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Usefulness of [^{18}F]FDG-PET kinetic analysis in non-enhancing primary central nervous system lymphoma: Case report

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A 62-year-old woman experienced headache and rapidly progressive left hemiparesis over 2 weeks. Diffusion-weighted and fluid-attenuated inversion recovery MR images of the head showed increased signal intensity in the right basal ganglia, periventricular white matter and the brain stem. Enhancement was not observed on a T1-weighted spin-echo MR image after the administration of a contrast material. An ^{18}F-fluorodeoxyglucose positron emission tomography ([^{18}F]FDG-PET) study with kinetic analysis showed decreased FDG transport and increased hexokinase activity in the lesions compared with the contralateral hemisphere. The diagnosis was made by biopsy of the right caudate head and pathologic specimens were positive for malignant large-cell lymphoma, B-cell phenotype. The patient received high-dose methotrexate with CHOP chemotherapy, and an [^{18}F]FDG-PET study with kinetic analysis showed decreased hexokinase activity after the first chemotherapy. Kinetic [^{18}F]FDG-PET analysis may be useful to diagnose and monitor the treatment effect in non-enhancing primary central nervous system lymphoma.

Key words: glucose transport, hexokinase, magnetic resonance imaging, PET (positron emission tomography, primary central nervous system lymphoma

INTRODUCTION

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL) has a characteristic dense and homogeneous enhancement pattern on magnetic resonance images (MRI) in the vast majority of immunocompetent patients,[1–3] while immunocompromised patients have variable MRI findings.[2,4] Non-enhancing PCNSL is rare.[2,5–7] We recently encountered a PCNSL patient who showed increased signal intensity in the basal ganglia, periventricular white matter of the right hemisphere and the brain stem without any enhancement effect by contrast material. ^{18}F-fluorodeoxyglucose positron emission tomography ([^{18}F]FDG-PET) is a useful tool to diagnose PCNSL showing a huge accumulation of FDG on the tumor.[8,9] However, our PCNSL patient did not display a significant increase in FDG uptake compared with the contralateral brain. Because of the lack of contrast enhancement and apparent increase in FDG uptake, it was difficult to make a correct diagnosis before biopsy. With human [^{18}F]FDG-PET studies, dynamic image acquisition separates regional FDG uptake into FDG transport and phosphorylation (hexokinase) activity[10] (Fig. 1). In our case, the [^{18}F]FDG-PET study with kinetic analysis showed decreased FDG transport and increased hexokinase activity in the lesions compared with the contralateral brain. The analysis suggested that FDG metabolism was accelerated in a situation of decreased FDG movement into the tumor. The transporter activity increased and hexokinase activity decreased after the chemotherapy. This report proposes the usefulness of the [^{18}F]FDG-PET kinetic analysis in unusual non-enhancing PCNSL.

CASE REPORT

A 62-year-old woman in previously good health suffered from a few weeks' history of mild headache. On the day of presentation to a neurosurgical clinic, she presented no focal neurological deficits but MRI revealed increased signal intensity in the basal ganglia, periventricular white matter of the right hemisphere and the brain stem on

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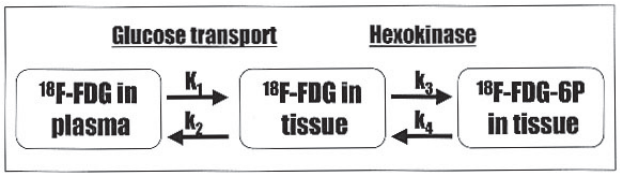

Fig. 1 Schematic expression of a 3-compartment model for ^{18}F-FDG kinetics. 6P = 6-phosphate.

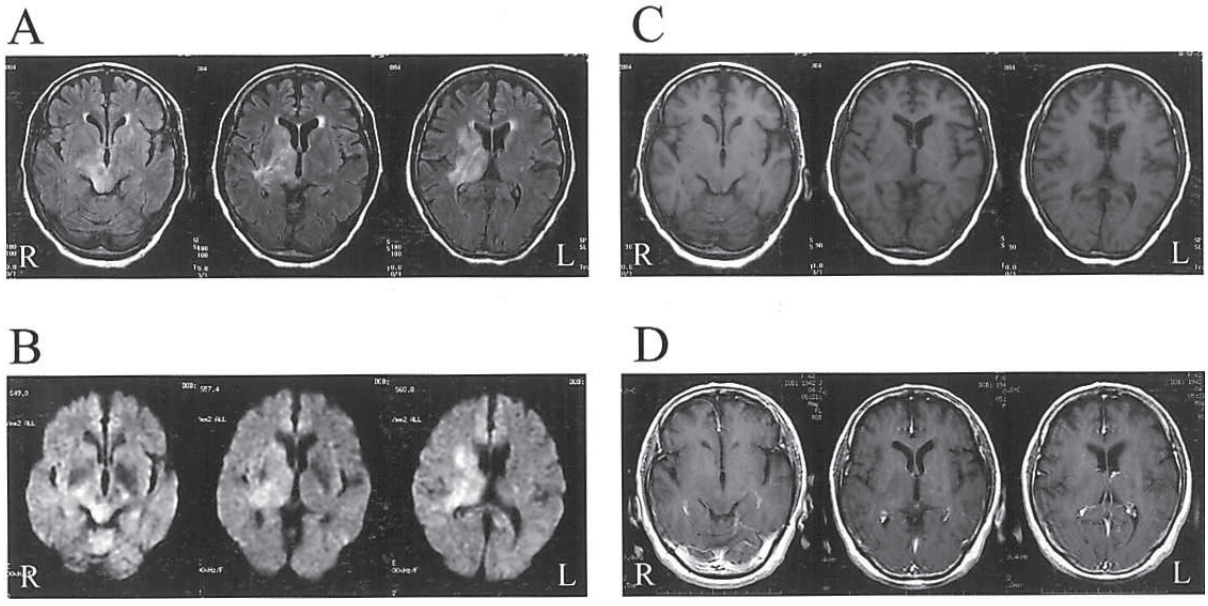

Fig. 2 MRI on the day of presentation to a neurosurgical clinic. Fluid-attenuated inversion recovery (FLAIR) (A) and diffusion-weighted images (DWI) (B) showed high-intensity areas in the right basal ganglia (thalamus and caudate head), periventricular white matter and brain stem (midbrain). The lesions were isointense or of low intensity on T1-weighted spin-echo images (C) and showed no enhancement effect after gadolinium administration (D).

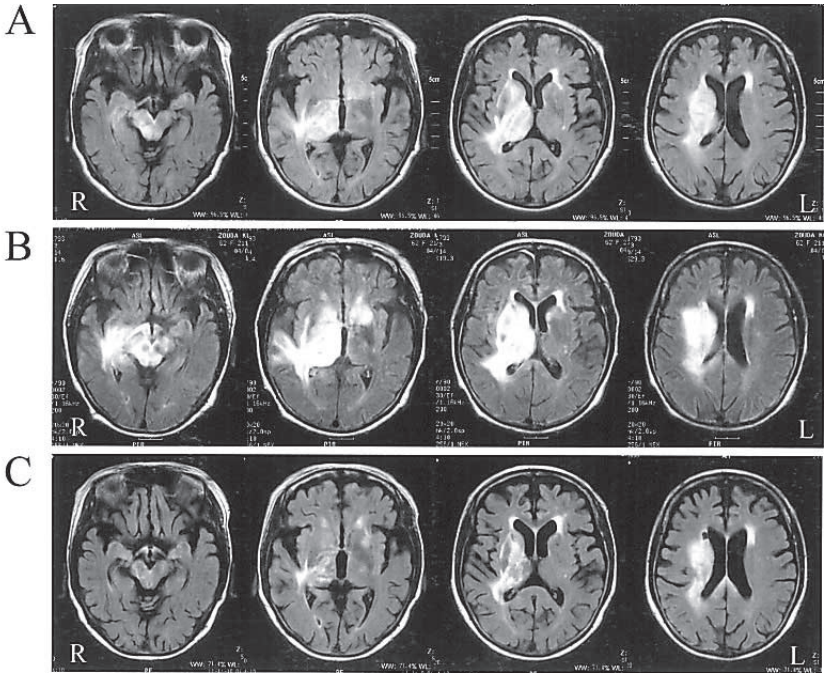

Fig. 3 MRI on admission to our department. FLAIR images showed high-intensity areas in the right basal ganglia, periventricular white matter and brain stem, which were similar to those obtained at the previous neurosurgical clinic (A). Two weeks later, FLAIR images demonstrated enlargement of the high-signal lesions (B). After the first course of chemotherapy, FLAIR images showed reduction of the lesions (C). These changes were well associated with her neurological findings.

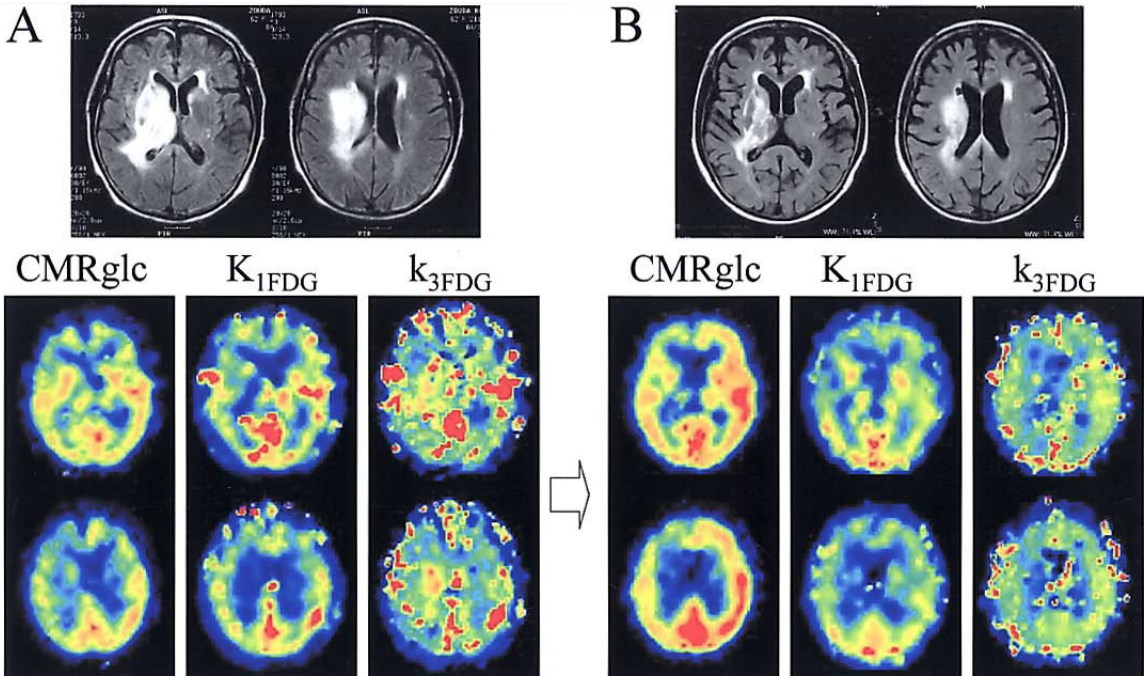

Fig. 4 [^{18}F]FDG-PET kinetic analysis before (A) and after (B) the treatment with high-dose methotrexate in combination with CHOP chemotherapy. [^{18}F]FDG-PET images displayed an insignificant increase in FDG uptake in the lesions compared with the contralateral brain. Kinetic analysis of this scan showed decreased FDG transport (K_1) and increased hexokinase activity (k_3) in the lesions compared with the contralateral brain. After the first chemotherapy, [^{18}F]FDG-PET study showed decreased FDG uptake in the lesions compared with that obtained before the chemotherapy and kinetic analysis of this study revealed increased FDG transport (K_1) and decreased hexokinase activity (k_3) compared with those obtained before the chemotherapy.

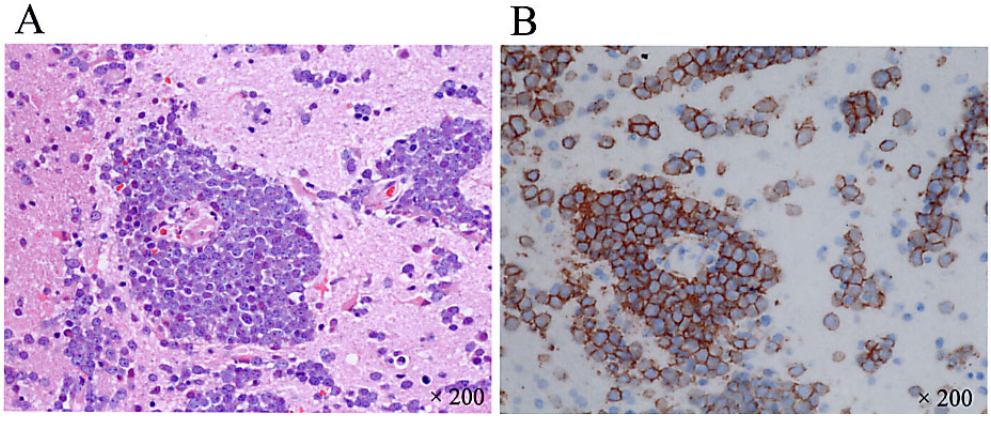

Fig. 5 Pathological findings. (A) Section of biopsy showed typical appearance of PCNSL with angiocentric collection of atypical lymphoid cells infiltrating the surrounding brain parenchyma. HE. (B) Section of the tumor immunostained with a B-cell marker (CD20) showed prominent immunoreactivity of tumor cells.

fluid-attenuated inversion recovery (FLAIR) (Fig. 2A) and diffusion-weighted images (DWI) (Fig. 2B). The lesions gave nonspecific signal change on T1-weighted spin-echo images without mass effect (Fig. 2C). T1-weighted spin-echo images after intravenous Gd-DTPA (0.1 mmol/kg body weight) showed no enhancement effect of the lesions (Fig. 2D). Corticosteroid pulse treatment (1 g of methylpredonisolone for 3 days) was

conducted for suspected encephalitis or vasculitis, but the MRI findings did not improve after the treatment (Fig. 3A). Two weeks later, she developed left hemiparesis and was then referred to our hospital for further examination and treatment. At the time of admission, she had mild cognitive dysfunction and left hemiparesis (MMT 4/5). The tumor markers were negative for the cause of brain metastasis. Raised lymphoma markers including serum LDH (393 U/*l*, normal range 110–220) and soluble IL-2 receptor (841 U/*l*, normal range 135–483) were observed. Her hemiparesis continued to worsen over the next 2 weeks and MRI showed enlargement of the lesions on the FLAIR image (Fig. 3B). Again T1-weighted spin-echo images after intravenous Gd-DTPA showed no enhancement of the lesions at this time. A PET study with [^{18}F]FDG was obtained on day 14 of hospitalization (Fig. 4A). Enteral and parenteral sources of glucose were withheld for 6 hours before the PET examination. A 60-minute dynamic PET scan (40 seconds × 1; 20 seconds × 2; 40 seconds × 4; 60 seconds × 4; 180 seconds × 4; 300 seconds × 8) was performed using a Siemens EXACT HR+ PET scanner after an intravenous injection of [^{18}F]FDG at a dose of 153 MBq. Arterial blood samples were withdrawn from the brachial artery at 15-second intervals for the first 3 minutes, followed by increasingly longer intervals to 60 minutes, to measure arterial plasma radioactivity using an auto well gamma counter (ARC-400, Aloka, Tokyo, Japan). The blood sample obtained at 30 minutes after the injection was analyzed for blood glucose concentration and was within the normal range (101 mg/d*l*). The [^{18}F]FDG-PET images did not display a significant increase in FDG uptake in the lesions compared with the contralateral brain (ipsilateral; CMRglc 39.4 μmol/min/100 g vs. contralateral; CMRglc 35.1 μmol/min/100 g). Kinetic evaluation of this scan showed decreased FDG transport (ipsilateral; K_1 0.048 m*l*/min vs. contralateral; K_1 0.073 m*l*/min) and increased hexokinase activity (ipsilateral; k_3 0.075 min^{-1} vs. contralateral; k_3 0.049 min^{-1}) in the lesions compared with the contralateral brain (Fig. 4A). Biopsy of the right caudate head revealed malignant lymphoma of diffuse, large B-cell type (Fig. 5). A high-dose of methotrexate (3.5 g/m^2) in combination with CHOP (cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and predonisolone) chemotherapy was administrated. Her neurological findings gradually recovered after the first chemotherapy and MRI showed improvement of the lesions on the FLAIR images (Fig. 3C). An [^{18}F]FDG-PET study after the first chemotherapy showed decreased FDG uptake in the lesions compared with that obtained before the chemotherapy (CMRglc 39.4→30.4 μmol/min/100 g) (Fig. 4B). Kinetic analysis of the second study revealed increased transporter activity and decreased hexokinase activity as compared with before the chemotherapy (Fig. 4B).

DISCUSSION

Non-enhancing PCNSL

Primary central nervous system lymphoma (PCNSL) has a characteristic dense and homogenous enhancement pattern on magnetic resonance images (MRI) in >90% of patients, which may suggest the diagnosis even before histological confirmation.[1–3] In unusual cases, however, PCNSL may be non-enhancing.[2,5–7] Lack of enhancement can be explained in some cases by previous corticosteroid treatment,[2,6] but it has also been described before treatment[6] and often results in the delay of correct diagnosis of this disease. The MRI differential diagnosis in our case includes vasculitis, toxic-metabolic disorders, encephalitis, demyelinating disease and gliomatosis cerebri. None of these diseases can be ruled out from the MRI findings alone.

FDG-PET in PCNSL

Physiological or biochemical alterations of brain tumors, which distinguish neoplastic tissue from normal brain, allow visualizing the tumor with PET using a radiolabeled tumor tracer. Fluorodeoxyglucose (FDG) is a glucose analogue, which is taken up rapidly and metabolized intensely by most neoplastic cells. [^{18}F]FDG-PET has been used as a promising tool to diagnose PCNSL because the tumor has very high cellular density with an accelerated glycolytic metabolism, and therefore shows a huge concentration of FDG, superior not only to normal brain tissue but also high-grade gliomas.[8,9] However, the present PCNSL case did not show a significant increase in FDG uptake in the lesions compared with the surrounding or contralateral brain. One of the reasons for the lack of increased FDG uptake in the present case is steroid therapy, because the patient had received high dose methylpredonisolone therapy approximately one month before the PET examination. Rosenfeld et al. reported a case in which steroid therapy for PCNSL erased the abnormal FDG accumulation and contrast enhancement of the tumor.[9] Although patients with PCNSL commonly show a dramatic clinical improvement with rapid resolution of the tumor after corticosteroid administration,[11] the present patient deteriorated and the MRI findings worsened after the steroid therapy. Therefore, it was unlikely that corticosteroid therapy in this patient suppressed the uptake of FDG.

FDG-PET kinetic analysis

For the exact interpretation of tumor tracer uptake, it is necessary to determine whether the changes are related to tracer transport and metabolism. With human [^{18}F]FDG-PET studies, dynamic image acquisition (measuring the rate of accumulation of [^{18}F]FDG in the brain over time) allows modeling of regional FDG transport and phosphorylation rates.[10] The model separates FDG uptake into 2 compartments with flux rates characterized by kinetic

parameters (K_1, k_2, k_3, k_4), as shown in Figure 1. In this model, the movement of FDG from the plasma to the tissue compartment represents primarily the BBB-related transport of FDG and thus reflects the activity of the glucose transporter (K_1). It may be argued that the application of this model to brain tumor is not valid because this model of FDG kinetics and interpretation is originally based upon healthy cerebral tissue. For example, the K_1 may also include extravasation of the tracer into the extracellular space through the disrupted BBB in the tumor. The K_1 (0.077 ± 0.013 m*l*/min) value in the tumor in 6 well-enhancing PCNSL patients (unpublished data) was lower than that observed in the normal human gray matter (0.102 ± 0.028 m*l*/min).[10] On the other hand, the CMRglc (78.2 ± 18.4 μmol/min/100 g) and the k_3 values (0.094 ± 0.023 min^{-1}) in the tumor in 6 well-enhancing PCNSL patients (unpublished data) were higher, than those observed in the normal human gray matter (CMRglc: 40.6 ± 6.6 μmol/min/100 g and k_3: 0.062 ± 0.019 min^{-1}).[10] These results suggest that the increased FDG phosphorylation rather than the increased FDG transport and extravasation are the mechanisms responsible for the high degree of FDG uptake in typical PCNSL. In the present non-enhancing PCNSL case, the [^{18}F]FDG-PET study with kinetic analysis showed a decreased K_1 value and increased k_3 value in the lesions compared with the contralateral brain. Although the k_3 value of the present case (0.075 min^{-1}) was slightly lower than that observed in well-enhancing PCNSL (0.094 min^{-1}), the calculated value of CMRglc is markedly increased if the K_1 value of the tumor is comparable to that in well-enhancing PCNSL. It has not been examined whether the FDG transport is decreased or not in non-enhancing PCNSL. It is conceivable that the extravasation of FDG into the tumor through the BBB is theoretically small in non-enhancing PCNSL, resulting in a net decrease in the K_1 value. The [^{18}F]FDG-PET kinetic study after the first chemotherapy showed decreased FDG uptake in the lesions concomitant with increased transporter activity and decreased hexokinase activity compared with those obtained before the chemotherapy. These changes were well associated with clinical recovery and improvement of the MRI abnormality. In conclusion, further experiences are necessary to determine the ultimate value of an [^{18}F]FDG-PET kinetic study, and this analysis may be useful to diagnose and monitor the treatment effect in unusual non-enhancing PCNSL.

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