Acta Medica et Biologica
Vol. 40, No. 3, 115-121, 1992

Regional Cerebral Blood Flow in Parkinson's Disease Measured with N-isopropyl-p-[^{123}I]iodoamphetamine (IMP) SPECT

Ikuo ODANO[1], Mamiko NISHIHARA[1], Atsushi ISHIKAWA[2], Hiroko HAYASHI[1], Shoichi HIGUCHI[1], Katsuhiko IBAYASHI[3] and Kunio SAKAI[1]

[1]Department of Radiology, Niigata University School of Medicine, Asahimachi 1, Niigata 951, Japan; Department of [2]Neurology and [3]Neurosurgery, Niigata University, Brain Research Institute, Niigata 951, Japan

Received April 22, 1992

Summary. **N-isopropyl-p-[^{123}I]iodoamphetamine (IMP) SPECT studies were performed on 21 patients (13 females; 45-73 yrs) with idiopathic Parkinson's disease (PD) and 10 age-matched normal controls (39-69 yrs). Regional Cerebral Blood Flow (rCBF) was quantitatively measured by the arterial blood sampling method. When compared with normal controls, global CBF, and rCBF in the frontal cortex and in the basal ganglia were reduced 22.1% ($p<0.01$), 25.0% ($p<0.05$) and 25.6% ($p<0.01$), respectively. The reduction of rCBF in the basal ganglia was significantly correlated ($p<0.05$) with symptoms such as gait disturbance, frozen gait and motor disability score. However, no significant correlation was observed between the severity of dementia and any regional reduction of CBF, including the frontal or parietal cortices. These data show that the severity of dementia in PD may be related to other factors but not with CBF. Quantification of rCBF with ^{123}I-IMP SPECT imaging is useful for evaluation and follow-up patients with PD.**

INTRODUCTION

Positron emission tomography(PET) and single photon emission computed tomography (SPECT) are useful to evaluate alterations of cerebral blood flow and metabolism. However, PET has several limitations in daily clinical use, and SPECT is more clinically available. Among the most recent radiopharmaceuticals for SPECT imaging, N-isopropyl-p-[^{123}I]iodoamphetamine (IMP) has been particularly useful. This agent has high first pass extraction by brain tissue, and long retention in the brain. Therefore, the early images of ^{123}I-IMP SPECT represent the distribution of regional cerebral blood flow (rCBF).[1,2]

Since Parkinson's disease results from degeneration of the dopaminergic nigrostriatal neurons,[3] we can speculate that dopamine depletion from the basal ganglia may alter local cerebral blood flow and metabolism, and that such alterations may be demonstrated by PET and SPECT studies. However, it may be difficult to demonstrate cerebral blood flow abnormalities without a quantitative measurement of the ^{123}I-IMP SPECT images, as these may be diffusely distributed in the brains of Parkinson's patients.

The purpose of this study was to measure rCBF in Parkinson's patients using ^{123}I-IMP SPECT, and to assess a possible relationship between rCBF and symptoms or signs of Parkinson's disease.

MATERIALS AND METHODS

1) Subjects

We analyzed 21 patients, 8 males and 13 females, with idiopathic Parinson's disease ranging in age from 45 to 73 years (mean 59 yrs), and 10 age-matched normal volunteers (range of 39-69, mean 56 yrs). The duration of the disease ranged from 1 to 22 years. The level of clinical disability was rated using the Hoehn and Yahr scale.[4] Two patients were in stage I, 5 in stage II, 10 in stage III and 4 in stage IV. Symptoms such as bradykinesia, rigidity, tremor, gait disturbance, frozen gait and pulsion sign were graded from 0 to 3 in severity, and the sum of these scores was called the Motor Disability Score (MDS), as shown in Table 1. The severity of cerebral atrophy was graded 1 to 4, on the basis of a widening of the sulci and

dilatation of the lateral ventricles on X-ray CT (Fig. 1). Dementia in the patient population was assessed using the Hasegawa's dementia scale,[5] as shown in Table 2. All patients had been on anticholinergic drug or levodopa prior to the ^{123}I-IMP studies. Patients in whom parkinsonism was drug-induced or was a secondary manifestation of multineuronal system diseases such as vascular parkinsonism and progressive

Table 1. Grading of Symptoms and Motor Disability Score (MDS) of Patient Population

Symptoms	Grading*
Bradykinesia (0~3)	1.4±1.0
Rigidity (0~3)	1.2±0.5
Tremor (0~3)	1.2±0.6
Gait Disturbance (0~3)	1.2±1.0**
Frozen Gait (0~3)	0.6±0.7**
Pulsion Sign (0~3)	1.6±1.0
MDS (0~18)	7.3±3.7**

* mean±SD, **$p<0.05$

Table 2. Dementia Scale of Patient Population

	Hasegawa's scale	Number of patients
Normal	32.5 — 31.0	10
Subnormal	30.5 — 22.0	9
Predementia	21.5 — 10.5	2
Dementia	10.0 — 0.0	0

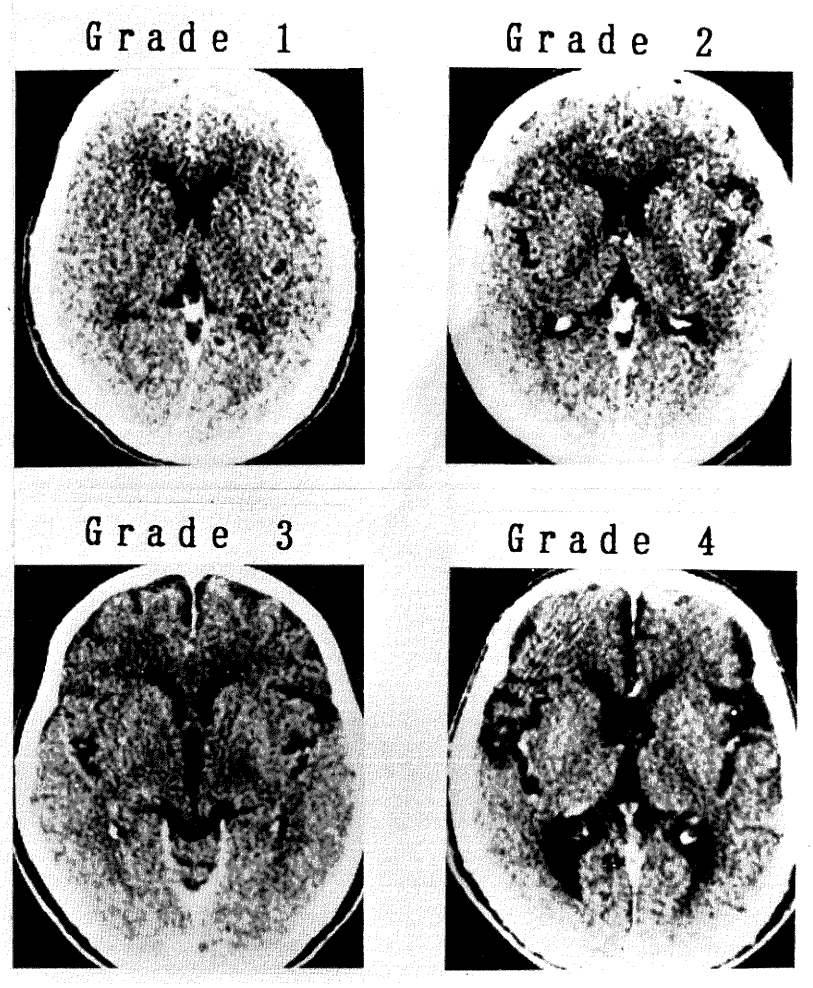

Fig. 1. Grading of cerebral atrophy on CT, on the basis of the widening of the sulci and dilatation of the ventricles (1=normal; 4=most abnormal).

Table 3. Clinical and Laboratory Data of Patient Population

Patient No.	Age/ Sex	Stage	Duration (yrs)	Dementia scale	Atrophy on X-CT	Symtoms (score)						
						B	R	T	G	F	P	MDS
1	61/F	1	2	32.5	2	0	1	1	0	0	0	2
2	61/F	1	1	30.5	2	0	1	0	0	0	1	2
3	52/M	2	13	32.5	2	0	1	2	0	0	0	3
4	67/M	2	7	32.5	2	0	1	2	0	0	1	4
5	63/F	2	2	24.5	2	1	1	1	1	0	1	5
6	58/F	2	6	28.5	2	0	1	1	0	0	1	3
7	52/F	2	4	32.5	2	1	1	1	1	0	0	4
8	49/F	3	8	21.0	1	1	1	1	1	0	1	5
9	53/F	3	8	25.5	2	1	1	1	2	1	2	8
10	52/F	3	7	32.5	2	2	2	1	3	2	3	13
11	45/M	3	8	32.5	2	2	1	1	1	1	3	9
12	58/M	3	6	23.0	2	2	2	2	2	0	1	9
13	57/F	3	5	32.5	1	1	1	2	1	1	2	8
14	71/F	3	18	25.0	3	1	1	0	1	0	2	5
15	70/F	3	9	32.5	3	1	1	2	1	0	2	7
16	55/M	3	22	32.5	3	2	1	1	1	1	2	8
17	64/M	3	6	32.5	3	2	1	1	2	1	1	8
18	61/F	4	5	23.5	3	3	2	1	1	0	2	9
19	71/M	4	12	28.5	3	3	2	2	3	2	3	15
20	73/M	4	7	12.5	4	3	2	1	2	1	3	12
21	51/F	4	14	30.5	2	3	2	1	3	2	2	13

B=Bradykinesis, R=Rigidity, T=Tremor, G=Gait Disturbance, F=Frozen Gait, P=Pulsion Sign, MDS=Motor Disability Score

supranuclear palsy were excluded. Table 3 summarizes the patients' data, including duration of the disease, stage, dementia scale, degree of cerebral atrophy and symptoms.

2) Data acquisition and analysis

A dose of 3.5 to 4.5 mCi of ^{123}I-IMP was injected intravenously (i.v.). Fifteen min later, SPECT studies were performed with a dual detector Siemens ZLC/75 Rota Camera and Shimadzu Head-tome SET-050, equipped with a Scintipac 2,400 computer system. All patients and normal volunteers had ear-plugs, and eyes were closed prior to injection. SPECT data were acquired as follows: sampling angle 6 degrees; sampling time 60 min; slice thickness 6 mm; 64 by 64 matrix. Transaxial slices were reconstructed from the prefiltered raw data (Wiener and Butterworth filter) by the filtered backprojection algorithm using a Shepp and Logan filter. Absorption correction was performed with Sorenson's method ($\mu = 0.12\ cm^{-1}$), but no scatter correction was used. The resolution of the Rota Camera system was 20.5 mm full width at half-maximum (FWHM) in the center of the reconstructed transverse section, and that of the Head-tome was 10.0 mm. Each SPECT transaxial slice was obtained parallel to the orbito-meatal (OM) line. On the same day, an X-ray CT with a GE CT/T 8,800 system was obtained in the same position, the same slice thickness and the same magnification as the SPECT study.

Regional cerebral blood flow(F) was measured using an arterial blood sampling method, modified by Kuhl,[2] which uses the microsphere model:

$$F = R \cdot C_b/(N \cdot A)$$

where R is the constant withdrawal rate of arterial blood in ml/min; actually, this value was 1 ml/min.. A is the total activity (from 0 to 5 min) of arterial whole blood withdrawn in μCi, and N is the fraction of A that is true tracer activity. C_b is the activity concentration derived from the images. The value of N was measured using an octanol extraction of the arterial blood reference sample. Eleven fundamental SPECT studies of a phantom (21 cmϕ × 19 cm) were

performed, filling these with water of different activity concentrations. A standard activity curve was obtained, in which the activity of the SPECT images on the computer were linearly related with the activity in the phantom measured with a well-counter. C_b was calculated by comparison with the curve.

The reproducibility of this quantification was evaluated by performing this study twice on 7 patients with cerebrovascular diseases, with a 7-day interval between studies. The reproducibility was judged good, as shown in Fig. 2.

Twenty-four by twenty-four milimeter square ROIs were drawn on the computer images. On the transaxial slice that included the basal ganglia, three ROIs were placed in the frontal cortex of each hemisphere, two ROIs in the temporal cortex, one ROI in the basal ganglia and one in the occipital cortex. On the slice that included the centrum semiovale, two ROIs were placed in the parietal cortex. On the slice 18-24 mm above the OM line, one ROI was placed in the hemisphere of the cerebellum. Anatomical identification of each position was made by superimposition of the SPECT films on the X-ray CT films. CBF in each region was calculated as a mean of right and left side rCBF.

RESULTS

Results of the regional cerebral blood slow measurements in the patient population are summarized in Table 4. Figure 3 illustrates the results of the supratentorial global CBF and rCBF of all patients and normal controls. When compared with the controls, supratentorial global CBF, frontal cortex, temporal cortex, occipital cortex, parietal cortex, basal ganglia and cerebellar blood flow were all reduced in the Parkinson's patients (Fig. 3). A marked reduction of the flow was observed in the frontal cortex and in the basal ganglia. The patient shown in Fig. 4 and 5 exemplified this situation.

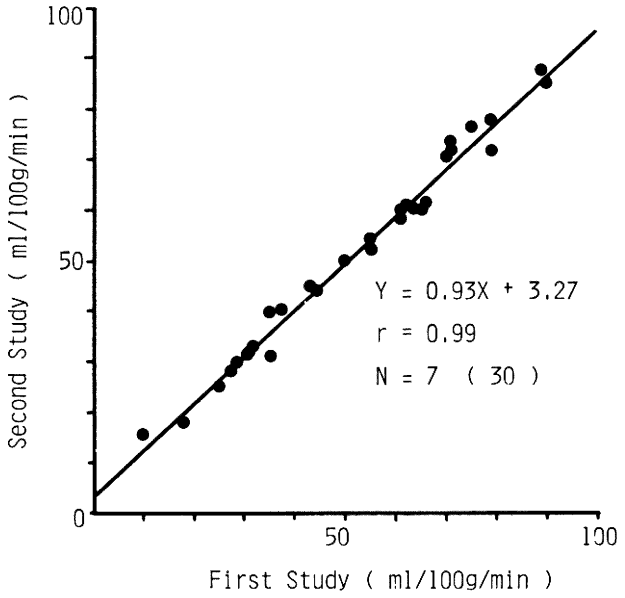

Fig. 2. Reproducibility of the method for quantification of rCBF.

Table 4. Regional CBF of Patient Population

Patient No.	rCBF (ml/100 g/min)						
	GL	F	T	O	P	BG	CB
1	47	41	45	55	46	50	58
2	58	53	61	57	59	60	70
3	44	41	43	47	47	44	48
4	51	49	49	52	54	53	64
5	76	67	72	87	77	69	93
6	41	35	40	50	40	42	53
7	34	32	35	36	33	31	40
8	53	52	55	48	56	55	64
9	48	42	50	51	49	48	64
10	38	32	38	42	40	37	47
11	44	42	44	47	44	41	50
12	46	41	49	49	46	49	64
13	59	53	63	60	58	54	63
14	53	48	54	55	54	46	66
15	35	34	35	37	35	34	49
16	39	34	45	39	37	37	51
17	27	27	30	26	25	31	36
18	47	46	51	51	41	55	67
19	34	33	33	32	36	33	41
20	30	27	35	36	23	36	48
21	48	45	48	51	47	41	54

GL=global CBF, F=frontal cortex, T=temporal cortex, O=occipital cortex, P=parietal cortex, BG=basal ganglia, CB=cerebellum

We analyzed seven factors which might be related to rCBF in Parkinson's disease, i.e. age, sex, duration of the disease, stage (Hoehn and Yahr's scale), laterality of symptoms, severity of symptoms and cerebral atrophy on X-ray CT. Although there was no significant correlation between rCBF and age, sex or laterality of symptoms, we observed an inverse relationship between rCBF in the basal ganglia and duration or stage of the disease.

There was an inverse correlation between rCBF in all regions and the symptoms graded in Table 1.

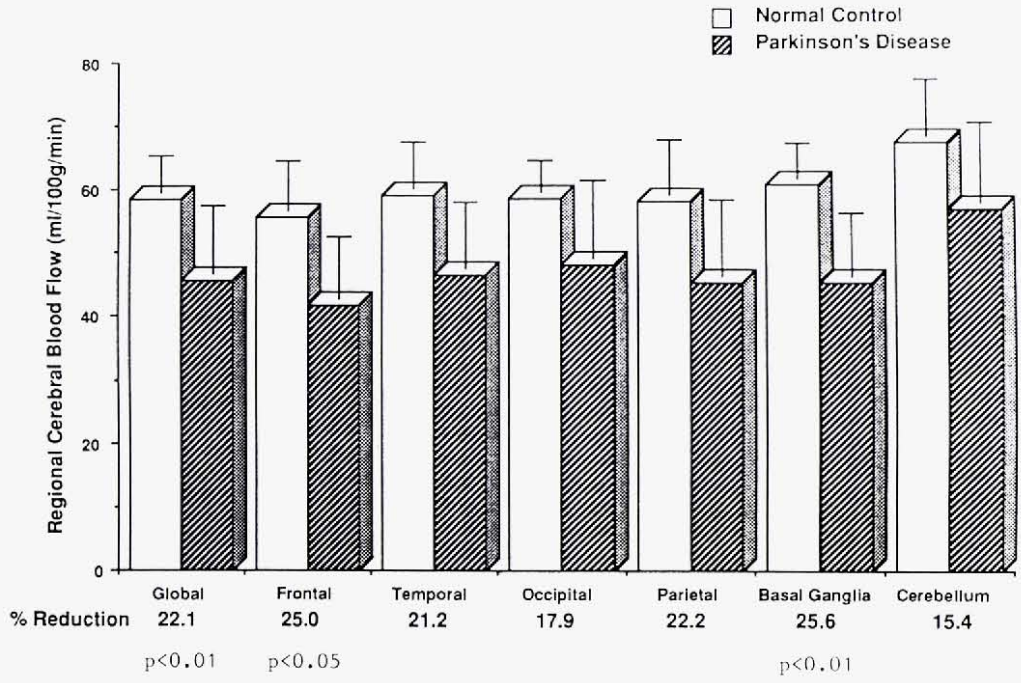

Fig. 3. Regional CBF of Parkinson's patients and normal controls. Regional CBFs of Parkinson's patients were reduced in all supratentorial areas and cerebellum.

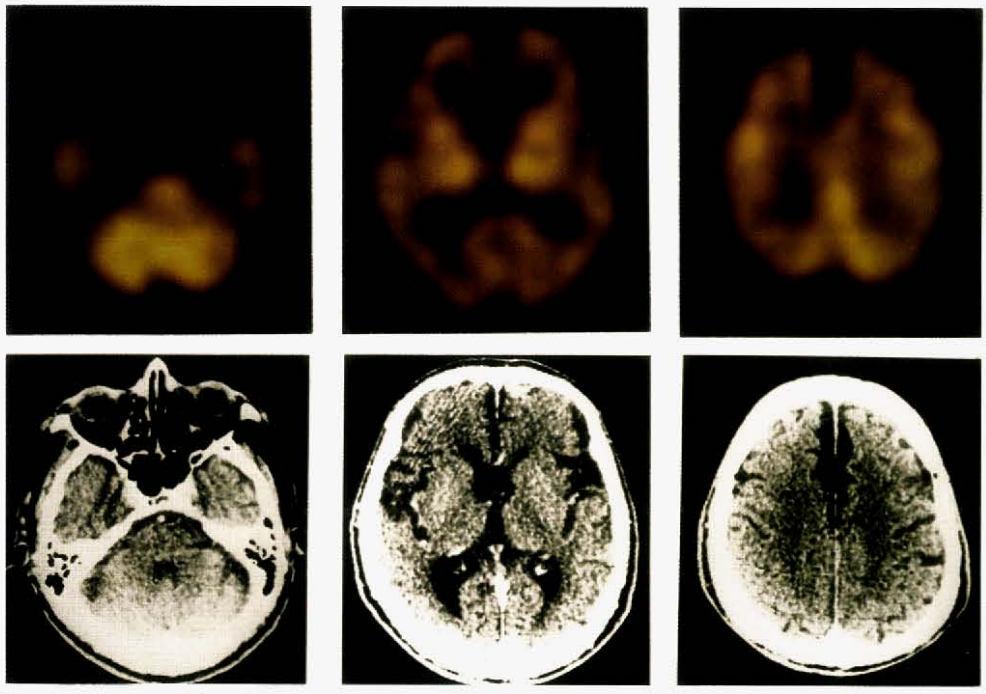

Fig. 4. 61-year-old male with severe cerebral atrophy on CT. Transaxial images of ^{123}I-IMP SPECT are symmetrical. Regional CBF has decreased to 46 ml/100 g/min in the frontal cortex, and to 41 ml/100 g/min in the parietal cortex. This case was not combined with Alzheimer's disease.

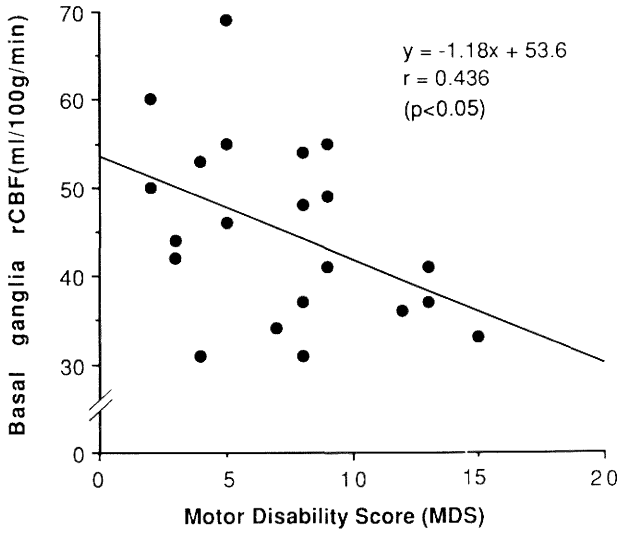

Fig. 5. A significant inverse correlation ($p<0.05$) observed between the basal ganglia and motor disability score (MDS).

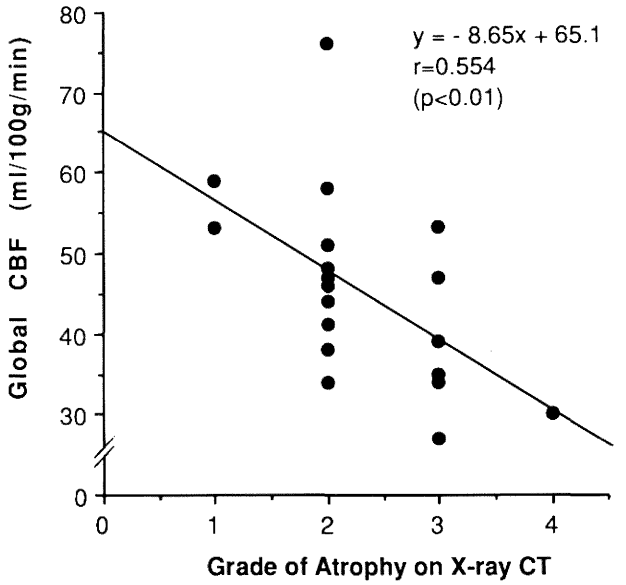

Fig. 6. A significant inverse correlation observed between global CBF and grade of atrophy on CT.

Moreover, we observed a significant inverse correlation ($p<0.05$) between rCBF reduction in the basal ganglia and gait disturbance, frozen gait or motor disability score (Fig. 6).

The severity of atrophy correlated inversely with age, reduction of global, frontal and basal ganglia CBF ($p<0.01$), as shown in Fig. 7. However, we found no significant correlation between the severity of atrophy and duration of the disease, stage, symptoms and motor disability score; neither was any significant correlation between the dementia scale and reduction of regional CBF found.

DISCUSSION

It is generally accepted that many of the symptoms of Parkinson's disease are related to a degeneration of the dopamine-containing nigrostriatal pathway and neurotransmitter receptor alterations.[6] Dopamine depletion in the basal ganglia may cause changes in the cerebral metabolism and blood flow. In patients with Parkinson's disease studied by the xenon-133 inhalation method, a mean CBF reduction from 8% to 20% was found.[7-10] A similar reduction of cortical CBF was reported using ^{15}O and PET imaging.[11,12] Using quantitative ^{123}I-IMP SPECT, we demonstrated that the supratentorial global CBF was reduced 22%, the frontal cortex 25%, and the basal ganglia 26%.

When a relationship between rCBF and factors related with the disease was sought, we found an inverse correlation between rCBF in the basal ganglia and the duration of the disease, stage symptoms of Parkinson's disease. In particular, gait disturbance, frozen gait and the motor disability score were all closely related to the reduction of rCBF in the basal ganglia. Kuhl reported that as the glucose metabolism measured with the ^{18}FDG method decreased, the severity of bradykinesia increased.[13] This suggests that dopamine depletion in the basal ganglia is closely related to the reduction of rCBF and glucose metabolism and that these changes may cause symptoms. In patients with unilateral symptoms of Parkinson's disease studied with ^{15}O and PET imaging, rCBF in the contralateral basal ganglia was reported to be higher.[11] However, we could not find a significant laterality of rCBF in the basal ganglia, probably because only two of our patients had unilateral symptoms.

Cerebral atrophy is supposed to alter rCBF. The severity of cerebral atrophy was closely related to a reduction in the global, frontal and basal ganglia CBF. However, there was no correlation between cerebral atrophy and the duration, stage, symptoms or motor disability score. This suggests that a reduction of rCBF in the basal ganglia in Parkinson's patients is related not only to brain atrophy but also to other causes, one of which is vasoconstriction due to loss of dopaminergic innervation of blood vessels in more advanced patients.[11,12]

Dementia is usually observed in patients with

Parkinson's disease.[1,4,15] It has been reported that as the glucose metabolism decreases, the development of mild to moderate dementia increases.[13] Since Parkinson's and Alzheimer's disease may be associated,[15] a reduction of rCBF in the parietal or frontal cortex could be related to the severity of dementia. No significant relationship between rCBF reduction and cognitive impairment could be demonstrated using the xenon-133 inhalation method.[10] In our study, we classified and analyzed our patients in four groups on the basis of Hasegawa's dementia scale. There was no significant relationship between the severity of dementia and the reduction of any regional CBF including the frontal and parietal cortices. Alzheimer's patients were excluded from our patient population. Therefore, our study suggests that the severity of dementia in Parkinson's disease may be related to other factors but not to the regional cerebral blood flow. Our study has demonstrated that quantitative ^{123}I-IMP SPECT imaging is a useful method in the evaluation and follow-up of patients with Parkinson's disease.

Acknowledgements. The authors thank Dr. Hiroshi Tsukamoto of the Department of Radiology and Radiological Science, the Johns Hopkins Medical Institutions, for the preparation of illustrations.

REFERENCES

1) Winchell HS, Baldwin RM, Lin TH: Development of ^{123}I-Iabeled amines for brain studies: localization of ^{123}I iodophenyl-alkylamines in rat brain. *J Nucl Med* **21**: 940-946, 1980.
2) Kuhl DE, Barrio JR, Huang S: Quantifying local cerebral blood flow by N-isopropyl-p-[^{123}I]iodoamphetamine (IMP) tomography. *J Nucl Med* **23**: 196-203, 1982.
3) Hornykiewicz O: Dopamin (3-hydroxytyramine) and Brain Function. *Pharmacol Rev* **18**: 925-964, 1966.
4) Hoehn M, Yahr M: Parkinsonism: onset, progression, and mortality. *Neurology* **17**: 427-442, 1967.
5) Hasegawa K, Inoue K, Moriya K: An Investigation of dementia rating scale for the elderly. *Clinical Psych* **16**: 965-969, 1974.
6) Reisine TD, Fields JZ, Yamamura HI, Bird ED: Neurotransmitter receptor alterations in Parkinson's disease. *Life Sci* **21**: 335-344, 1977.
7) Lavy S, Melamed E, Cooper G, Bentin S: Regional cerebral blood flow in patients with Parkinson's disease. *Arch Neurol* **36**: 344-348, 1979.
8) Bes A, Guell A, Fabre N, Dupui Ph: Cerebral blood flow studied by Xenon-133 inhalation technique in Parkinsonism: loss of hyperfrontal pattern. *J Cereb Blood Flow Metabol* **3**: 33-37, 1983.
9) Henriksen L, Boas J: Regional cerebral blood flow in hemiparkinsonian patients. Emission computerized tomography of inhaled ^{133}Xenon before and after levodopa. *Acta Neurol Scand* **71**: 257-266, 1985.
10) Globus M, Mildworf B, Melamed E: Cerebral blood flow and cognitive impairment in Parkinson's disease. *Neurology* **35**: 1135-1139, 1985.
11) Wolfson L, Leenders KL, Brown LL, Jones T: Alterations of regional cerebral blood flow and oxygen metabolism in Parkinson's disease. *Neurol* **35**: 1399-1405, 1985.
12) Leenders Kl, Wolfson L, Gibbs JM: The effects of Ldopa on regional cerebral blood flow and oxygen metabolism in patients with Parkinson's disease. *Brain* **108**: 171-191, 1985.
13) Kuhl DE, Metter EJ, Riege WH: Patterns of local cerebral glucose utilization determined in Parkinson's disease by the [^{18}F]fluorodeoxyglucose method. *Ann Neurol* **15**: 419-424, 1984.
14) Lieberman A, Dziatolowski M, Kupersmith: Dementia in Parkinson disease. *Ann Neurol* **6**: 355-359, 1979.
15) Boller F, Mizutani T, Roessmann U, Gambetti P: Parkinson disease, dementia, and Alzheimer disease: clinicopathological correlations. *Ann Neurol* **7**: 329-335, 1980.