PET Study of Striatal Fluorodopa Uptake and Dopamine D2 Receptor Binding in a Patient with Juvenile Parkinsonism

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Introduction

Juvenile parkinsonism (JP), dopa-responsive dystonia (DRD) and hereditary progressive dystonia with marked diurnal fluctuation (HPD) are all major syndromes which are characterized both by parkinsonism and dystonia in the early decades of life and by good response to L-dopa treatment. Although the clinical entity and pathomechanism of the disorder and their relationship have been discussed in the past at great length, it still difficult to differentiate clinically JP from DRD or HPD. Positron emission tomographic (PET) study using [^{18}F]6-fluorodopa (^{18}FDOPA) has been able to provide efficient information on the pre-synaptic function of nigrostriatal dopaminergic neurons in patients with parkinsonism or dystonia[1-10]. Furthermore, it is known that the PET study of the post-synaptic D2 receptor function using ^{11}C-YM-09151-2 (^{11}C-YM), N-[(2RS, 3RS)-1-benzyl-2-methyl-3-pyrrolidinyl]-5-chloro-2-methoxy-4-methylaminobenzamide, a highly selective antagonist to the brain dopamine D2 receptor, can be very informative [11-14], as regards the pathomechanism of these L-dopa responsive disorders. Of particular importance is information on striatal fluorodopa uptake and dopamine D2 receptor binding. We report here on the neuroimaging data of these, and on the cerebral glucose metabolism, in a patient with JP.

Patient and Methods

PATIENT

A 17-year-old girl had an uneventful birth and normal growth until 7 years of age. There was no significant family history except consanguinity on her mother's side. At age 8, she noted abnormal gait; she always walked on tiptoe except when stationary. Her gait became gradually worse, and she developed a tendency to fall over backwards. At age 9, she received treatment with L-dopa and muscle relaxants. After medication, her general condition improved appreciably, and she became able to walk more comfortably. Unfortunately, her gait became gradually worse again, particularly when she walked long distance. At age 12,

she complained of clumsiness in upper limbs, and these symptoms started to fluctuate. At age 15, she had to take greater dose of L-dopa, and involuntary movement began to appear in her legs.

On admission, she was a well-developed and well-nourished girl, 152 cm in height and 45 kg in weight. She was alert and well-oriented. Neurological examination revealed marked akinesia and rigidity in all four limbs, especially the upper ones. There was mild postural tremor in the upper limbs and prominent dystonia in the lower. These findings almost improved by L-dopa treatment. Although diurnal fluctuation of the symptoms was uncertain, marked improvement was seen after sleep. Although wearing-off and on-off phenomena were also uncertain, involuntary movement suspected dopa-induced dyskinesia was seen in her legs. Based on these clinical features, she was diagnosed as JP with dystonia.

Routine blood tests and cerebrospinal fluid examination were normal, as were serum ceruloplasmin and copper levels. Magnetic resonance imaging (MRI) was normal in the cerebral hemispheres, basal ganglia, cerebellum and brainstem.

PET STUDIES AND DATA ANALYSIS

PET studies of fluorodopa uptake and glucose metabolism were performed with a model PT-931 scanner (CTI Inc., USA), and the study of dopamine D2 receptor was performed with a model SET-2400W scanner (Shimazu, Japan), at the Cyclotron and Radioisotope Center, Tohoku University, Sendai, Japan. These studies were approved by the Research Ethics Committee of Tohoku University School of Medicine. Informed consent was obtained from the patient and her parents. The patient's head was positioned in the scanner with her eyes closed, and the whole procedure was performed in a semi-darkened room with minimal background noise. Before the emission scan, a 15-min ^{68}Ge-^{68}Ga transmission scan was performed.

In the study of fluorodopa uptake, ^{18}FDOPA was synthesized as descrived by Adam et al[15] with a radiochemical purity of more than 99%. After an intravenous bolus injection of ^{18}FDOPA (7.7 mCi) into the patient, a series of 5 min emission scans was performed over 60 min, and emission data were simultaneously collected from seven contiguous axial sections, each about 6 mm in thickness from orbitomeatal (OM) line + 66 to OM + 22 mm. After data collection, the latter six continuous images of the same brain slices, scanned between 30 and 60 min after administration of ^{18}FDOPA, were added and composite images were obtained in order to improve the contrast between dopaminergic and nondopaminergic brain regions, in order to aid the definition of anatomical regions of interest according to the method of Nagasawa et al[4]. Moreover, the ^{18}FDOPA uptake rate constant was calculated pixel-by-pixel utilizing the Patlak graphical analysis method[16,17] to generate the parametric image for the image plane that had the highest contrast between the striatum and background. In this

analysis, the input function was the dynamic image pixel values of the cerebellum as a reference tissue region which was devoid of dopaminergic terminals.

In the study of dopamine D2 receptor, ^{11}C-YM was synthesized according to the method of Hatano et al[13]. After an intravenous bolus injection of ^{11}C-YM (3.06 mCi), twenty emission scans were performed in series over 90 min using a SET-2400W. After data collection, the latter five continuous images of the same brain slices scanned between 60 and 90 min after administration of ^{11}C-YM were added and composite images were obtained in order to improve the contrast between dopaminergic and nondopaminergic brain regions.

In the study of glucose metabolism, ^{18}FDG was synthesized according to the method of Ido et al[18]. ^{18}FDG (5.3 mCi) was injected as an intravenous bolus. 30 to 60 min after the injection, a series of three emission scans, each of 10 min duration, was performed at standard points 16, 63 and 110 mm above and parallel to the OM line. Each emission data was simultaneously collected from seven contiguous axial sections. A total of 21 slices parallel to the OM line with a slice thickness of 6 mm were analyzed. Twenty blood samples were collected from the brachial artery during the study, and they were immediately centrifuged, and the arterial plasma radioactivities of ^{18}FDG were measured with a cross-calibrated well- counter. The cerebral metabolic rate for glucose (CMRGlc) was calculated using the operational equation derived by Phelps et al[19] and Huang et al[20] from that of Sokoloff et al[21].

Results

PET images of three contiguous axial sections added between 30 and 60 min after administration of ^{18}FDOPA and images of ^{18}FDOPA uptake rate constant, of a young normal subject (33-year-old male) are shown in Fig 1 A and B. High concentration of ^{18}FDOPA and its labeled metabolites and high value of ^{18}FDOPA uptake rate constant in the bilateral striata are clearly visible. On the other hand, for this patient diagnosed as JP, ^{18}FDOPA accumulation and its uptake rate constant were markedly decreased in the putamen on both hemispheres. ^{18}FDOPA uptake was preserved only in the bilateral lower parts of the caudate nucleus. (Fig 2 A and B).

There was a high accumulation of ^{11}C-YM in the caudate nucleus and the putamen on both hemispheres (Fig 3), which indicated no decrease of dopamine D2 receptor binding in the striatum of this patient.

The CMRGlc was almost normal in the whole brain including both basal ganglia without asymmetry in this patient (Fig 4).

Discussion

The clinical entities or nosological concepts of JP, DRD and HPD and the relationship of these disorders have been controversial[7-10,22-28]. Yokochi[27] suggests that"dopa-responsive syndrome" may be divided into two groups; one is "dopa-responsive disease characterized by

dystonia" and the other is "dopa-responsive disease characterized by parkinsonism". The former included DRD and HPD and the latter included JP and Parkinson's disease. However, there are some difficulties in clinically differentiating JP from DRD or HPD.

In comparison with Parkinson's disease, JP is clinically characterized as follows: there is a much higher familial incidence; disease progression is much slower; more cases lack tremor, which, if it exists, occurs mostly in posture or in action, but not at rest; dystonic movements are observed more often, especially in cases of onset at an early age; more effective responses to L -dopa are observed; adverse effects such as wearing-off phenomenon and dopa-induced dyskinesia sometimes appear in the extremities[27)]

The present case has no family history of parkinsonism. Initially she noted gait disturbance due to dystonia of the legs at 8 years of age, and its symptoms were slowly progressive and developed parkinsonism with postural tremor. The clinical effect of L-dopa was remarkable. Wearing-off or on-off phenomenon was not obviously observed. However, dopa-induced dyskinesia was seen in the legs. Diurnal fluctuation was uncertain, but her symptoms improved after sleep. Based on these clinical features, JP is probably the most appropriate as diagnosis. However, it remains difficult to differentiate her condition clearly from DRD or HPD.

There have been several reports on PET studies using ^{18}FDOPA in patients with DRD [6-8,10)]. Nygaard et al[7)], Takahashi et al[8)] and Snow et al[10)] reported normal striatal ^{18}FDOPA uptake in DRD patients. Sawle et al[6)] described that modest reduction of ^{18}FDOPA uptake was observed in the striatum of 6 patients with typical DRD, but such a finding was not as evident as that observed in Parkinson's disease. Okada et al[9)] reported a Japanese patient with HPD, so-called "Segawa's disease", studied by PET using ^{18}FDOPA. They observed no significant difference in ^{18}FDOPA uptake into the striatum of the patient compared with age matched controls. On the other hand, Snow et al[10)] reported marked decrease of ^{18}FDOPA uptake into the striatum in three patients with JP who were under 20 years of age.

The PET study using ^{18}FDOPA in the present case shows marked decrease of ^{18}FDOPA uptake into both putamen and caudate nucleus compared with the control case. This finding is different from those in patients with dystonia syndromes such as DRD and HPD, and it is rather similar to Parkinson's disease. Therefore, we diagnosed this patient as JP with conviction on the basis of her clinical features and the result of ^{18}FDOPA PET study.

Fluorodopa is metabolised to fluorodopamine by L-aromatic amino acid decarboxylase, and this enzyme is located primarily within the nigrostriatal nerve endings in the striatum. We consider that the accumulation of ^{18}FDOPA in striatum provides an index of the pre-synaptic function of the dopaminergic pathway. The decrease of the striatal ^{18}FDOPA uptake in this patient may indicate a defect in the decarboxylation, disturbance of vesicular uptake and decreased capasity for storage of ^{18}FDOPA. It may also indicate neuronal loss in the substantia nigra, findings which may be similar to pathogenesis observed in Parkinson's disease.

On the other hand, there have been few reports about dopamine D2 receptor in JP. In Parkinson's disease, it has been described that striatal dopamine D2 receptor binding was raised in untreated patients at an early stage, but reduced in chronically treated patients with fluctuating response to L-dopa at an advanced stage, by PET studies[29-34] or post-mortem studies[35,36]. In this patient with JP, ^{11}C-YM was highly accumulated in the striatum, which indicates no decrease of dopamine D2 receptor binding. It suggests that the post-synaptic D2 receptor function in the striatum is almost normal in this patient with JP.

Also there have been few reports about cerebral glucose metabolism in JP. However, in Parkinson's disease, some PET studies[37,38] have demonstrated the diffuse and mild decrease of cerebral glucose metabolism, whereas others[39] have described these as normal in the patient without dementia. Especially in Parkinson's disease with dementia, severe hypometabolism in the temporoparietal cortex, which is similar to that seen in Alzheimer's disease, has also been described[37,38]. In this patient with JP, the CMRGlc did not decrease in the whole cerebrum. This suggests that there is no marked morphological changes with loss of synapses due to decreased numbers of cortical neurons or degeneration of axons.

A PET study measuring striatal fluorodopa uptake is essential for the diagnosis of JP, as well as for distinguishing from DRD and HPD. This is the first report to have performed three types of PET study, involving fluorodopa uptake, dopamine D2 receptor binding and glucose metabolism, in a JP patient. Such studies can provide efficient information about the pathomechanism of JP.

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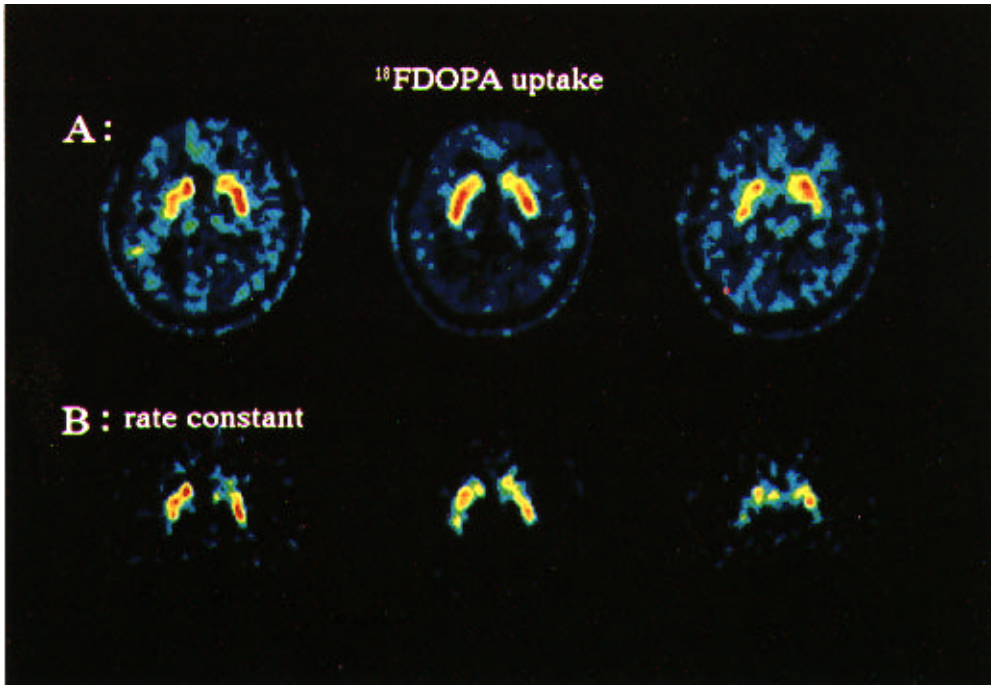

Figure 1. PET images of three contiguous axial sections added between 30 and 60 min after administration of ^{18}FDOPA (A), and parametric images (Patlak Image) of the ^{18}FDOPA uptake rate constant (B), of a young normal subject. High concentration of ^{18}FDOPA and its labeled metabolites and high value of ^{18}FDOPA uptake rate constant in the bilateral striata were clearly visible.

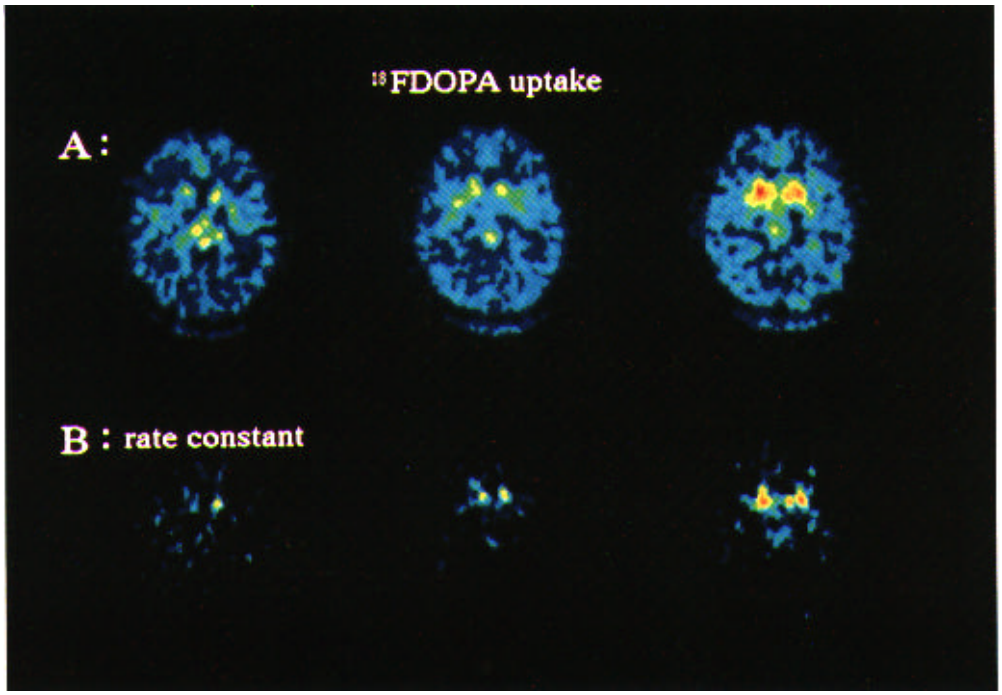

Figure 2. PET images of three contiguous axial sections added between 30 and 60 min after administration of ^{18}FDOPA (A), and parametric images (Patlak Image) of the ^{18}FDOPA uptake rate constant (B), of this patient with JP. ^{18}FDOPA accumulation and its uptake rate constant were markedly decreased in the putamen on both hemispheres. ^{18}FDOPA uptake was preserved only in the bilateral lower parts of the caudate nucleus.

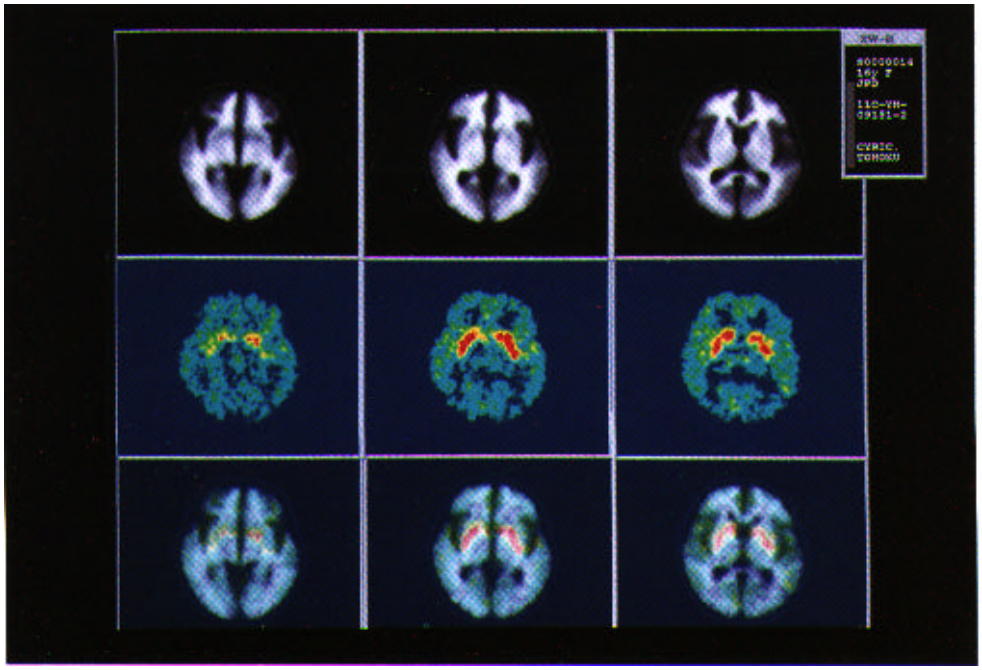

Figure 3. Aligned MR images, PET images added between 60 and 90 min after administration of ^{11}C-YM and the overlapped images at the same brain slices, of this patient with JP. ^{11}C-YM was highly accumulated in the caudate nucleus and the putamen on both hemispheres, which indicated no decrease of dopamine D2 receptor binding in the striatum.

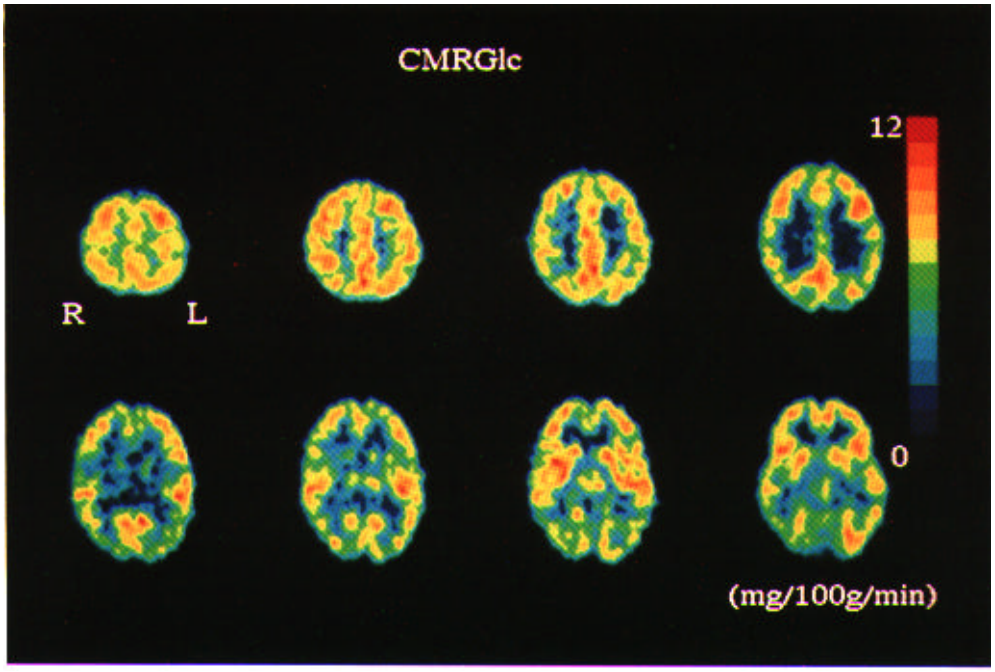

Figure 4. PET images of cerebral metabolic rate for glucose (CMRGlc) of this patient with JP. The CMRGlc was almost normal in the whole cerebrum including both basal ganglia without difference between right and left.