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Introduction

It is not easy to achieve a definite clinical diagnosis for juvenile parkinsonism (JP) distinguishing from dopa-responsive dystonia (DRD) or hereditary progressive dystonia with diurnal fluctuation (HPD). A clinical entity of individual disorder or relationships between them have been often discussed. Positron emission tomography (PET) with [^{18}F]6-fluoro-L-dopa (FDOPA) can provide an efficient information on the presynaptic function of nigrostriatal dopaminergic neurons in patients with parkinsonism or dystonia[1-8]. We measured dopamine metabolism in a patient with both parkinsonism and dystonia. Her clinical symptoms were characterized by early onset in childhood and good response to L-dopa treatment. However, brain dopamine metabolism in this case was quite different from those in patients with DRD or HPD reported previously[6-8]. In the present study, we discuss the differential diagnosis in this case from a viewpoint of dysfunction of dopamine metabolism measured by PET using FDOPA.

Patient and Methods

PATIENT

A 16-year-old girl had an uneventful birth and a normal course of growth and development during the first 7 years of life. At 8 years of age, she was pointed out her abnormal gait, which was always on tiptoe except when she stopped. Her gait became worse gradually with tending to fall backward. At age 9 years, she was diagnosed as spastic paraparesis and received treatment with L-dopa and muscle relaxants. After medication her general condition became rapidly well. Marked improvement was noted in gait and she walked more comfortably. However, her gait became worse gradually again, when she walked a long distance. After 12 years of age, her symptoms started to fluctuate. She complained clumsiness in upper limbs when her general condition was worse. At age 15 years, she took more increased dose of L-dopa but the drug response became poor. Moreover, involuntary movement also appeared in her legs.

On examination, 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 severe akinesia, severe rigidity in all limbs (especially cog-wheel type in upper limbs), mild postural tremor in upper limbs, and severe dystonia in lower limbs. These findings almost became improved by L-dopa (500 mg/day). Diurnal fluctuation of her symptoms was uncertain, but improvement was seen with her sleep. Although wearing-off and on-off phenomena were also uncertain, involuntary movement which was suspected of dopa induced dyskinesia was seen in her legs.

There was no significant family history except consanguinity on her mother's side.

Blood tests and routine cerebrospinal fluid examination were normal. Magnetic resonance imaging (MRI) of the brain was also normal.

Positron Emission Tomography (PET)

[^{18}F]FDOPA scans were performed on a scanner, PT-931 (CTI Inc.,USA), at the Cyclotron and Radioisotope Center, Tohoku University, Sendai. Japan. This study was approved by the Research Ethics Committee of the Tohoku University, School of Medicine. The patient gave her written informed consent after a full explanation of the procedure. The patient was positioned in the scanner. with the orbitomeatal (OM) line parallel to the detector rings according to the brain slice by MRI. A cross of light was projected onto mark on the patient's head from three dimensions, and the head was positioned at 40 mm above and parallel to the OM line. All the procedure was performed in a semidarkened room. The patient's eyes were closed during PET study.

A 15-min transmission scan was collected using a retractable germanium 68-gallium 68 ring source. [^{18}F]FDOPA was synthesized as described by Adam et al.[9] with a radiochemical purity of more than 99 %. After an intravenous bolus injection of FDOPA (7.7mCi) into the patient, positron tomography was carried out using PT-931 with an 8 mm axial and transaxial resolution. 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 OM+66 to OM+22 mm.

Data Analysis

After data collection, the latter six continuous images of the same brain slises scanned between 30 and 60 min after administration of FDOPA were added and composite images were obtained in order to improve the contrast between dopaminergic and nondopaminergic brain regions to aid the definition of anatomical regions of interest according to the method of Nagasawa et al.[4]. MRI was examined in detail at the same head position as the PET study to obtain accurate overlays between the anatomic and functional image data. Two different images. the composite image and MRI, were registered and

matched using image scaling to bring the disparate pairs of image data into congruence at the level of the caudate nucleus and the putamen.

Results

Brain CT and PET slices at the level of the caudate nucleus and the putamen of a normal subject are shown in Fig.1. FDOPA and its labeled metabolites were highly concentrated in the caudate nucleus and the putamen of both hemispheres. On the contrary, in this patient, FDOPA accumulation was decreased markedly in the putamen of both hemispheres. FDOPA uptake was preserved only in the bilateral lower parts of the caudate nucleus.(Fig.2 and 3)

Discussion

Clinical entities of JP, DRD and HPD or relationships among these disorders have been discussed by many authors[7,8,10-16]. Moreover, nosological concepts of these disorders are often overlapped and are still controversial.

Yokochi[15] suggested the clinical entity of "dopa-responsive syndrome", which was divided into two groups; "dopa-responsive disease characterized by dystonia" and "dopa-responsive disease characterized by parkinsonism". The former included HPD and DRD and the latter included JP and Parkinson's disease. JP was further divided into two subgroups; "dystonia-parkinsonism syndrome" and "young onset Parkinson's disease (YOPD)".

The clinical characteristics of JP compared to Parkinson's disease are briefly given as follows; There is a much higher familial incidence. Progression is much slower and prognosis appears benign. Half of cases are rigid and bradykinetic type without tremor. If tremor exists, it occurs in posture or in action, but not at rest. Dystonic features are more often exhibited, especially in cases of much younger onset. Marked effective responses to L-dopa are observed. Adverse effects such as wearing-off phenomenon and dopa induced dyskinesia sometimes appear in the extremities.[15]

In the present case, there is no definite family history, and her initial symptom was gait disturbance due to dystonia of legs at age 8 years. That symptom was slowly progressive, and developed parkinsonism with postural tremor. L-dopa response was markedly remarkable, and wearing-off or on-off phenomenon was not obviously observed. However, involuntary movement of legs was seen, which was suspected of dopa induced dyskinesia. Diurnal fluctuation was uncertain, but her symptoms improved with sleep. Based on these clinical features, JP is probably most appropriate as diagnosis. However, it is difficult to differentiate her clinical symptoms clearly from those of DRD or HPD. We investigated FDOPA uptake into striatum of this patient using PET in order to obtain a further supportive evidence for the presumptive clinical diagnosis.

There have been several reports about PET study in patients with DRD[6,7]. Sawle et al.[6] described that modest but significant reduction of FDOPA uptake was observed in the caudate nucleus and the putamen of 6 patients with typical DRD, but such finding was not so much as that observed in Parkinson's disease. Takahashi et al.[7] reported normal FDOPA uptake into striatum in patients with DRD. Okada et al.[8] reported a Japanese patient with HPD, so called "Segawa's disease" , studied by PET using FDOPA. They observed no significant difference in the FDOPA uptake into both striata of a patient with HPD compared with age matched controls. Martin et al.[5] also described that, in patients with dystonia-parkinsonism, some patients reduced FDOPA uptake into the striata, but others preserved in normal ranges.

The PET study in the present case shows marked reduction of FDOPA uptake into both putamen and caudate nucleus compared with control. 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 on the basis of her clinical features and the result of PET study. We consider the present case may belong to group III or dystonia-parkinsonism syndrome according to the classificationin by Yokochi[10,15].

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

Base on the present study, the PET study measuring dopamine metabolism in the nigrostriatal system can provide efficient information about the dysfunctions which are correlated with clinical symptoms, and this study is essential to diagnosis of JP distinguishing from DRD and HPD.

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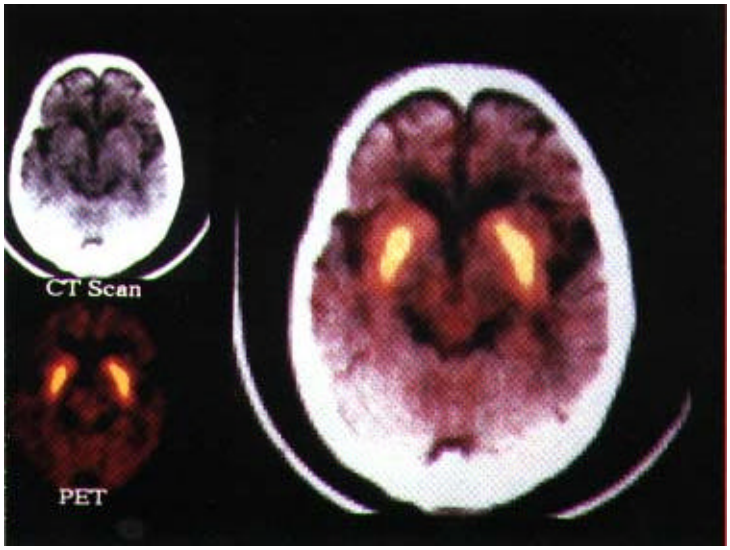

Fig. 1. Two different images obtained by [^{18}F]Fluorodopa (FDOPA) positron emission tomogrophy (PET) and computed tomography (CT) were overlapped at the level of the caudate nucleus and the putamen from a normal subject. FDOPA activity was symmetrically accumulated in the caudate nucleus and the putamen on both hemispheres.

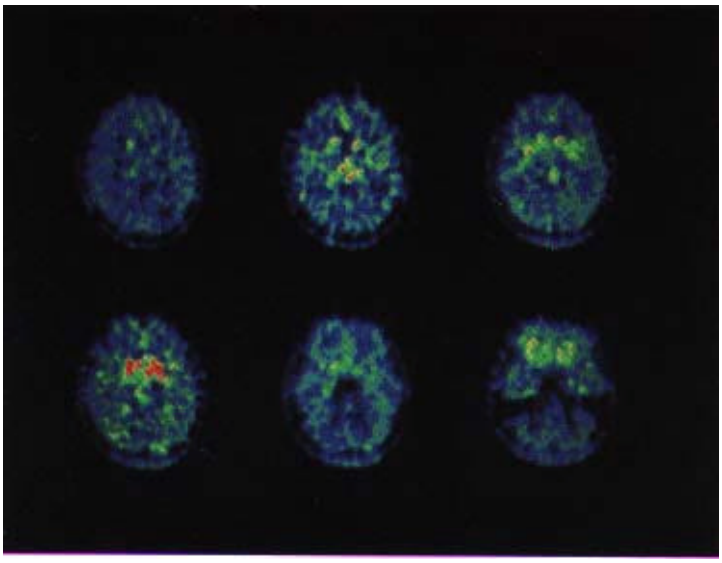

Fig. 2. PET images of six contiguous axial sections added between 30 and 60 min after administration of FDOPA. FDOPA accumulation was markedly decreased in the striata, except for the lower parts of the caudate nucleus on both hemispheres.

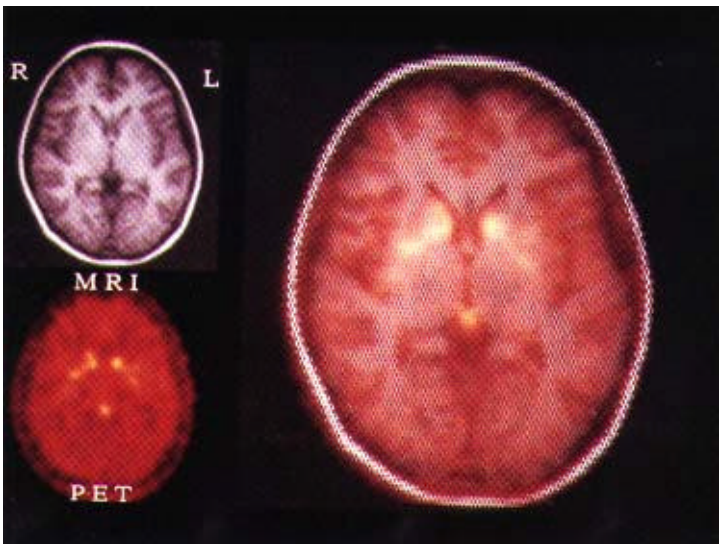

Fig. 3. Two different images obtained by FDOPA PET and magnetic resonance (MR) were overlapped at the level of the caudate nucleus and the putamen from this patient. FDOPA accumulation was obviously decreased in both striata.