Movement Disorders
Vol. 22, No. 9, 2007, pp. 1278–1285

[^{123}I] FP-CIT Spect Study in Vascular Parkinsonism and Parkinson's Disease

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Abstract: There is substantial evidence to support a role for small vessel disease (SVD) as a cause for vascular parkinsonism (VP). Using [^{123}I] FP-CIT SPECT (single photon emission computed tomography), we have tried to determine whether VP patients have pre-synaptic dopaminergic function similar to PD patients, and whether the severity of parkinsonian symptoms as well as the levodopa response in VP patients are correlated with pre-synaptic dopaminergic dysfunction. Thirteen patients fulfilling operational clinical criteria for VP had [^{123}I] FP-CIT scans. Mean [^{123}I] FP-CIT uptake in the basal ganglia was significantly lower in VP patients than in healthy controls, and the asymmetry index was not significantly different between these groups. In contrast, compared with the PD group, only the mean asymmetry index was significantly lower in VP patients. None of the parameters measured was significantly different between VP patients who had an insidious onset of parkinsonism (VPi) and those who had an acute onset (VPa). There was a significant correlation between the bilateral basal ganglia FP-CIT uptake reduction in the VP patients and UPDRS motor scores, but not with the mean % reduction in motor UPDRS after levodopa. We suggest that in the majority of VP patients, pre-synaptic dopaminergic function is reduced. The presence of a rather symmetrical FP-CIT uptake in the basal ganglia may help to distinguish VP from PD and could therefore be used as a criterion for the clinical diagnosis of VP. © 2007 Movement Disorder Society

Key words: vascular parkinsonism; FP-CIT SPECT; L-dopa challenge; criteria

Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) have provided circumstantial support for the concept of vascular parkinsonism (VP).[1–5] There is also histopathological evidence to support a role for small vessel disease (SVD) as a cause for parkinsonism. In a recent study, brains of patients with parkinsonism that lacked evidence of a specific neurodegenerative process revealed significantly more severe microscopic SVD-associated pathology and more macroscopic lacunar infarcts than non-parkinsonian control patients.[6] Although the mechanism by which vascular lesions of the brain cause parkinsonism has still to be clarified, two types of VP can be identified based on clinical features and histopathological findings: one with an insidious onset and vascular lesions diffusely located in the watershed areas (VPi); the other with an acute onset and strategic infarcts in areas that theoretically can decrease thalamocortical drive[7] and lead to a predominantly contralateral hypokinetic rigid syndrome or (VPa).[6]

The ligand ^{123}I-FP-CIT ([^{123}I]-2β-carbomethoxy-3β-(−4-iodophenyl)-*N*-(3-fluoropropyl)-nortropane) binds specifically and with high affinity to pre-synaptic dopamine transporters. Results obtained with ^{123}I-FP-CIT have been shown to be reliable and reproducible[8–10] in

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Received 30 March 2006; revised 22 December 2006; accepted Accepted 01 March 2007

Published online 7 May 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.21479

showing a reduction of pre-synaptic tracer uptake which correlates with disease duration and severity of Parkinson's disease (PD).[10,11] Using [^{123}I] FP-CIT SPECT (single photon emission computed tomography), we have aimed to determine whether VP patients have pre-synaptic dopaminergic function similar to PD patients, whether VPa and VPi patients can be distinguished in regard to their pre-synaptic dopaminergic function, and whether the severity of parkinsonian symptoms as well as the levodopa (L-dopa) response in VP patients are related to pre-synaptic dopaminergic dysfunction.

METHODS

Participants

Thirteen patients fulfilling proposed clinical criteria for VP[6] were examined clinically, and with [^{123}I] FP-CIT. All patients were selected consecutively from the Movement Disorders clinics at UCLH NHS Foundation Trust, and at the National Hospital for Neurology and Neurosurgery, Queen Square, London, UK. They had parkinsonism defined by the presence of bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions in either upper limb or lower limb, including the presence of reduced step length) and at least one of the following: tremor, muscular rigidity, and postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction. Their parkinsonism could be related to cerebrovascular disease on MRI using a previously described approach.[6] Six VPa patients had an acute or delayed progressive onset of parkinsonism within 1 year of a stroke with infarcts in or near areas that can increase the basal ganglia motor output or decrease the thalamocortical drive directly (substantia nigra in one, globus pallidus/putamen area in the others). The parkinsonism at onset consisted of a controlateral bradykinetic rigid syndrome in three of them, and development of shuffling gait in the 3 others. In 4 VPa patients the clinical syndrome had progressed to become symmetrical. The other seven VP patients had an insidious onset of parkinsonism with extensive subcortical white matter lesions, bilateral symptoms at onset, and the presence of early shuffling gait or early cognitive dysfunction (but without clinical features suggestive of DLB such as hallucinations and fluctuating cognition). In one of these the clinical syndrome had progressed to become asymmetrical. Patients with a history of repeated head injury, definite encephalitis, neuroleptic treatment at onset of symptoms, presence of cerebral tumor or communicating hydrocephalus on CT or MRI scan, or other alternative explanations for parkinsonism were excluded. None of the VP patients showed evidence of hypometric or slowing of saccadic eye movements.

[^{123}I] FP-CIT SPECT scan results were compared with those of 14 healthy volunteers and 14 PD patients, of which 12 in each group came from historical database results.[12] All scans were obtained under identical conditions. PD was diagnosed in accordance with accepted clinical criteria.[13] This study was approved by the Joint Ethics Committee of University College London/University College London Hospitals and patients signed informed consent.

Data Acquisition

The clinical assessment and the SPECT scans were ideally performed on separate days (not more than one week apart) though the clinical assessment with L-dopa challenges occasionally was performed on the day of the [^{123}I] FP-CIT SPECT scan examination. All patients and controls were examined by the same investigator (JZ), who assessed the Unified Parkinson's Disease Rating Scale (UPDRS) in VP patients when "off."[14] SPECT investigations were performed at the Institute of Nuclear Medicine/University College London, London. Prior to scanning, subjects received potassium iodide orally to block thyroid uptake of radioactive iodide. [^{123}I]-FP-CIT was injected intravenously at a dose of 185MBq on the morning of the scanning day. Imaging was carried out 3.5 to 5 hours later (time intervals between groups were not significantly different) in a way similar to our previous study[12] using a GE XCT single detector gamma camera/STAR computer system (GE, Milwaukee, WI) fitted with a high resolution parallel hole collimator.

Data Processing

Routine protocols for data processing were used similar to a previous study[12] and in summary included Hanning 2D pre-filtering (cut-off frequency = 1.2 cycles/cm) of all projections followed by back-projection reconstruction algorithm. Attenuation correction was always applied using the Chang method[15] and an attenuation coefficient of 0.12/cm. Transaxial slices were obtained with single pixel (3.3 mm) thickness.

Data Analysis

Analysis of the [^{123}I] FP-CIT scans was done in a random order by two investigators (AE and FF) blinded to the clinical diagnosis of the participants. Protocols for data analysis of [^{123}I] FP-CIT SPECT scans are described in more detail elsewhere.[12] AE and FF alternated in analyzing each scan while the other investigator checked the technique and results. They used methods identical to the previous studies.[12] The results and analysis methods used in

each scan were then second-checked by DC. Briefly, 3 measurements were made.

Calculation of Total Striatal Binding Potential Index (BP%).

All slices containing the striatum (basal ganglia BG) were added up into a single thick transaxial cut, whose thickness varied from 10 to 15 pixels, i.e. 33–49.5 mm. Regular regions of interest (ROI) were placed around the BG and in the brain background (Bk) (occipital cortex) on the summed transaxial slices. After reading total radioactivity counts for each region (right and left BG and Bk), total striatal binding potential BP% was obtained using the following formula: $[(BG - Bk)/Bk] \times 100$ for each hemisphere, where: basal ganglia uptake = BG = specific + non-specific binding, and background = Bk = non-specific binding (occipital cortex).

Calculation of Subregional Striatal Binding Index (SBi).

Three contiguous striatal slices with the highest counts and best definition of caudate and putamen were added together to obtain a midstriatal 9.9 mm thick "best striatal slice." Circular ROIs of identical size were utilized to sample total radioactivity counts for striatal subregions in each hemisphere, one each for caudate nucleus, anterior putamen and posterior putamen. Then simple radioactivity ratios were calculated (SBi) by dividing all subregional counts by the background counts. Caudate over putamen ratios were also calculated.

Calculation of Total Striatal Binding Potential (BP%) Asymmetry Index.

The absolute value of the BP% asymmetry index was obtained using the following formula:

$[(R-L)/(R+L)] \times 2 \times 100$; R = striatum, contralateral to the most affected side of the body, L = striatum, ipsilateral to the most affected side of the body.

L-Dopa Response.

VP patients who were already on dopaminergic therapy were asked to withhold this for at least 12 hours before the L-dopa challenge test. The 4 patients who were not regular users of L-dopa received domperidone 60 mg daily for three days before the challenges to block any unwanted peripheral dopaminergic effects. The motor section of the UPDRS[14] was carried out before and at least 60 min after the administration of 200/50 mg L-dopa/benserazide. The mean % reduction in motor UPDRS after L-dopa was also calculated. Furthermore, case notes were scrutinized to describe the response to L-dopa as uncertain, poor, transient, good or excellent, to complement the "responses" observed after acute L-dopa challenge. Maximal doses, duration of L-dopa therapy, and the occurrence of motor complications were also checked.

Statistical Analysis

Group means were calculated and compared using Mann Whitney *U*-Test. The correlation between [^{123}I] FP-CIT SPECT results and clinical parameters (disease duration, UPDRS motor scores) was examined with Spearman's rho.

RESULTS

Patients

At the time of scanning the mean age in VP patients (74.1 years, range: 56–89) was significantly higher than in healthy controls (66.3 years, range: 49–85), and the PD group 66.0 years (53–82). Mean disease duration was not significantly different between VP patients (6.6 years, range 2–18) and PD patients (8.3 years, range 2–21). The clinical characteristics of VP patients are shown in Table 1.

Clinical Assessments

The UPDRS motor scores of VP patients while being "off" are shown in Table 1. Their mean UPDRS motor score was 25.8 (range 4–61).

L-Dopa Response

In case notes, the response was noted to be *good* in 1 patient, in whom it was complicated after 4 years by wearing-off and mild choreatic and dystonic dyskinesia in one leg, *transient* in 2, *poor* in 3, and *uncertain* in 5. In 2 patients L-dopa had never been prescribed. Mild choreatic dyskinesia and wearing-off had been noted in one transient responder 5 years after treatment, two others had shown moderately severe foot dystonia after 1 and 3 years. All patients had been able to take L-dopa with carbidopa or benserazide up to 750 mg daily, except of four of them who took 500 mg daily, and two only 375 mg daily. The dosage could not have been increased because of severe nausea and vomiting even under domperidone or dystonia. Mean duration of L-dopa treatment was 4.5 (0.5–15) years. All VP patients underwent an acute L-dopa challenge and the responses are shown in Table 1. The mean % reduction in motor UPDRS after L-dopa was 14% (range 0–60%). In 2 patients the UPDRS motor score after the L-dopa challenge was decreased by more than 30%, a response that in clinically definitive idiopathic Parkinson disease would be predictive of a sustained long term response of L-dopa.[17] In one responder, a 56 years old man who experienced a sudden onset of bradykinesia and postural tremor of the right hand a few years before, the tremor disappeared com-

TABLE 1. *Clinical characteristics of all VP subjects*

Group no.	Age (yr)	Sex	Disease duration (yr)	Onset	UPDRS part 3	MMSE < 24	L-dopa challenge (%)	MRI-scan
1	70	M	6	Insidious	61[s]	−	<5	WMC
2	66	F	3	Insidious	24[s]	−	21	WMC, R-PO, L+R: P,CN,GP,T
3	81	F	10	Insidious	13[s]	−	0	WMC
4	67	M	11	Acute	30[a]	−	0	WMC, R: P,GP,PO
5	76	F	4	Insidious	4[s]	−	<5	WMC
6	56	M	2	Acute	5[a]	−	60	L: P
7	78	F	10	Acute	27[s]	−	52	WMC, PO, L+R: P,CN,GP
8	76	M	7	Insidious	26[s]	+	19	WMC
9	77	M	5	Insidious	60[s]	+	0	WMC, L+R: P
10	89	M	18	Acute	26[s]	−	15	WMC, R+L: GP, Mes.
11	67	F	3	Insidious	35[a]	−	<5	WMC, L: GP
12	82	M	4	Acute	11[s]		0	WMC, R+L: GP
13	79	F	3	Acute	13[s]	−	0	WMC, R: GP, SN

Group data are shown as mean ± S.D. UPDRS-3 reflects the motor sub-score of the Unified Parkinson's disease rating scale while "off". MMSE: mini-mental state examination.[16] [s]: signs were symmetrical. [a]: signs were asymmetrical. WMC: diffuse confluent white matter changes, mainly located in the watershed areas (periventricularly and deep white matter). P: lacunar infarction in the putamen; CN: in the caudate nucleus; GP: in the Globus Pallidus; T: in the thalamus; PO: in the pons; Mes.: in mesencephalon (near red nucleus); SN: substantia nigra; L: left; R: right.

pletely and bradykinesia improved importantly after his first L-dopa dose ever. The other responder was a 78 years old woman who noticed a sudden onset of lower body parkinsonism dominated by shuffling gait. When challenging her with L-dopa her parkinsonism had become more generalized with only little action tremor. All features improved importantly after L-dopa, including her gait, consistent with the descriptions in her case notes where the response was noted to be good. Both responders showed striatal lesions on MRI. The descriptions of L-dopa responses in case notes complemented well the responses observed after the acute L-dopa challenges. In one of the two challenged responders, a good response was described in the case notes, in the other L-dopa was not tried before. In all others in whom an uncertain, poor or transient response was noted the response after challenge had turned out negative.

^{123}I-FP-CIT SPECT

Mean BG BP% (right and left averaged) was significantly lower in both VPa and VPi groups compared to healthy controls (Table 2). In contrast, caudate/putamen ratios and ratios between caudate and posterior putamen (all right and left averaged) were significantly higher in both VPa and VPi groups compared to healthy controls (Table 2). The asymmetry index was not significantly different between these groups. In contrast, compared to the PD group, only the mean asymmetry index was significantly lower in both VP groups (Table 2, see also Fig. 1), and none of the other parameters was significantly different. None of the parameters measured was significantly different between VPi and VPa groups. Although some VPa patients showed a "punched out" FP-CIT uptake in the putamen or globus pallidus corre-

TABLE 2. *Striatal binding potential index, subregional ratios, and asymmetry in VP patients, controls, and PD patients (Mann-Whitney U test comparison between two independent samples)*

	Number	Total striatal BP% R, mean	Total striatal BP% L, mean	Total striatal BP% R+L, mean	Caudate/putamen ratio, mean	Caudate/post putamen ratio, mean	AI, mean
VPi	7	26.6 (4.4–51)	28 (9.4–62)	27.3 (6.9–56.5)	1.47◇ (1.22–1.63)	1.85# (1.39–2.56)	6.6* (1–18.2)
VPa	6	24.8 (7–53.9)	26.4 (13.9–50.1)	25.6 (16.1–52.0)	1.47◇◇ (1.33–1.76)	1.79## (1.45–2.24)	10.9◆ (1.8–28.79)
PD	14	20.9(8.4–44.6)	22.6 (2.4–53.8)	22.2 (5.4–49.2)	1.60 (1.25–2.1)	1.97 (1.43–3.03)	35.3 (3.8–111.9)
Normal	14	69.4 (48.5–91.5)	68.5 (52.2–97.3)	69 (51.7–94.4)	1.18 (1.02–1.46)	1.39 (1.22–1.91)	5.3 (0.4–11.6)

Values in parentheses are in ranges.
VPi versus PD: *Only the asymmetry index is significantly different (2 tailed test) $P = 0.002$.
VPa versus PD: ◆Only the asymmetry index is significantly different (2 tailed test) $P = 0.021$.
VPi versus Normal: BP% R + L; $P = 0.001$, ◇ Caudate/putamen ratio: $P = 0.004$, # Caudate/post putamen ratio: $P = 0.006$.
VPa versus Normal: BP% R + L: $P = 0.001$, ◇◇ Caudate/putamen ratio: $P = 0.004$, # # Caudate/post putamen ratio: $P = 0.007$.

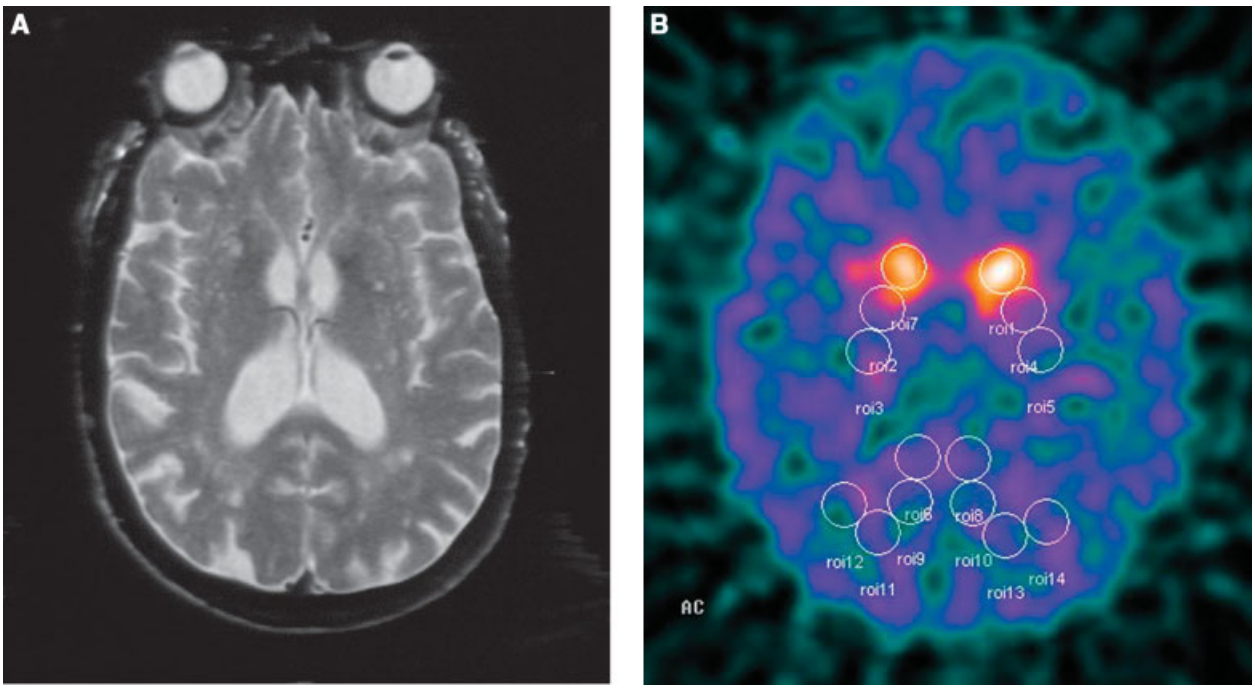

FIG. 1. (a) T2 weighted axial MRI scan of a 77-year-old VPi patient with a slowly, progressive frontal gait disorder showing vascular lesions diffusely in the white matter and bilaterally in the putamen. (b) DAT-SPECT scan of this patient showing striatal FP-CIT uptake reduction in a similar distribution as in PD, only less asymmetrical.

sponding to a focal infarction, asymmetry indexes in these cases were still lower than in PD (see Fig. 2). None showed a "punched out" FP-CIT uptake in the caudate nucleus. There was a significant correlation between the bilateral BG BP% in the 13 VP patients and UPDRS motor scores during off ($r = -0.587$; $p = 0.035$), but not disease duration. The BG BP% of those patients taking antiparkinson drugs was not significantly different from those not taking it. The bilateral BG BP% was neither significantly correlated with the percentage change of UPDRS after L-dopa. The BG BP% in the two L-dopa responders was lower (mean 29.5, range 28.4–30.5) than in the healthy controls (mean 69.0, range (51.7–94.4), but not compared to the 11 non-responders (mean 26.0 range 6.9–56.5).

DISCUSSION

VP patients did not meet accepted clinical criteria for PD,[13] mainly due to a lack of the following supportive criteria: only three patients had a unilateral onset, in all of them the onset was acute; persistent asymmetry was present in only 2 of these patients; in only 1 VP patient (pill-rolling) rest tremor was present, he had a lacunar infarct in the mesencephalon; the clinical course in only 4 patients was more than 10 years; at start of this study, none of the VP patients responded excellently on L-dopa.

In a recent clinico-pathological study[6] two types of VP were identified based on clinical features and histopathological findings: one with an acute or delayed progressive onset with strategic infarcts and parkinsonism at onset consisting of a controlateral bradykinetic rigid syndrome or shuffling gait, within 1 year after a stroke (VPa); and the other with an insidious onset of parkinsonism with extensive subcortical white matter lesions presenting with bilateral symptoms, the presence of early shuffling gait (the classical "lower body parkinsonism") or early cognitive dysfunction (VPi). All the VPa patients in that study had a distinctive clinical presentation at onset with symptoms related to a focal lesion. However, they could not be reliably distinguished from the VPi patients by neurological examination later in the disease process. The superimposition of diffuse SVD on the lacunar infarcts may explain this observation.

We have found a significant pre-synaptic dopaminergic deficit in both VPi and VPa groups compared to healthy controls. The dopaminergic deficit in the VP patients demonstrated by [^{123}I] FP-CIT SPECT was as marked as in our PD control group and it also affected the striatum in a pattern similar to that described in PD, where—in accordance with neuropathological evidence of selective degeneration of nigrostriatal neurons[18]—a predominant reduction of tracer uptake is typically seen in the posterior putamen.[19] This was reflected in the caudate/putamen radioactivity ratios which in VP pa-

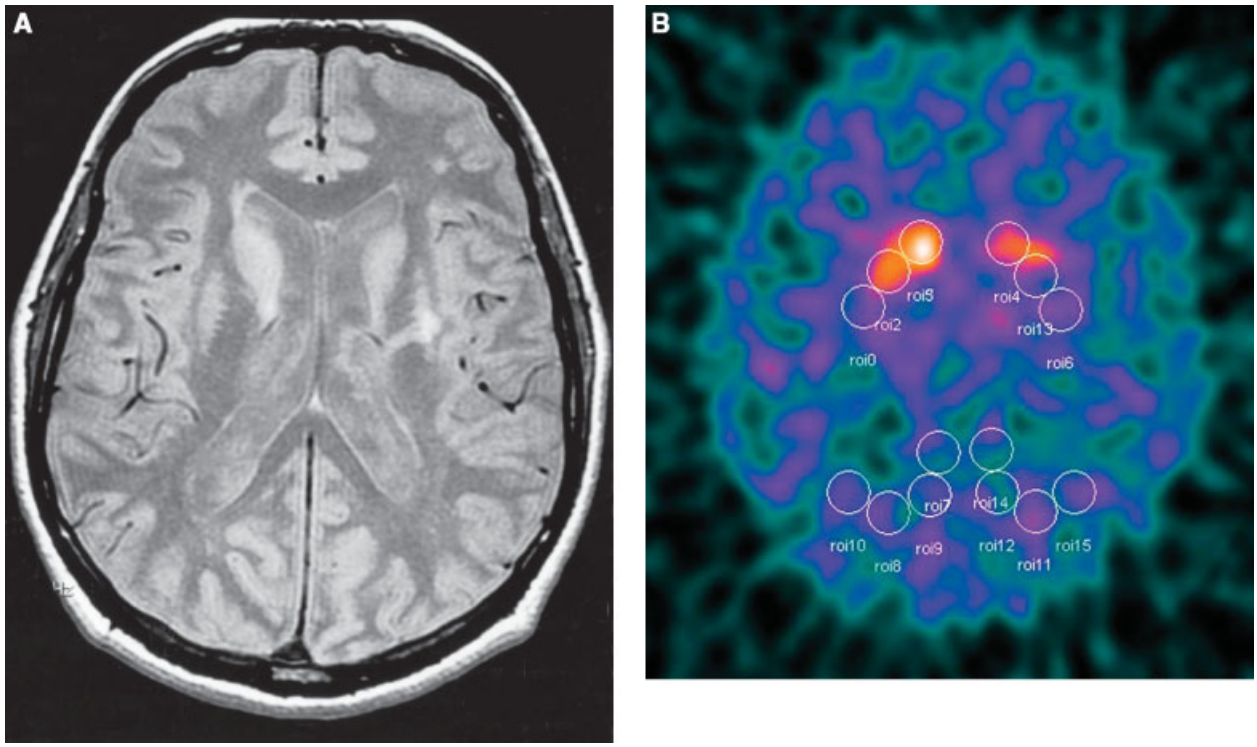

FIG. 2. (a) Proton density weighted axial MRI scan of a 56-year-old VP patient showing a lacunar infarction involving the left corona radiata and extending inferiorly into the putamen. Two years earlier, the patient had experienced a sudden onset of bradykinesia and postural tremor of the right hand, no right arm swing when walking, with normal power and no rigidity, together with transient dysphasia, dysarthria and right-sided facial weakness. Subsequently, there was slow and gradual improvement. The L-dopa response was positive. (b) His SPECT scan revealed FP-CIT uptake reduction that was much more severe in the left than in the right striatum. The asymmetry index was 5.81.

tients, similarly to the PD group, were significantly higher than in the healthy controls. Unexpectedly, our VPi patients showed a pre-synaptic dopaminergic deficit similar to VPa patients. This suggests that MRI may underestimate the degree of ischemia and gliosis in VP patients which may also involve the nigrostriatal system. These functional imaging findings are supported by post mortem studies of VP in which nigral cell loss and gliosis in the substantia nigra occurs in a similar pattern to that commonly described in PD,[6,20] in which medial cell groups of the rostral portion of the substantia nigra are only slightly involved compared to the severe damage to the lateral parts.[18,21]

Our results are in agreement with a few reported cases[22–27] where pre-synaptic dopaminergic dysfunction in VPa was seen with SPECT. One SPECT study also showed pre-synaptic dopaminergic dysfunction, but the relationship between parkinsonism and vascular lesions in those patients was unclear since parkinsonism had developed after a lacunar stroke and strategic lesions had been excluded by CT scan.[28] Some of our VPa patients showed a "punched out" FP-CIT uptake in the putamen or globus pallidus corresponding to a focal infarction, similar to cases reported by Peralta et al.[26] and Plotkin et al.[27] None of our scans had a contralateral unilateral "punched-out" appearance with normal uptake on the ipsilateral side [^{123}I] FP-CIT as was described by Kolokouris and colleagues.[25] Two previous SPECT imaging studies[24,30] showed normal pre-synaptic tracer binding in VP patients. This may be explained by the different inclusion criteria used (for instance, no or only minimal upper limb involvement[29,30]), resulting in predominantly lower limb disease severity[30] (mean UPDRS 12.6 vs 25,8) and a much shorter mean disease duration[30] (3.6 vs 6.6 years) than in our study. These inconsistencies suggest that VP is heterogeneous, and that subtypes in which pre-synaptic dopaminergic function is preserved occur despite their absence in this study.

There was a clear correlation between the extent of [^{123}I] FP-CIT tracer uptake reduction and disease severity in common with PD patients.[10,11] However, unlike PD,[10,11] the disease duration was not correlated to the extent of [^{123}I] FP-CIT tracer uptake reduction, probably because of a more non-linear disease progression in VP or perhaps due to the small number of VP patients examined.

Asymmetry of degeneration of nigrostriatal dopaminergic projections to the motor striatum is a hallmark of

PD that underlies the common initial asymmetry of clinical features at presentation. The clinical presentation of VP at onset may also be asymmetrical, especially when the disease onset is acute. However, at the time of scanning the parkinsonism was relatively symmetrical in most of them. This could explain our observation that the mean "asymmetry index" comparing right to left striatal FP-CIT binding in VP patients was similar to healthy volunteers, and lower than in PD. This is consistent with the notion that the disease in the vascular group usually is more diffusely distributed than in PD.[6] It also provides further support for the notion that this disorder is distinct from PD. The presence of MRI evidence of diffuse SVD, in most patients, may explain this observation. Substantial asymmetry of pre-synaptic uptake reduction in VP patients[22–24] may be a less common finding and reflect the heterogeneity of the syndrome. These patients had all presented with asymmetrical parkinsonism of sudden onset caused by a rare vascular lesion in the contralateral substantia nigra or the upper peduncle/thalamus area, and SPECT had been performed in the acute phase.

The [^{123}I] FP-CIT uptake was not significantly correlated with the mean % reduction in motor UPDRS after levodopa. Only 2 of our 13 VP patients, both VPa, showed a positive response to L-dopa. VP in general has been considered to respond poorly or not at all to L-dopa treatment.[4,31–33] In a retrospective study, however, we recently, described a good or excellent response to L-dopa in some pathologically confirmed VP cases.[34] Similar to these pathologically confirmed cases the 2 L-dopa responsive patients in the present study showed vascular damage in the putamen and globus pallidus area and both had a decreased [^{123}I] FP-CIT uptake. A positive response in the two VP patients may reflect the presence of a remaining pool of striatal dopaminergic nerve terminals in a dysfunctional nigrostriatal pathway which remains adequate to convert exogenous L-dopa into dopamine and thus to restore the intrinsic dopaminergic drive.[35] The absence of a L-dopa response in the other patients with a pre-synaptic dopaminergic deficit shows that dysfunction of the striatal dopamine receptors or the non-dopaminergic thalamocortical pathway also contribute to the pathophysiology of VP. Plotkin et al.[27] recently described a L-dopa unresponsive VP patient (case 3) with a pronounced [^{123}I] FP-CIT deficit in whom IBZM SPECT showed impairment of D2 receptors.

We recently suggested that VP may be a result of focal infarcts in strategic areas disrupting the basal ganglia motor output or more diffuse small vessel disease disrupting the thalamocortical pathways. Our current findings suggest that in both situations the pre-synaptic nigrostriatal pathways may be affected, and may contribute to the emergence of Parkinsonism, even though chronic ischemia in VPi patients could not be detected by ^{1}H-Magnetic Resonance Spectroscopy.[36]

The control group was significantly younger than the VP group and one could postulate that the [^{123}I] FP-CIT uptake reduction in VP patients could have been (partially) caused by the age difference. In agreement with human post-mortem study which showed fallout of dopaminergic neurons with advancing age in the substantia nigra pars compacta at a rate of 5–7% per decade,[18] striatal [^{123}I] FP-CIT binding decline of 4% per decade has been observed in healthy controls.[37,38] The influence of this age difference therefore, is likely to be negligible compared to the mean total striatal [^{123}I] FP-CIT binding reduction of 62% in our VP patients.

Although data on the effects of dopaminergic medication on [^{123}I] FP-CIT SPECT binding in humans are not yet available, we think that our results are unlikely to be influenced by this. Lavalaye et al.[39] concluded that subchronic and acute administration of dopaminergic medication (L-dopa and pergolide) in rats do not influence [^{123}I] FP-CIT SPECT binding. The 4 VP patients who were not on chronic administration of L-dopa also showed a reduced pre-synaptic [^{123}I] FP-CIT uptake similar to the others. A dopamine agonist was taken chronically by only 1 VP patient, in whom it was discontinued 12 hours before the [^{123}I] FP-CIT SPECT scan investigation.

In summary, this is the first systematic SPECT study in VP where the diagnosis was made using operational clinical criteria based on a previous clinico-pathological study, and where MRI was also performed to detect the degree of vascular involvement in each case.

We have demonstrated a clear tracer uptake reduction on [^{123}I] FP-CIT SPECT in VP patients compared with that in healthy volunteers. Although the deficit and its pattern were similar to PD, the pre-synaptic dopaminergic system impairment in our VP patients was less asymmetrical. The reduction of pre-synaptic dopaminergic function was related to the severity of parkinsonism, but not to disease duration.

We conclude that in the majority of VP patients, fulfilling stringent operational diagnostic criteria, the pre-synaptic dopaminergic function is reduced. Although only two VP patients responded well to L-dopa, we recommend that all patients with clinically suspected VP should receive an adequate trial of L-dopa (1 gam of L-dopa a day for three months).

Addendum: After the study was completed two patients have come to autopsy. In patient 9, who died 2 years ago, a diagnosis of VP was confirmed post-mortem. Patient 11 came to autopsy a few months ago and a definite diagnosis of MSA instead of VP was made. Excluding the latter patient from the analysis does neither change any of the results nor any of the conclusions in this study.

Acknowledgments: This study was supported by GE Healthcare Biosciences and the Reta Lila Weston Institute of Neurological Studies.

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