

The metabolic landscape of cortico-basal ganglionic degeneration: regional asymmetries studied with positron emission tomography

D Eidelberg, V Dhawan, J R Moeller, J J Sidtis, J Z Ginos, S C Strother, J Cederbaum, P Greene, S Fahn, J M Powers, D A Rottenberg

Abstract

Regional metabolic rate for glucose (rCMRGlc) was estimated using [¹⁸F]fluorodeoxyglucose (FDG) and positron emission tomography (PET) in five patients (four men, one woman; mean age 68; mean disease duration 2.4 years) with clinical findings consistent with the syndrome of cortico-basal ganglionic degeneration (CBGD). Left-right rCMRGlc asymmetry, $(L - R)/(L + R) \times 100$, was calculated for 13 grey matter regions and compared with regional metabolic data from 18 normal volunteers and nine patients with asymmetrical Parkinson's disease (PD). In the CBGD group mean metabolic asymmetry values in the thalamus, inferior parietal lobule and hippocampus were greater than those measured in normal control subjects and patients with asymmetrical PD ($p < 0.02$). Parietal lobe asymmetry of 5% or more was evident in all CBGD patients, whereas in PD patients and normal controls, all regional asymmetry measures were less than 5% in absolute value. Measures of frontal, parietal and hemispheric metabolic asymmetry were found to be positively correlated with asymmetries in thalamic rCMRGlc ($p < 0.05$). The presence of cortico-thalamic metabolic asymmetry is consistent with the focal neuropathological changes reported in CBGD brains. Our findings suggest that metabolic asymmetries detected with FDG/PET may support a diagnosis of CBGD in life.

Cortico-basal ganglionic degeneration (CBGD) is an often misdiagnosed extrapyramidal syndrome characterised by progressive unilateral rigidity associated with lateralised cortical signs and involuntary movements.¹⁻⁶ While focal cortical findings (that is, limb apraxia, cortical sensory impairment, alien limb syndrome or cortical reflex myoclonus) are essential for diagnosis, other signs such as supranuclear gaze palsy, gait disturbance and action tremor may also be present.⁵⁻⁷ Dementia, when evident, occurs only late in the clinical course. The motor manifestations of CBGD are typically refractory to levodopa and dopamine agonists. MRI and CT scans may be unrevealing early in the clinical course, although some degree of asym-

metrical cerebral atrophy may develop as the disease progresses.^{2,4}

Although the presence of focal cortical dysfunction is necessary for the clinical diagnosis of CBGD, the extrapyramidal manifestations may dominate the presenting picture. Consequently, CBGD may be confused with typical early Parkinson's disease (PD). In an effort to define metabolic parameters that might distinguish CBGD patients from PD patients in life, we used [¹⁸F]fluorodeoxyglucose (FDG) and positron emission tomography (PET) to study patients with clinical signs suggestive of CBGD and compared the results with those reported by us previously in PD patients and normal volunteers.⁸

Methods

We studied five patients [four men and one woman, mean (SD) age 68 (5) years, mean disease duration 2.4 years] with clinical findings compatible with CBGD. The diagnosis of CBGD with neuronal achromasia was confirmed at necropsy in one of these patients (Patient 1). All patients presented with unilateral limb rigidity or tremor which progressed to involve the other limbs within three years of onset. At least two of the following lateralised cortical findings were present in each of the five patients: limb apraxia (4/5), cortical sensory impairment (4/5), and pyramidal signs (5/5). Intellectual decline was not evident in these patients, and there were no oculomotor abnormalities; motor symptoms were universally refractory to levodopa and dopamine agonists. Family histories were negative in all patients, and there was no history of drug exposure, head injury, encephalitis, or metabolic disease. Space-occupying lesions and cerebrovascular lesions were excluded with MRI and/or CT examinations. CT scans in patients 1 and 5 showed mild asymmetrical fronto-parietal cortical atrophy. MRI in patient 3 showed symmetrical biparietal atrophy; MRI scans in the remaining two patients were normal. PET measurements in these patients were compared with values reported by us previously for a group of PD patients and normal control subjects.⁸ A summary of clinical data is provided in table 1.

Case reports

Patient 1 This 65 year old right handed woman developed an action tremor of the right arm five years before the study. Over the following year, she developed an occasional

Department of
Neurology, Memorial
Sloan-Kettering
Cancer Center,
New York
D Eidelberg*†
V Dhawan*†
J R Moeller*
J J Sidtis*
J Z Ginos*
S C Strother*
D A Rottenberg*

Cornell University
Medical College,*
New York
J Cederbaum

Department of
Neurology, North
Shore University
Hospital, †Manhasset,
New York

Department of
Neurology,
Neurological Institute,
New York
P Greene
S Fahn

Department of
Pathology, Columbia
Presbyterian Medical
Center, New York,
USA
J M Powers

Correspondence to:
Dr Eidelberg, Department of
Neurology, North Shore
University Hospital, Cornell
University Medical College,
300 Community Drive,
Manhasset, New York, NY
11030, USA.

Received 2 May 1990
and in final revised form
22 October 1990.

Accepted 11 December 1990

Table 1 CBGD Patients

Case	Age/Sex/Side ^a	Duration of Illness	Limb Apraxia	Involuntary Movements	Cortical Sensory Impairment	Pyramidal Signs	Cortical Atrophy
1	65/F/R	5 years	+	+	-	+	Mild ^b
2	63/M/L	1 year	+	-	+	+	-
3	67/M/R	4 years	-	+	+	+	Mild ^c
4	68/M/R	3 years	+	+	+	+	-
5	76/M/R	1 year	+	+	+	+	Mild ^b

Abbreviations: F, female; M, male; L, left; R, right.

a Side refers to the laterality of the presenting signs and symptoms.

b Asymmetrical fronto-parietal atrophy.

c Symmetrical biparietal atrophy.

tremor of the right lower extremity, became unsteady in her walking, and had occasional falls. By the time she was 63, she was falling frequently. At that time, she was found to have cogwheel rigidity of the right arm and leg, right sided bradykinesia, and an action tremor of the right upper extremity. There was generalised hyperreflexia which was worse on the right side, but plantar reflexes were flexor. A CT scan was normal. She was placed on levodopa without relief. By the time of PET study, at the age of 65, she had generalised bradykinesia and rigidity as well as right arm apraxia and involuntary writhing movements of the right arm. Occasionally, the right arm would rise in the air by itself. Speech was extremely soft and laboured, without aphasia; intellectual functions were preserved. She was unable to stand without assistance and was wheelchair bound. A second CT scan revealed mild fronto-parietal atrophy, worse on the left side. The patient died of aspiration at the age of 66.

Necropsy examination revealed mild gyral atrophy of the posterior frontal and anterior parietal lobes bilaterally, more marked on the left, and the left medullary pyramid was reduced in size. Coronal sections confirmed the gyral atrophy with sparing of white matter and revealed grey discolouration and slight atrophy of the putamen bilaterally, also more marked on the left. Transverse sections of the brainstem disclosed asymmetrical depigmentation of pars compacta of the substantia nigra, more notable on the left, but sparing of locus ceruleus. The cerebellum was in general unremarkable. Microscopically, moderate neuronal loss was observed in the lateral putamen, globus pallidus, caudate nucleus, lateral thalamus, and pars compacta bilaterally, but more prominently on the left side. This neuronal loss was accompanied by astrocytosis and also by loss of myelinated fibres in the pallidum, putamen and left pyramid. Lewy bodies, neurofibrillary tangles and Pick bodies were not detected; spongiform degeneration or status spongiosus was not seen. Neuronal loss with astrocytosis was also observed in the deeper neocortical layers of the grossly atrophic areas. This was seen in association with the most notable microscopic finding: ballooned or swollen, achromatic neurons. These neurons appeared to be enlarged, distorted, and eosinophilic pyramidal cells of layer V and, less frequently, layer III and were restricted primarily to atrophic posterior frontal-anterior parietal cortex. Their cytoplasm was faintly fibrillar, hyaline or vacuolated and could not be stained with Nissl stains, but were argyrophilic

with the Bielschowsky stain. In summary, subcortical asymmetrical neuronal loss and astrocytosis were identified primarily in the lateral putamen and substantia nigra, while swollen, achromatic neurons were noted primarily in deep layers of the frontoparietal neocortex.

Patient 2 This 62 year old right handed man developed a postural tremor of the left hand one year before the study. Over the following year, he developed progressive left sided bradykinesia and rigidity, gradually affecting all four limbs, and he began to fall. He was given levodopa and bromocriptine without benefit. By the time of the study, at the age of 63, he had masked facies and generalised bradykinesia, which was worse on the left side. There was an action tremor affecting the left arm as well as apraxia, particularly in dressing. Additionally, he was found to have an impairment of left hand proprioception and graphesthesia; pinprick and vibratory sensation were preserved. There was marked left sided hyperreflexia with an equivocal left plantar response. Intellectual function and speech were unimpaired. An MRI scan was normal.

Patient 3 This 67 year old right handed man developed an action tremor of the right arm four years before the study. Subsequently, he began dragging his right leg and noticed slurred speech. By the age of 65 he had severe cogwheel rigidity of the right arm and leg with dystonic posturing of the right arm and hand. Graphaesthesia was impaired in the right hand with preservation of the primary sensory modalities. In addition, there was moderate rigidity and action tremor of the left arm and leg and generalised bradykinesia. He had generalised hyperreflexia with an extensor plantar response on the right; speech was dysarthric and of low volume. He had difficulty with serial seven's, but his mental status was otherwise normal. A CT scan was normal. He was placed on levodopa and bromocriptine without benefit. By the time of the PET study, two years later, he was wheelchair bound and mute, but could follow simple commands. An MRI scan showed symmetrical biparietal atrophy.

Patient 4 This 68 year old right handed man developed difficulty manipulating a pen with his right hand three years before the study, followed by progressive difficulty in using his right hand. Over the next year he began dragging the right leg and fell repeatedly. His wife noticed that his speech was halting, and that he occasionally used the wrong words. The response to levodopa was poor. At the time of the study, he had mild, generalised bradykin-

esia and rigidity, more pronounced on the right. He had continual groping movements with the right arm, which he was aware of, but could not suppress. There was marked apraxia and loss of graphaesthesia and stereognosis of the right hand with similar, but milder, difficulties on the left. Reflexes were increased on the right but both plantar reflexes were flexor. Speech was slow but of normal volume, and the mental status was unimpaired. An MRI scan was normal.

Patient 5 This 75 year old man with a history of alcohol abuse and pernicious anaemia began falling and having difficulty using his right arm approximately one year before the study. He gradually developed a coarse postural and action tremor of the right arm. A trial of levodopa and bromocriptine was pursued without benefit. By the time of the study at the age of 76, he had generalised cogwheel rigidity and bradykinesia, most severe in the right arm, and an action tremor of both arms, much more severe on the right. In addition, he had groping movements of the right arm which could only briefly be suppressed. Stereognosis and praxis were impaired in the right arm, and voluntary movements of the left arm were mirrored on the right. Reflexes were absent at the ankles and normal elsewhere; there was spasticity of both legs with bilateral extensor plantar responses. Speech and mentation was normal. A CT scan showed mild fronto-parietal atrophy, more severe on the left side.

Control Subjects Eighteen normal volunteer subjects [mean (SD) age 27 (5) years] without a history of recent medical illness, neurological disease, developmental disorder or substance abuse, served as a control population for the metabolic studies. The group consisted of 12 men and six women; all but two of the subjects were right handed. Regional metabolic measurements in CBGD patients were also compared with similar values from nine typical PD patients [mean (SD) age 52 (10) years]. These patients, described by us previously, (patients 1–5 and 11–14,⁸), had asymmetrical Parkinsonism, but lacked the lateralised cortical signs characteristic of CBGD; these patients all responded consistently to anti-Parkinsonian medication. All control subjects had a complete neurological examination, audiometric screening and neuropsychological evaluation before FDG/PET scanning.

FDG/PET

Patients and control subjects fasted overnight and were allowed a light breakfast six hours before FDG/PET scanning. Patients taking levodopa and other anti-Parkinsonian drugs remained on these medications during PET studies. FDG, produced by a modification of Tewson's synthesis,⁹ was more than 97% radiochemically pure (specific activity 500 mCi/mole). With the PC4600 positron camera,¹⁰ serial PET images (10 × 1 min, 5 × 2 min, 3 × 5 min, 3 × 10 min) were obtained following the injection of 5–10 mCi of the tracer during a controlled resting state: eyes patched and auditory stimulation (music and intermit-

tent verbal commands delivered through acoustically isolated earphones). The time course of plasma ¹⁸F radioactivity was determined by sampling radial arterial blood.

Region of interest (ROI) analysis was performed on 128 × 128 PET reconstructions that were corrected for random coincidences, electronic dead time and tissue attenuation. A single scalar correction was used to compensate for scatter effects in transmission, cross-calibration, and emission scans. Twenty four (12 per hemisphere) standardised cortical and subcortical grey matter (GM) ROIs and two cerebellar and two brainstem ROIs were outlined on reconstructed PET brain slices with reference to a neuroanatomical atlas.¹¹ In four CBGD studies compartmental GM rate constants (k_1 – k_3) and cerebral blood volume were estimated from the time course of blood and regional brain radioactivity.¹² To reduce noise, individual subjects' mean rate constants, averaged across GM ROIs, were used to "functionalise" raw-count images acquired between 45 and 55 minutes after tracer injection.^{13–15} In the remaining study (patient 5), rCMRGlC was determined using average GM rate constants derived from the four dynamic FDG/PET studies.^{14,15} "Peak" rCMRGlC values were obtained by averaging the upper 10% of functionalised ROI pixel values. Whenever anatomical regions straddled contiguous PET brain slices, rCMRGlC was calculated by weighting component ROI values by the number of thresholded pixels. To facilitate comparison with previously published rCMRGlC data, the lumped constant was assumed to be 0.42.^{7,13} Absolute rCMRGlC values were obtained from patient and control scans for a standard set of ROIs in the two hemispheres. Regional metabolic asymmetry was computed as $(L - R)/(L + R) \times 100$, where L and R refer to left- and right-sided rCMRGlC, respectively. Group mean regional differences for CBGD and PD patients and normal volunteers were compared using the following procedures: 1) paired Student's *t* tests incorporating the Bonferroni correction for multiple comparisons; 2) analysis of variants (ANOVA) with the Newman-Keuls multiple comparison test to determine which groups were different from each other. Differences between groups were considered significant when comparisons using both methods exceeded 95% confidence limits ($p < 0.05$). Intrasubject correlations were calculated between contrast measures in different brain regions.

FDOPA/PET

In patient 2 (table 1), presynaptic dopaminergic function was assessed with [¹⁸F]fluoro-L-dopa (FDOPA) and PET using a method described by us previously.⁸ Rate constants for FDOPA uptake (K_1) for right and left striatum were calculated using a multiple-time graphical approach.^{8,16} Mean striatal K_1 and the left-right difference in striatal K_1 were compared with values derived from the typical PD patients using Student's *t*-test.⁸

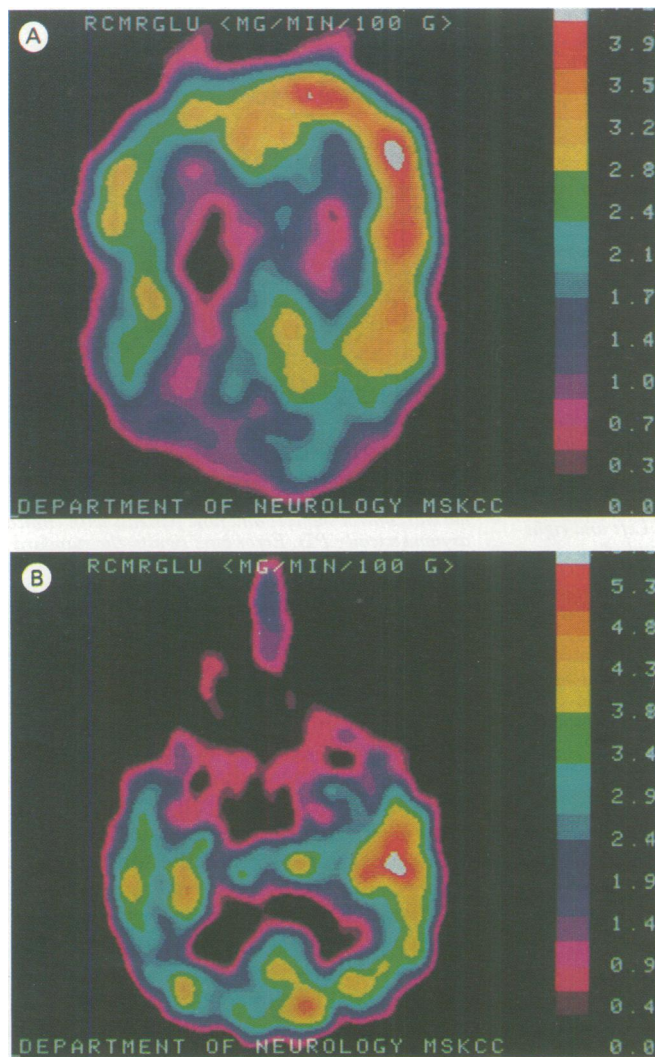


Figure 1 Patient 1: [^{18}F] fluorodeoxyglucose (FDG)/PET brain slices at the level of the fronto-parietal cortex (A) and the thalamus (B). Pixel values refer to cerebral metabolic rate for glucose (mg/min/100 gm), as indicated by the colour stripes. This patient with cortico-basal ganglionic degeneration displayed an asymmetrical reduction in glucose metabolism most apparent in the left cerebral cortex and thalamus.

Results

FDG/PET

Typical FDG/PET images from a CBGD patient (patient 1) are demonstrated in fig 1. In CBGD patients, estimated values for k_1 [0.048 (0.005), mean (SEM)] were significantly lower than control values [(0.084 (0.004), $p < 0.0001$)] but not PD values [0.061 (0.004) $p = 0.11$]. Estimated values for k_2 and k_3 for CBGD patients did not differ from PD or control values. The mean global metabolic rate (GMR) for CBGD patients [(3.95 (0.47)] was significantly lower than mean values for normal subjects [(6.41 (0.197) $p < 0.0001$)] and PD patients [(4.90 (0.28), $p < 0.001$)]. Mean rCMRGLU values for the CBGD group were reduced ($p < 0.05$) in the lateral temporal, paracentral, and inferior parietal regions, and in the frontal operculum compared to the normal group (fig 2). Mean rCMRGLU values for CBGD and PD patients did not differ significantly.

Left-right rCMRGLU asymmetry measures for the CBGD patients are given in table 2. Mean metabolic asymmetry measures differed significantly between groups in each of the

following brain regions: thalamus ($p < 0.02$), hippocampus/medial temporal cortex ($p < 0.01$), and the inferior parietal lobule ($p < 0.0001$). In each of these regions, mean asymmetry for the CBGD group was greater than that of normals or asymmetrical PD patients (fig 3). Asymmetry measures in normal subjects and asymmetrical PD patients did not differ significantly. No significant between group differences in metabolic asymmetry were observed in other brain regions.

Individual metabolic asymmetry measures reached statistical significance (t tests) inconsistently in 4/5 of the CBGD patients studied. With the exception of the hippocampus/medial temporal region in patient 2 and the frontal operculum in patient 5, all significant metabolic asymmetries reflected reduced glucose metabolism contralateral to the most affected limbs. Parietal lobe asymmetry of 5% or more was evident in all CBGD patients, whereas in PD patients and in normal controls all regional asymmetry measures were less than 5% in absolute value. All parietal asymmetries reflected lower glucose metabolism contralateral to the most severely involved limbs. Hippocampal asymmetry exceeded 5% in the four patients in whom this region was identified; these asymmetries were directed opposite to the parietal lobe asymmetries.

Pairwise correlation of regional asymmetry measures revealed thalamic asymmetries to be positively correlated with metabolic asymmetries in the medial and lateral frontal cortex ($r = 0.89$; $p < 0.05$) and inferior parietal lobule ($r = 0.90$; $p < 0.04$), and with total hemispheric asymmetries ($r = 0.90$; $p < 0.04$). Parietal lobe asymmetries were found to be negatively correlated with metabolic asymmetries in the hippocampus ($r = -0.99$; $p < 0.01$). Other inter-regional asymmetry correlations in CBGD patients were not significant. We found no significant pairwise correlation between regional asymmetry measures in PD patients or normal subjects.

FDOPA/PET

An FDOPA/PET image (patient 2) at two hours post-injection is illustrated in fig 4. FDOPA uptake rate constants (K_i) for left and right striatum were 6.75 and 4.69 ($\text{min}^{-1} \times 10^{-3}$) respectively, reflecting a relative reduction in K_i contralateral to the worse affected limbs. These values were lower than those measured in two normal volunteer subjects [(14.94 (2.42)], but the significance of this observation cannot be determined because of the small sample size. These K_i values did not differ from mean striatal K_i values derived from 11 PD patients [(6.1 (0.85); $p = 0.89$)]. In this patient, the difference between right and left K_i values was also not different from the mean K_i difference in PD patients [(1.32 (0.50) $p = 0.67$)].

Discussion

We suggested the diagnosis of CBGD in five patients based upon clinical findings of lateralised cortical dysfunction in the setting of

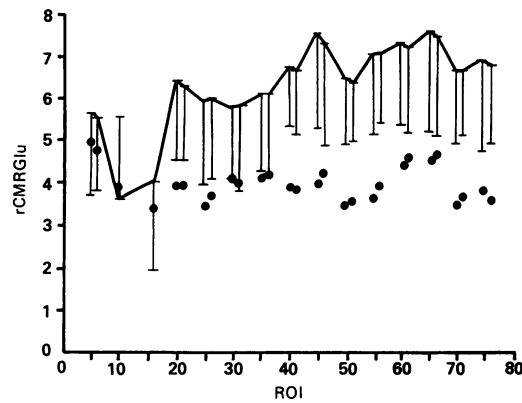


Figure 2 Mean regional cerebral metabolic rate for glucose (mg/min/100 g) values for five patients with cortico-basal ganglionic degeneration (open circles) and 18 normal control subjects: rCMRGlc values plotted as a function of region-of-interest (ROI) number (#) and hemisphere to produce metabolic profiles. Left and right hemisphere values are plotted as ROI # and (# + 1), respectively. Error bars footed on the control profile represent the 95% confidence intervals for the difference between regional means incorporating the Bonferroni correction for multiple comparisons. ROI Code: 5, cerebellum; 10, brainstem; 15, midbrain; 20, basal ganglia; 25, thalamus; 30, hippocampus/medial temporal cortex; 35, lateral temporal cortex; 40, opercular cortex; 45, posterior temporal cortex; 50, medial frontal cortex; 55, lateral frontal cortex; 60, calcarine cortex; 65, cuneus; 70, inferior parietal cortex; 75, paracentral cortex.

progressive, asymmetrical levodopa-resistant Parkinsonism. In one case, the diagnosis was confirmed pathologically by the presence of neuronal achromasia. We found that, as a group, these CBGD patients were metabolically distinguished from control populations primarily by greater mean metabolic asymmetry in the thalamus, hippocampus and inferior parietal cortex. It should be noted that the demonstration of focal alterations in glucose metabolism and metabolic asymmetries with FDG/PET may be confounded by the presence of underlying cortical atrophy on CT or MRI scans. Although focal cortical atrophy may affect rCMRGlc measurements because of volume averaging with surrounding cerebrospinal fluid, partial volume effects may be reduced by our thresholding strategy.¹⁷ Moreover, significant metabolic asymmetries were detected in three CBGD patients without discernible anatomical asymmetry in CT and/or MRI scans. CT disclosed

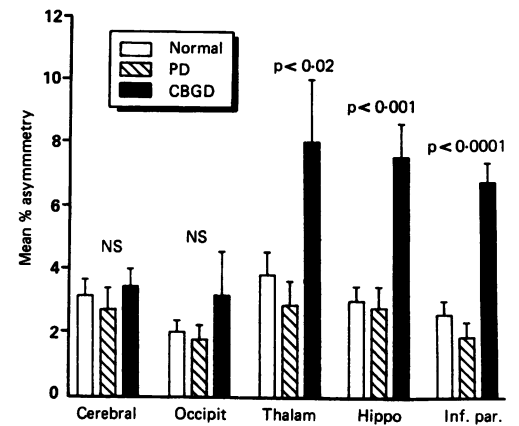


Figure 3 Mean absolute left-right rCMRGlc asymmetry measures in five cortical-basal ganglionic degeneration (CBGD) patients compared with: 18 normal control subjects and nine patients with clinically asymmetrical PD. Error bars signify the standard error of the mean. Significant asymmetries in thalamic, inferior parietal and hippocampal glucose metabolism were evident in the CBGD patients compared with normal volunteers and PD patients. (CEREBEL = cerebellum, OCCIPUT = occipital lobe, THALAM = thalamus, HIPPO = hippocampus/medial temporal, INF PAR = inferior parietal lobule).

asymmetrical cortical atrophy in two other patients, but the radiographic changes were mild and would not fully account for the cortical rCMRGlc asymmetries noted on the PET scans. Furthermore, the additional finding of thalamic rCMRGlc asymmetries which correlate with metabolic asymmetries in associated cortical regions suggests that the cortical asymmetries are not an artifact of asymmetrical loss of cortical tissue.

Although mean absolute hippocampal, thalamic and inferior parietal asymmetries measured were significantly greater in the CBGD population, the patients' individual asymmetry values were less consistent. As shown in table 2, significant metabolic asymmetries were present in a variety of brain regions, including several not characteristically involved in necropsy descriptions (for example, the hippocampus/medial temporal cortex (ROI 30) and the calcarine cortex (ROI 60)^{12,6}). Moreover, some of the significant metabolic asymmetries, notably in the hippocampus (patient 2) and operculum and cerebellum (patient 5), indicated relative metabolic reductions ipsilateral to the more severely affected

Table 2 CBGD: Metabolic Left-Right Asymmetries

Case No.	Regions													
	Cereb	BasGgl	Thal	Hippo	Lat-Temp	Oper	Post-Temp	Med-Front	Lat-Front	Calc	Cuneus	Infr-Par	Paracntrl	
1	2.92	1.27	-14.68†	7.18	-10.79*	-12.35‡	-3.41	-6.89‡	-14.03‡	-6.21	1.39	-7.28*	-	
2	3.82	3.83	9.21	-10.48†	-1.03	2.98	-3.97	3.33	2.94	1.85	-0.65	8.20†	8.33	
3	-3.94	-4.68	2.93	5.41	-1.65	0.30	-7.17	-3.04	-2.34	0.67	-	-5.00	-	
4	-1.70	4.86	-7.93	7.32	-4.34	-0.70	1.37	-0.68	-2.94	-6.92*	0.74	-5.80	2.25	
5	5.02	-6.22*	-5.56	-	7.08	10.97‡	1.24	-1.16	-5.74	-0.42	-4.55	-7.83	4.84	
Mean	3.48	4.17	8.06	7.60	4.99	5.46	3.43	3.02	5.61	3.21	1.83	6.82	5.14	
SD	1.24	1.84	4.41	2.11	4.04	5.77	2.41	2.45	4.89	3.12	1.84	1.37	3.06	
PD (n = 9)														
Mean	2.75	2.57	2.91	2.83	1.75	3.59	2.35	1.67	3.65	1.81	0.93	1.91	2.07	
SD	1.95	2.31	2.28	1.90	1.36	2.04	2.02	1.06	2.20	1.38	0.65	1.45	2.53	
NORMAL (n = 18)														
Mean	3.18	3.23	3.87	3.05	2.79	2.49	4.37	1.65	2.58	2.05	2.27	2.63	3.38	
SD	2.21	2.00	3.11	1.90	2.75	1.92	3.48	1.19	2.00	1.57	2.15	1.82	2.54	

Metabolic asymmetries $\geq 5\%$ are underlined. Statistically significant differences in regional asymmetry between CBGD patients and 18 subjects are designated as: * (p < 0.05); † (p < 0.01); ‡ (p < 0.001)

Cereb Cerebellum; BasGgl Basal ganglia; Thal Thalamus; Hippo Hippocampus; Lat-Temp Lateral temporal; Oper Operculum; Post-Temp Posterior temporal; Med-Front Medial frontal; Lat-Front Lateral frontal; Calc Calcarine; Cuneus Cuneus; Infr-Par Inferior parietal; Paracntrl Para central

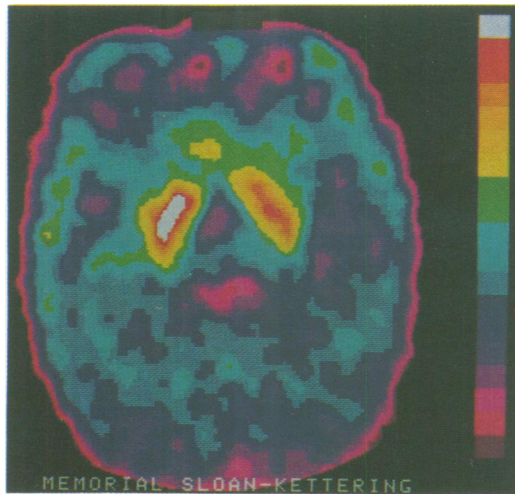


Figure 4 Patient 2: [^{18}F] fluorodopa (FDOPA)/PET brain slice at the level of the basal ganglia. The colour stripe quantifies ^{18}F radioactivity at two hours after FDOPA injection (black: 0 cpm/voxel; white: 31 cpm/voxel). Striatal FDOPA uptake was relatively lower on the right side, contralateral to the more severely affected limbs (see text).

limbs. Whether these asymmetries reflect multiple foci of pathological involvement in the two hemispheres or remote functional consequences of disease in related brain regions is uncertain. The precise relevance of these metabolic asymmetries to the pathobiology of CBGD can be clarified only with the study of more patients and better necropsy correlations.

We did, however, find that the 5% threshold for regional metabolic asymmetries may be practical in differentiating the FDG/PET scans of CBGD suspects from normals and asymmetrical PD patients. As opposed to normals and classical hemi-Parkinsonians, all CBGD patients had several regional metabolic asymmetries of 5% or more, even in regions where asymmetries did not reach actual statistical significance. Additionally, inferior parietal metabolic asymmetries in all these patients were consistently at or above the 5% level. This suggests that the finding of parietal lobe metabolic asymmetries of this magnitude in clinically asymmetrical drug resistant Parkinsonians may be helpful in supporting the diagnosis of CBGD and in differentiating this disease from asymmetrical PD. More studies are needed to ascertain the utility of metabolic imaging with PET in the differential diagnosis of the akinetic-rigid movement disorders.^{18–21}

The presence of significant metabolic asymmetries in patients with presumed CBGD is consistent with previous PET investigations using different metabolic tracers. Watts *et al*^{3,4} reported two clinically diagnosed CBGD patients with reduced frontal blood flow (rCBF) and oxygen metabolism (rCMRO₂) contralateral to the most severely affected limbs. Similarly, Sawle *et al*²² noted coupled decreases in rCBF and rCMRO₂ in the frontal, parietal and temporal cortices of six individuals with presumed CBGD as well as reduced striatal FDOPA uptake. These investigators, however, did not comment upon the existence of correlations between different metabolically asymmetrical regions and possible remote diaschisis effects.

In addition to significant metabolic asymmetries, we found CBGD patients to have:

- 1) lower mean k_1 values;
- 2) lower global metabolic rate for glucose [GMR];

- 3) lower mean rCMRGlc in the lateral temporal paracentral, inferior parietal and frontal opercular regions.

We feel, however, that these findings must be interpreted with caution, given potential ageing effects in the comparison of populations not strictly controlled for this parameter. Nonetheless, significant alterations in kinetic rate constants, global and regional metabolic rates for glucose, and metabolic asymmetries have not been documented consistently in investigations of normal ageing,^{23–25} suggesting that the metabolic changes encountered in CBGD may not be attributed simply to the advanced age of these patients.

Contrary to expectations, estimates of GM rate constants revealed a decreased mean k_1 (forward, or uptake kinetic rate constant) in the CBGD group—compared with normal, but not age-matched, control subjects. CBGD patients, however, did not differ from the PD group with respect to the estimated kinetic rate constants. Since kinetic rate constants have not been found to change in the course of normal ageing,²³ the k_1 difference between CBGD and normal may indicate a pathological alteration in glucose transport in this disorder. We have similarly found a significant decline in k_1 in PD patients.⁸ It is possible that k_2 and/or k_3 abnormalities may also be present in CBGD, but may not have reached statistical significance because of the small sample size and the large coefficient of variation associated with these parameters.^{12,15} The significant decline in mean GMR for the CBGD group is probably not solely a reflection of reduced mean k_1 , as the mean GMR for this group was significantly lower than both the PD and the normal control groups, whereas mean k_1 did not differ significantly between the CBGD and PD groups. Similarly, it is unlikely that the reduction in glucose metabolism was merely an ageing effect.^{23,24} It is likely that the significant decline in global and regional glucose metabolism in CBGD is a reflection of the extensive and regionally selective cortical neuronal loss documented in necropsy studies.^{1–6}

Although metabolic imaging with PET may be useful in distinguishing CBGD from typical PD and other Parkinsonian syndromes, the assessment of nigrostriatal dopaminergic function with FDOPA/PET is less specific. The reduction in striatal FDOPA uptake described in our CBGD patient is quantitatively similar to that encountered by us in typical PD,⁸ and by others in the hypokinetic movement disorders.^{21,22,26} Differential FDOPA uptake in the caudate and putamen^{22,26} could not be assessed with the resolution of our tomograph.

Our PET results in CBGD patients are consistent with published neuropathological findings.^{1,2,6,7} Rebeiz *et al*¹ were the first to recognise CBGD as a distinct clinicopathological entity, although they termed the illness corticodentatonigral degeneration after the loci of major histopathological change. In

their three original patients, these authors (and subsequently others²⁻⁷) noted the presence of asymmetric gliosis and achromatic or pale neuronal inclusions in the parietal, posterior frontal and paracentral cortices, and in the substantia nigra—generally more pronounced contralateral to the more affected limbs. These morphological changes may be the substrate for the distinctive clinical manifestations and PET scan asymmetries reported here in living patients.

The finding of a significant positive correlation between cortical metabolic asymmetries, particularly in the inferior parietal lobule, and those occurring in the thalamus, reflects the close anatomical and functional relationship of these structures. The presence of uncrossed cortico-thalamic diaschisis in CBGD patients is consistent with the pathological finding of localised thalamic cell loss and gliosis,^{1,2,6} which was presumed secondary to cortical neuronal loss.¹

Interestingly, the original authors noted that the thalamic pathology was most pronounced in the nucleus lateralis posterior,¹ the structure most closely associated with the inferior parietal lobule.^{27,28} Whether the reversed asymmetry in hippocampal metabolism found in some of our patients represents a form of crossed diaschisis is uncertain, but is not a manifestation of primary pathology, as this region seems to be spared pathologically.^{1,2,6} Although we have been unable to demonstrate an interrelationship between cortical and thalamic metabolic asymmetries in normal or PD brains, Akiyama *et al*²⁹ have reported a correlation between cortical and thalamic metabolic asymmetries in Alzheimer's disease. Focal cortical hypometabolism and cortico-thalamic diaschisis may be evident in both CBGD and Alzheimer's disease, but these two entities are clearly distinguishable on clinical grounds—our patients presented with progressive lateralised motor dysfunction and not with intellectual decline. Furthermore, while some histopathological resemblance has been noted between CBGD and Pick's disease, the topography of the pathological⁶ and metabolic changes³⁰ is quite different in the two diseases and suggest a major nosological distinction.

In conclusion, our FDG/PET findings, which are consistent with previous clinical and pathological descriptions of CBGD, may allow for the distinction of this entity from typical PD in life. Although the diagnosis of CBGD can only be confirmed at necropsy, the variety of histopathological changes found in the brains of patients with putative CBGD^{5,6} suggests that the clinical syndrome may have several neuropathological substrates. Thus, in addition to supporting the clinical diagnosis of CBGD, FDG/PET may also prove useful ante mortem insights into the metabolic pathologies which underlie this unusual illness.

The authors wish to thank Dr Jerome Posner for referring patient 2 to us, and Mr George Abramson and Mrs Karen Knipper for manuscript preparation. This work was supported in part by National Institutes of Health Grant NS-23473 and a grant from the Parkinson's Disease Foundation.

- 1 Rebeiz JJ, Kolodny EH, Richardson EP Jr. Corticodentatonigral degeneration with neuronal achromasia. *Arch Neurol* 1968;18:20-33.
- 2 Case Records of the Massachusetts General Hospital: Case 38-1985. *New Eng J Med* 1985;313:739-48.
- 3 Watts RL, Williams RS, Growden JD, *et al*. Corticobasal ganglionic degeneration. *Neurology* 1985;35:178.
- 4 Watts RL, Mirra SS, Young RR, Burger PC, Villier JA, Heyman A. Cortico-basal ganglionic degeneration (CBGD) with neuronal achromasia: clinical-pathological study of two cases. *Neurology* 1989;39:140.
- 5 LeWitt P, Friedman J, *et al*. Progressive rigidity with apraxia: the variety of clinical and pathological features. *Neurology* 1989;39:140.
- 6 Gibb WRG, Luthert PJ, Marsden CD. Corticobasal degeneration. *Brain* 1989;112:1171-93.
- 7 Riley DE, Lang AE. Corticobasal ganglionic degeneration (CBGD): further observations in six additional cases. *Neurology* 1988;38:360.
- 8 Eidelberg D, Moeller JR, Dhawan V, *et al*. The metabolic anatomy of Parkinson's disease: Complementary ¹⁸F-fluorodeoxyglucose and ¹⁸F-fluorodopa positron emission tomographic studies. *Movement Disorders* 1990;5:203-13.
- 9 Tewson TJ. Synthesis of no-carrier-added fluorine-18 2-fluoro-2-deoxyglucose. *J Nucl Med* 1983;24:718-21.
- 10 Kearfott KJ, Carroll LR. Evaluation of the performance characteristics of the PC4600 Positron Emission Tomograph. *J Comput Assist Tomogr* 1984;8:502-13.
- 11 Eycleshymer AC, Schoemaker DM. *A cross-sectional anatomy*. New York: Appleton-Century, 1911.
- 12 Evans AC, Diksic M, Yamamoto YL, *et al*. Effect of vascular activity in the determination of rate constants for the uptake of ¹⁸F-labelled 2-fluoro-2-deoxy-D-glucose; error analysis and normal values in older subjects. *J Cereb Blood Flow Metab* 1986;6:724-38.
- 13 Phelps ME, Huang SC, Hoffman EJ, *et al*. Tomographic measurement of local cerebral glucose metabolic rate in humans with [¹⁸F] 2-fluoro-2-deoxy-D-glucose. Validation of method. *Ann Neurol* 1979;6:371-88.
- 14 Rottenberg DA, Moeller JR, Strother SC, *et al*. The metabolic pathology of the AIDS dementia complex. *Ann Neurol* 1987;22:700-6.
- 15 Dhawan V, Moeller JR, Strother SC, Evans AC, Rottenberg DA. Effect of selecting a fixed dephosphorylation rate on the estimation of rate constants and rCMRglu from dynamic [¹⁸F] fluorodeoxy-glucose/PET data. *J Nucl Med* 1989;30:1483-8.
- 16 Patlak CS, Blasberg RG, Fenstermacher JD. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. *J Cereb Blood Flow Metab* 1983;3:1-7.
- 17 Strother SC, Allard C, Moeller JR, *et al*. Methodological factors affecting patterns of regional cerebral glucose metabolism as determined by ¹⁸F-fluorodeoxyglucose/positron emission tomography. *J Cereb Blood Flow Metab* 1987;7:S443.
- 18 De Volder AG, Francart J, Laterre C, *et al*. Decreased glucose utilization in the striatum and frontal lobe in probable striatonigral degeneration. *Ann Neurol* 1989;26:239-47.
- 19 Goffinet AM, De Volder AG, Gillain C, *et al*. Positron tomography demonstrates frontal lobe hypometabolism in progressive supranuclear palsy. *Ann Neurol* 1989;25:131-9.
- 20 Foster NL, Gilman S, Berent S, *et al*. Cerebral hypometabolism in progressive supranuclear palsy studied with positron tomography. *Ann Neurol* 1988;24:399-406.
- 21 Leenders KL, Frackowiak RSJ, Lees AJ. Steele-Richardson-Olszewski syndrome: brain energy metabolism, blood flow and fluorodopa uptake measured by positron emission tomography. *Brain* 1988;111:615-30.
- 22 Sawle GV, Brooks DJ, Thompson PD, *et al*. PET studies on the dopaminergic system and regional cortical metabolism in corticobasal degeneration. *Neurology* 1989;39:163 [suppl].
- 23 Hawkins RA, Mazziotta JC, Phelps ME, *et al*. Cerebral glucose metabolism as a function of age in man: influence of the rate constants in the fluorodeoxyglucose method. *J Cereb Blood Flow Metab* 1983;3:250-3.
- 24 Creasey H, Rapoport SI. The aging human brain. *Ann Neurol* 1985;17:2-10.
- 25 Haxby J, Grady C, Koss E, *et al*. Longitudinal study of cerebral metabolic asymmetries and associated neuropathological patterns in early dementia of the Alzheimer's type. *Arch Neurol* 1990;47:753-60.
- 26 Brooks D, Ibanez V, Sawle GV, *et al*. Variation in anterior and posterior putamen, and head of caudate ¹⁸F-Dopa uptake in idiopathic Parkinson's Disease and atypical parkinsonian syndromes. *Neurology* 1990;40:168.
- 27 Eidelberg D, Galaburda A. Inferior parietal lobe: divergent architectonic asymmetries in the human brain. *Arch Neurol* 1984;41:843-52.
- 28 Eidelberg D, Galaburda A. Symmetry and asymmetry in the human posterior thalamus. *Arch Neurol* 1982;39:325-35.
- 29 Akiyama H, Harrop R, McGeer PL, *et al*. Crossed cerebellar and uncrossed basal ganglia and thalamic diaschisis in Alzheimer's disease. *Neurology* 1989;39:541-8.
- 30 Kamo H, McGeer PL, Harrop R, *et al*. Positron emission tomography and histopathology in Pick's disease. *Neurology* 1987;37:439-45.