Striatal blood flow, glucose metabolism and \(^{18}\text{F}-\text{Dopa}\) uptake: difference in Parkinson’s disease and atypical Parkinsonism

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**Abstract**

Striatal blood flow, glucose metabolism and \(^{18}\text{F}-\text{Dopa}\) uptake were studied in eight patients with idiopathic Parkinson’s disease and eight with atypical Parkinsonism. Patients with atypical Parkinsonism had no specific cause for the Parkinsonian symptoms and were clinically different from Parkinson’s disease with lack of resting tremor and a poor response to dopaminergic drugs. Decreased \(^{18}\text{F}-\text{Dopa}\) uptake in the putamen was observed in patients with Parkinson’s disease and atypical Parkinsonism compared with normal controls. \(^{18}\text{F}-\text{Dopa}\) uptake in the head of the caudate was also significantly reduced in both conditions but relatively less in Parkinson’s disease. Decreased blood flow and glucose metabolism in the striatum associated with a global cerebral decrease were also observed in patients with atypical Parkinsonism compared with controls, while they were preserved in patients with Parkinson’s disease, indicating affected neurons not only in the striatum but also in the cerebrum in patients with atypical Parkinsonism compared with patients with Parkinson’s disease. The differences in the caudate \(^{18}\text{F}-\text{Dopa}\) uptake, and blood flow and glucose metabolism in the cerebrum including the striatum between Parkinson’s disease and atypical Parkinsonism assessed by PET may be due to the differences in the pathophysiological mechanism between Parkinson’s disease and atypical Parkinsonism.

There are “atypical” Parkinsonian patients who do not have any specific causes for the Parkinsonian symptoms and are clinically different from idiopathic Parkinson’s disease based on the lack of resting tremor and poor response to dopaminergic drugs. The pure akinetic type has been considered to be a different clinical entity from idiopathic Parkinson’s disease by some investigators. Patients with atypical Parkinsonism may have the other brain lesions with or without striatal dopamine depletion and are poorly responsive to levodopa.

In Parkinson’s disease, regional cerebral glucose metabolism (rCMRGlc) measured with \(2-(\text{\textsuperscript{18}}\text{F})\text{-fluoro-2-deoxy-D-glucose}\) (\(\text{\textsuperscript{18}}\text{F}-\text{FDG}\)) have been surveyed by many investigators. Recently the levodopa analogue \(6-\text{L-fluorodopa}\) has been labelled with \(\text{\textsuperscript{18}}\text{F}\) and a decreased uptake of \(6-\text{L-(\text{\textsuperscript{18}}\text{F})fluorodopa}\) \(\text{(\text{\textsuperscript{18}}\text{F}-\text{Dopa})}\) in the striatum has revealed the loss of dopaminergic nerve terminals in patients with Parkinson’s disease in vivo. Furthermore, some studies have shown the difference of caudate \(\text{\textsuperscript{18}}\text{F}-\text{Dopa}\) uptake between Parkinson’s disease and atypical Parkinsonism. Few reports, however, are available on the combination of glucose metabolism and \(\text{\textsuperscript{18}}\text{F}-\text{Dopa}\) uptake in Parkinson’s disease and atypical Parkinsonism.

We studied blood flow and glucose metabolism in the head of the caudate and putamen separately for measuring the energy consumption as a whole in each region and \(\text{\textsuperscript{18}}\text{F}-\text{Dopa}\) uptake for measuring the function of dopaminergic nerve terminals in the head of the caudate and putamen in patients with Parkinson’s disease and atypical Parkinsonism to clarify the pathophysiological similarity and difference between these conditions.

**Materials and methods**

**Patients**

Eight patients diagnosed clinically as Parkinson’s disease and eight with atypical Parkinsonism were studied (table 1). Patients were clinically classified in stage I, II or III from Hoehn and Yahr, and none of them was demented. All patients with Parkinson’s disease had the three classic signs of resting tremor, rigidity and akinesia with no pyramidal signs, and responded well to levodopa. Patients with atypical Parkinsonism were classified into either the akinetic type or the akinetic rigid type. There might be a criticism that patients with atypical Parkinsonism were not classified into specific diseases or syndromes, however, most cases with atypical Parkinsonism were in the early stages of their disease and could not be categorised more precisely. Cases 9 and 10 with atypical Parkinsonism showed only akinesia without resting tremor nor rigidity. Case 11 had akinisia and neck rigidity without rigidity of the limbs. All three cases with the akinetic type showed impaired ocular movement. Cases 12, 13, 14, 15 and 16 had akinlesia and rigidity without resting tremor. All patients with atypical Parkinsonism had no specific cause, such as vascular damage, intoxication,
metabolic deficit, encephalitis or head injury, and levodopa was not effective in any of them. Cases 11, 12, 13 and 14 showed mild cortical atrophy, but the ventricular dilatation was minimal in all four. Patients with any abnormalities in the striatum on CT and/or MRI were excluded from this study.

Case reports of patients with Parkinson’s disease are omitted as the inter-patient differences in Parkinson’s disease is not discussed in this study. Case reports for patients with atypical Parkinsonism are as follows:

Case 9 A 54 year old right handed man started to complain of writing difficulty at the age of 50. This was followed by dysarthria (microphonia). There was a gradual progression of his symptoms. He later began to drag his right foot. On examination he showed impaired fine finger movement and adiadochokinesis. No postural hypotension was observed. Vertical eye movement were slightly impaired.

Case 10 A 76 year old man started to complain of walking difficulty and a tendency to fall, a few years previously. This was followed by dysarthria and difficulty in writing. Examination showed slightly impaired vertical eye movement. He showed no resting tremor nor rigidity. No postural hypotension was observed.

Case 11 A 61 year old man began to complain of sleep apnoea at the age of 59. He also noticed dysarthria, difficulty in writing and double vision. On examination he showed mild impairment of upgaze. He also showed neck rigidity without rigidity of the limbs. No postural hypotension was observed. His fine finger movement and coordination was mildly disturbed.

Case 12 A 74 year old woman developed a slow gait at the age of 71. This was followed by postural tremor. She also complained of anorexia and lost 5 kg in a year. On examination she showed mild rigidity in the limbs. No postural hypotension was observed.

Case 13 A 57 year old man had developed impotency at the age of 55. This was followed by walking difficulty, dysarthria and postural tremor. Postural tremor was dominant in his left hand. On examination he showed mild cogwheel rigidity in his limbs and postural hypotension (112/80 mm Hg in supine position, 80/60 standing). He also showed impaired fine finger movement and adiadochokinesis. Deep tendon reflexes were increased and a Babinski’s sign was present bilaterally.

Case 14 A 74 year old man started to complain of difficulty in handwriting at the age of 73. This was followed by walking difficulty and a tendency to fall. He also noticed dysarthria. On examination he showed mild rigidity of the limbs. No postural hypotension was observed. His fine finger movement and coordination was mildly disturbed.

Case 15 A 48 year old man complained of clumsiness in the right hand at the age of 44. This was followed by slow shuffling steps when walking. He also developed dysarthria. On examination he showed marked cogwheel rigidity of extremities. No postural hypotension was observed. His fine finger movement and coordination was mildly disturbed in the right side and slightly disturbed in the left side.

Case 16 A 71 year old man complained of postural tremor of both hands at the age of 67. This was followed by walking difficulty and dysarthria. On examination he showed moderate cogwheel rigidity of the limbs. No postural hypotension was observed.

Cases 1, 2, 11, 13 and 14 had received no treatment before the PET examination. The other cases received medication before the PET examination as shown in table 1, and medication was stopped at least 48 hours before the examination.

The 18F-Dopa uptake was measured in all cases except for cases 14 and 16, and regional cerebral blood flow (rCBF) was measured in all cases except for cases 13, 14 and 16. The tCMBGIC was measured in all cases except for cases 4 and 15.

For comparison, mean (SD) age, 47-3 (15-8) years, eight, mean (SD) age, 49-6 (14-0) years, and seven, mean (SD) age, 52-1 (13-6)
The region of cerebellar hemisphere was sited in the OM + 2 cm plane with a 1.4 × 1.8 cm rectangle. The ROIs of the head of the caudate and putamen were outlined visually on the 18F-Dopa image by reference to the glucose or blood flow image and also the images of CT and/or MRI. They were generally sited in the OM + 5 cm plane, but another five slices in the OM + 2.7 cm, + 4.2 cm, + 5.7 cm, + 7.2 cm and + 8.7 cm planes were also taken and the most appropriate slice level of caudate head and putamen was sought. The ROI to the cerebral hemisphere was outlined visually on the glucose or blood flow image in the third slice, and excluded caudate and putamen to obviate the striatal difference among the groups (fig 1).

Two to seven mCi (54 to 260 MBq) of 18F-Dopa was injected intravenously and PET data was obtained every two minutes for 20 minutes, every four minutes for 40 minutes and at 70, 90, 120 minutes for 15 minutes. The tissue activity of 18F in the bilateral caudate and putamen was corrected by the non-specific retention of 18F in cerebellar hemispheres. The ratio of caudate or putamen to cerebellum increased steadily with time for 120 minutes after the injection (fig 2) and the ratio of caudate to putamen to cerebellum at 120 minutes was calculated.

The rCBF was measured just before the 18F-Dopa study by the oxygen-15 steady state technique, using continuous inhalation of 100 mCi (3.7 GBq) of oxygen-15 labelled carbon dioxide. Arterial blood sampling was performed from a catheter in the femoral artery four times during six minutes of emission scan. The rCMRGlc was measured on a different day within a week from the 18F-Dopa and CBF study using 18F-FDG. Three to seven mCi (110 to 260 MBq) of 18F-FDG was injected intravenously, and arterial blood samples were obtained at predetermined intervals from the time of injection until the end of scanning. The rCMRGlc was determined from the emission scan and blood curve data by using the model of Sokoloff et al19 and Phelps et al14 later modified by Brooks.15

Significant clinical asymmetry was observed in cases 1, 2, 3, 9, 13 and 15, and 18F-Dopa uptake was decreased more in the contralateral side in all of them. As no significant asymmetry in the clinical features and in the 18F-Dopa uptake was observed in all the other cases, values were calculated as the mean of the

Figure 1 The region of cerebellar hemisphere in the OM + 2 cm plane (rCe, lCe), and that of the head of the caudate (rC, lC), putamen (rP, lP) and global cerebral hemisphere (excluding caudate head and putamen) (rH, lH) in the OM + 5 cm plane. Upper two figures are images of rCMRGlc and lower two figures are images of 18F-Dopa uptake.

Table 2 PET results in patients with Parkinson's disease (PD) (1-8) and patients with atypical Parkinsonism (PKM) (9-16)

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*C—caudate; P—putamen; GC—global cerebrum (excluding caudate and putamen); *uptake ratio to cerebellum; ml/min/100 ml; mCi/mg/100 ml.
Striatal blood flow, glucose metabolism and \( ^{18} \text{F-Dopa} \) uptake: difference in Parkinson's disease and atypical Parkinsonism

![Diagram](image)

Figure 2  Time courses of radioactivity on the ratio of the head of the caudate to cerebellum (a), and that on the ratio of putamen to cerebellum (b) in normal controls, patients with Parkinson's disease stage I and II (PD I, II) and patients with Parkinson's disease stage III (PD III). Means and SDs are generally shown except where deviation bars are omitted for clarity.

Results

Time courses of radioactivity on the ratio of caudate to cerebellum and putamen to cerebellum in normal controls, patients with Parkinson's disease stage I and II, and patients with Parkinson's disease stage III are shown in figs 2a and 2b, respectively. Although there was no difference between the caudate and putamen in normal controls, the radioactivity of the putamen decreased more than that of the caudate in patients with Parkinson's disease. Both of them decreased more in patients with Parkinson's disease stage III than in patients with Parkinson's disease stage I and II.

All PET results in each patient with Parkinson's disease and with atypical Parkinsonism were shown in table 2. The uptake ratio of the caudate to cerebellum and the putamen to cerebellum at 120 minutes after the administration of \( ^{18} \text{F-Dopa} \) in patients with Parkinson's disease and atypical Parkinsonism were compared with normal controls in fig 3. Decreased \( ^{18} \text{F-Dopa} \) uptake in both regions was observed in patients with Parkinson's disease and atypical Parkinsonism compared with normal controls (\( p < 0.01 \)) by Scheffe's F-test, however, the caudate \( ^{18} \text{F-Dopa} \) uptake in Parkinson's disease was relatively spared. The \( ^{18} \text{F-Dopa} \) uptake in the putamen decreased more than that in caudate significantly in Parkinson's disease by t test (\( p < 0.01 \)). There was no statistical differences in the putaminal \( ^{18} \text{F-Dopa} \) uptake between Parkinson's disease and atypical Parkinsonism.

There was no significant difference in the rCBF of the caudate and putamen in patients with Parkinson's disease compared with controls, but the rCBF of both regions in patients with atypical Parkinsonism decreased in comparison with controls (\( p < 0.01 \)) and patients with Parkinson's disease (\( p < 0.01 \))(fig 4). The rCBF of the global cerebrum (excluding the caudate and putamen) in patients with atypical Parkinsonism was shown in fig 5.
trols (p < 0.01) and patients with Parkinson’s disease (p < 0.01) (table 2). The rCMRGlC of caudate and putamen also decreased significantly in patients with atypical Parkinsonism compared with controls (p < 0.01) and patients with Parkinson’s disease (p < 0.01) (fig 5). The rCMRGlC of the global cerebrum in patients with atypical Parkinsonism also decreased in comparison with controls (p < 0.01) and patients with Parkinson’s disease (p < 0.01) (table 2).

Images of [18F]-Dopa uptake at 120 minutes after injection (obtained by the PET data from 112 to 127 minutes after injection), rCBF and rCMRGlC at a level of the striatum in a control subject, in a patient with Parkinson’s disease (Case 5) and in a patient with atypical Parkinsonism (Case 11) are shown in figs 6a, b, and c, respectively.

Discussion
Decreased [18F]-Dopa uptake in the putamen in patients with Parkinson’s disease measured by PET in this study and in previous reports,4–6 is coincident with the dopamine depletion probably due to the hypofunction or decreased retention capacity of dopamine in dopaminergic nerve terminals in the putamen. Decreased but relatively spared [18F]-Dopa uptake in the head of the caudate in patients with Parkinson’s disease is also coincident with the previous PET studies,4–8 as well as with the previous neurochemical studies showing that dopamine levels are depressed more in the putamen than in the caudate in Parkinson’s disease.10 On the other hand, equally decreased [18F]-Dopa uptake in the putamen and in the caudate in atypical Parkinsonism seems to reflect the different pathogenesis of Parkinson’s disease and atypical Parkinsonism.

The unchanged rCBF and rCMRGlC in the putamen and caudate from normal controls, assuming that there was no change in the striatal energy consumption as a whole, in patients with Parkinson’s disease was also shown in this study. Preserved function of dopaminergic receptors has been measured by PET using [11C]-N-methylspiperone in patients with Parkinson’s disease,11 and hypometabolism of only dopaminergic nerve terminals might not affect the total metabolism of the putamen or caudate. Some reported increased striatal CMRGlC4 and others decreased striatal CMRGlC in patients with Parkinson’s disease. This inconsistency with our study and the others may be due to the different clinical stages at which the PET study was carried out. Patients with Parkinson’s disease in our study were in the relatively early stages and not demented, while we have a different result of decreased global cerebral glucose metabolism in demented patients with Parkinson’s disease (Hosokawa et al, in preparation).

Cases 9, 10, and 11 were not responsive to levodopa and showed symptoms of pure akinesia without resting tremor nor rigidity. This “pure akinet” type may be a different clinical entity from Parkinson’s disease12 in which a part of early phases of progressive supranuclear palsy (PSP) may be included.18 Although the relationship between pure akinesia and PSP remains unclear, PET results in the previous reports of decreased striatal CBF, oxygen and glucose metabolism in patients with PSP19–20 are similar to the present study of rCBF and rCMRGlC in patients with atypical Parkinsonism. Akinet rigid syndrome may be part of a spectrum of multiple system atrophy (MSA). Cases 12 and 16 may be close to striatoniiral degeneration (SND), case 13 was diagnosed as Shy-Drager’s syndrome, and cases 14 and 15 had additional cerebellar symptoms and signs and may be the early phase of olivopontocerebellar atrophy (OPCA). PET studies in patients with SND21 showed decreased striatal glucose metabolism, which was consistent with our results in patients with atypical Parkinsonism. The clinical diagnosis of atypical Parkinsonism may be replaced by the final diagnosis after specific symptoms and signs develop. The differentiation from Parkinson’s disease can be clinically performed and is of practical importance.

A decrease of rCBF and rCMRGlC in the caudate and putamen in patients with atypical Parkinsonism (in spite of no focal abnormalities in the striatum on CT and/or MRI), suggests the impairment of the total neuronal activity in the striatum, including the hypofunction of striatal non-dopaminergic neurons since the dopaminergic neurons comprise 10% or less of the striatal neurons from histological study of
Striatal blood flow, glucose metabolism and \[^{18}\text{F}-\text{Dopa}\] uptake: difference in Parkinson's disease and atypical Parkinsonism

Figure 6: Images of \[^{18}\text{F}-\text{Dopa}\] uptake at 120 minutes after injection (a), rCBF (b) and rCMRGlc (c) at a level of the striatum in a control subject, in a patient with Parkinson's disease (PD) (case 5) and in a patient with atypical Parkinsonism (PKM) (case 11). Striatal \[^{18}\text{F}-\text{Dopa}\] uptake decreased in PD and PKM compared with that in a control. The \[^{18}\text{F}-\text{Dopa}\] uptake in caudate in PD seemed relatively spared in comparison with that in putamen (a). The rCBF and rCMRGlc in global cerebrum including the caudate and putamen decreased in PKM compared to those in control and PD (b, c).

Furthermore, a decrease of rCBF and rCMRGlc in the cerebrum suggests the hypofunction of not only the caudate and putamen but also of the cerebrum in patients with atypical Parkinsonism.

There was no dissociation between rCBF and rCMRGlc in this study and we have previously observed good coupling between rCBF, rCMRO\(_2\) and rCMRGlc in PSP patients. This is because all the patients in this study and in the previous report\(^9\) were in the chronic state.

In conclusion, our study has shown the different PET results between idiopathic Parkinson's disease and atypical Parkinsonism. 1) Decreased \[^{18}\text{F}-\text{Dopa}\] uptake in the caudate and putamen with relative sparing of the caudate in patients with idiopathic Parkinson's disease, and equally decreased \[^{18}\text{F}-\text{Dopa}\] uptake in the caudate and putamen in patients with atypical Parkinsonism. 2) Normal rCBF and rCMRGlc in patients with Parkinson's disease and decreased rCBF and rCMRGlc of the caudate and putamen associated with global cerebral decrease in patients with atypical Parkinsonism. These results may underlie the similarity and the difference in the pathophysiological mechanism of idiopathic Parkinson's disease and atypical Parkinsonism.

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