionine positron emission tomography may monitor the activity of encephalitis
Author(s)	Hirata, Kenji; Shiga, Tohru; Fujima, Noriyuki; Manabe, Osamu; Usui, Reiko; Kuge, Yuji; Tamaki, Nagara
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# **<sup>11</sup>C-Methionine positron emission tomography may monitor the activity of encephalitis - a case report**

## **Abstract**

Encephalitis is generally diagnosed by clinical symptoms, cerebrospinal fluid examination, and imaging studies including CT, MR imaging and perfusion single photon emission tomography (SPECT). However, the role of positron emission tomography (PET) in diagnosis of encephalitis remains unclear. A 49-year-old woman presenting with coma and elevated inflammatory reaction was diagnosed as having encephalitis according to slow activity on electroencephalogram, broad cortical lesion in MR fluid attenuated inversion recovery image, and increased blood flow demonstrated by SPECT. PET revealed increased accumulation of <sup>11</sup>C-methionine (MET) in the affected brain tissues. After the symptom had improved two months later, the accumulation of MET as well as the abnormal findings of MR imaging and SPECT was normalized. This case indicated that MET PET may monitor the activity of encephalitis.

**Key Words:** encephalitis; positron emission tomography; methionine; therapy

monitoring

Encephalitis is an acute inflammation of the brain, usually caused by a viral infection. The clinical manifestations are characterized by fever, headache and altered level of consciousness (1). Examination of the cerebrospinal fluid (CSF) obtained by a lumbar puncture procedure is essential. The detection of viral DNA in CSF as well as antibodies to virus is a rapid, specific and highly sensitive method for viral encephalitis. CT and MR imaging can provide useful and sometimes complementary information. MR imaging has been reported to be sensitive and suggested to be performed routinely in the evaluation of patients with presumed encephalitis (2). Cerebral perfusion imaging with  $^{99m}\text{Tc}$  hexamethylpropyleneamine (HMPAO) single photon emission tomography (SPECT) can also depict the encephalitic lesions and provide useful information for differential diagnosis (3). However, positron emission tomography (PET) has rarely been performed for the diagnosis of encephalitis. The aim of this report is to present a case of encephalitis with elevated  $^{11}\text{C}$  methionine (MET) uptake in the cerebral hemisphere, and to discuss the usefulness of MET PET for encephalitis.

## **Case Report**

A 49-year-old woman was admitted for coma. Since she was diagnosed as schizophrenia at the age of 27, she had been given drug therapy including haloperidol, risperidone, timiperone, quetiapine, and zotepine. She was found unconscious at home by her family and brought to the hospital. On arrival, blood pressure was 120/70 mm Hg; heart rate was 55 beats/min; body temperature was 37.1 °C. She was vomiting and presenting with urinary incontinence, right-sided conjugate deviation of the eyes, and flexed right arm. Laboratory data revealed inflammatory response (CRP 4.02 mg/dl and WBC 10600/ $\mu$ l). Blood sugar level was elevated as 272 mg/dl.

Brain MR imaging performed on the day of admission showed no abnormalities; however, on day 4, the MR fluid attenuated inversion recovery (FLAIR) imaging and diffusion weighted imaging (DWI) revealed high signal intensity broadly in the right parietal, temporal, and occipital lobe (Fig. 1a, b, f, and g). Lesions were located predominantly in the gray matter rather than in the white matter. Apparent diffusion coefficient was reduced in the corresponding area. The lesions did not enhance after intravenous injection of 10 ml of gadolinium contrast agent (Magnevist(R), Bayer HealthCare, Berlin, Germany) (Fig. 1c and h). All the MR images were interpreted by a board-certified diagnostic radiologist specializing in neuroradiology (N. F.).

Electroencephalography showed slow waves in the right hemisphere. Lumbar puncture with an opening pressure of 172 mmH<sub>2</sub>O and a closing pressure of 140 mmH<sub>2</sub>O revealed CSF cell count 30/3  $\mu$ l (17 polynuclear and 13 mononuclear cells), total protein 32 mg/dl, and glucose 91 mg/dl. In the CSF sample, herpes simplex virus (HSV) antibodies were IgG positive but IgM negative, indicating previous infection. As for cytomegalovirus (CMV), varicella-zoster virus (VZV), and Epstein-Barr virus (EBV), neither IgG nor IgM were positive. PCR could not detect HSV-DNA.

<sup>99m</sup>Tc HMPAO SPECT performed on the day 7 (Fig. 1d and i) showed increased accumulation in the right parietal, temporal, and occipital lobe corresponding to abnormal area on MR FLAIR imaging. Clinical symptoms and radiological findings suggested that encephalitis was most possible despite a negative immunological test. To target both viral and bacterial encephalitis, antiviral (acyclovir) and antibacterial (cefazopran) therapy was started. The symptoms and laboratory data were gradually improved but not completely remitted. On day 26, we empirically performed MET PET (Fig. 1e and j), which had been reported to evaluate cerebral inflammatory lesions (4-6). The MET PET image, acquired with EXACT HR+ scanner (Asahi-Siemens Medical Technologies Ltd., Tokyo, Japan), demonstrated increased accumulation of MET in the

area corresponding to MR imaging with lesion-to-contralateral ratio of 1.34. We continued antibiotics therapy, and the symptoms were further improved.

MR imaging,  $^{99m}\text{Tc}$  HMPAO SPECT, and MET PET were performed again on the day 55, 57, and 62, respectively. In the MR study, high signal areas were almost normalized on FLAIR (Fig. 2a and f) and DWI (Fig. 2b and g). Gadolinium (Magnevist, 10 ml) enhancement was absent (Fig. 2c and h).  $^{99m}\text{Tc}$  HMPAO SPECT revealed normalized tracer accumulation in the area (Fig. 2d and i). MET PET (Fig. 2e and j) also showed normalized methionine uptake in the right hemisphere with lesion-to-contralateral ratio decreased to 1.01. She was discharged from our hospital soon after the PET scanning.

## **Discussion**

Consciousness disturbance, vomiting, positive inflammatory reaction, broad high signal on FLAIR image, and slow waves on electroencephalogram indicated inflammation in the central nervous system. Meningitis was less likely because of absence of severe headache and presence of coma, while encephalitis was compatible for these findings. Multiple sclerosis and acute disseminated encephalomyelitis are also

inflammatory diseases causing symptoms as seen in this case. However, these diseases were less likely because these demyelinating diseases preferably invade white matter with multiple lesions. To further confirm the diagnosis of encephalitis, we performed  $^{99m}\text{Tc}$  HMPAO SPECT on day 7, which showed high uptake in broad right cerebral hemisphere. Hyperfixation of  $^{99m}\text{Tc}$  HMPAO can be seen in encephalitis, luxury perfusion after cerebral infarction, and ictal seizure (7). Cerebral infarction was possible at first in this case; however, it was eventually denied because abnormal signals of MR FLAIR imaging and DWI disappeared. Because the patient did not present with epileptic attack, uptake due to ictal seizure was ruled out. Thus, we concluded that encephalitis was the most probable diagnosis. To distinguish viral from bacterial infection, we performed cerebrospinal fluid examination revealing slightly increased cellular count and slightly high glucose level. Such a finding can be seen in viral encephalitis but not often seen in bacterial encephalitis, which are characterized with markedly proliferated cells and reduced glucose. In this case, pathogen agents were detected in neither peripheral blood nor CSF. Therefore, we could not completely rule out bacterial origin and administered both antiviral and antibacterial agents.

MET PET has been applied in neurooncology over the last decade and reported



to be useful for differential diagnosis of malignant tumors from benign lesions (4, 8-12). Although MET shows relatively low uptake in inflammatory lesions (13), there are studies reporting MET accumulation in inflammatory brain lesions. Maeda *et al.* reported a patient with Rasmussen syndrome showing elevated MET uptake in the involved cerebral tissues (6). There are two reports of MET uptake in brain abscesses (5, 14). MET PET may detect inflammatory lesions because less amount of MET accumulates in the normal brain tissues. On the other hand, F-18 fluorodeoxyglucose, which strongly accumulates in inflammatory diseases of other organs, shows high physiological uptake also in normal brain tissues, resulting in low contrast of lesion with background.

The mechanism of MET accumulation in encephalitic lesions is considered to be increased density of inflammatory cells and activated transporter of amino acid (6). One may argue that MET PET reflects elevated blood flow demonstrated with HMPAO SPECT. Because we acquired the PET image later than 30 min after the injection, the uptake may represent cellular activity rather than blood flow. If the blood brain barrier (BBB) had been impaired, hyperpermeability could have contributed to elevated accumulation of MET. However, in this case, the lesion was not enhanced by

gadolinium in MR imaging, demonstrating intact BBB.

In conclusion, we observed high MET uptake in an active phase and normalized MET uptake in a cured phase, suggesting that MET PET can be useful to evaluate the activity of encephalitis. In the current case, MET PET, MR imaging and SPECT unfortunately was performed with time-lag; therefore, we cannot determine which examination was most accurate and most preceding. A prospective study comparing the diagnostic values of MR imaging, SPECT, and MET PET for monitoring encephalitis is worth performing.

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## Figure Legends

Fig. 1 In MR fluid attenuated inversion recovery (FLAIR) images, high signal intensity was observed in the right parietal, temporal, and occipital lobes (a and f). Diffusion weighted imaging (DWI) also showed high signal intensity in the lobes (b and g). Gadolinium enhancement was not observed (c and h).  $^{99m}\text{Tc}$  hexamethylpropyleneamine (HMPAO) single photon emission tomography (SPECT) revealed increased blood flow in the lesion (d and i). Positron emission tomography (PET), scanned 30 min after injection of 148 MBq  $^{11}\text{C}$  methionine (MET), demonstrated increased accumulation of MET in the corresponding area (e and j).

Fig 2. MR FLAIR (a and f) and DWI (b and g) showed normalized signal intensity in the right parietal, temporal, and occipital lobes. Gadolinium enhancement was absent (c and h).  $^{99m}\text{Tc}$  HMPAO SPECT showed no abnormal blood flow (d and i). In PET images scanned 45 min after injection of 336 MBq MET, the abnormal uptake previously observed was normalized (e and j).

Fig. 1

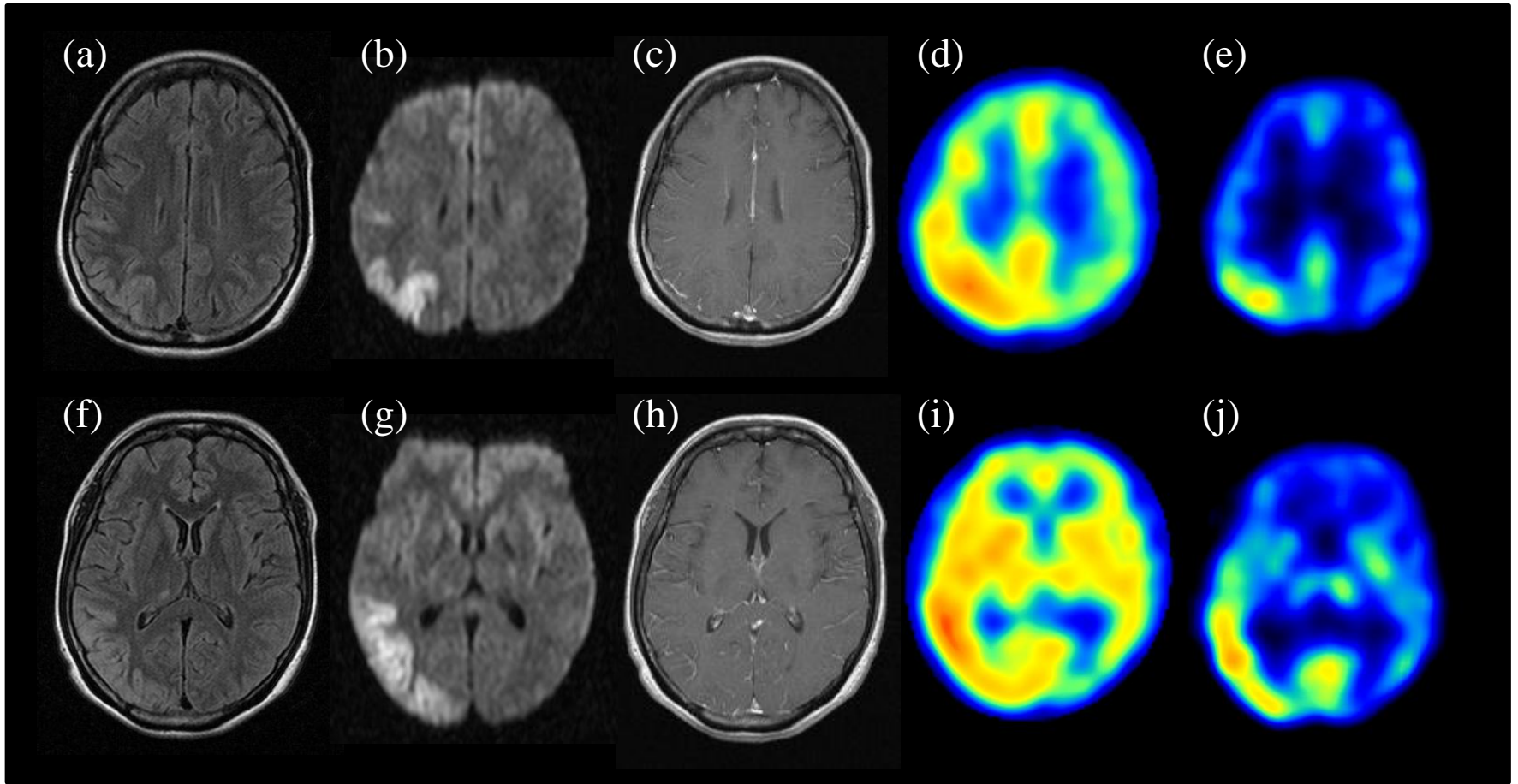


Fig. 2

