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Secondary Parkinsonism due to focal substantia nigra lesions: a PET study with [^{18}F]FDG and [^{18}F]Fluorodopa

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We present a 71 year old woman with predominantly right sided parkinsonism of sudden onset, but without tremor. Magnetic resonance imaging (MRI) depicted lesions affecting the substantia nigra (SN) bilaterally, but more pronounced on the left side. There were no other discernible structural lesions. Using positron emission tomography (PET), we investigated regional cerebral metabolic rate of glucose (rCMRG) using the tracer [^{18}F]-fluorodeoxyglucose (FDG), and striatal dopa decarboxylase capacity using the tracer [^{18}F]-L-6-fluorodopa (FDOPA). The degree and pattern of distribution of FDOPA uptake reductions (putamen > caudate nuclei) were similar to those in idiopathic Parkinson's disease (PD). FDG uptake also revealed similar changes (reductions in frontal cortex and cerebellum, but increases in thalamus), except for putamen which showed reduced rCMRG. In conclusion, the absence of tremor at rest accords with experimental SN lesions. The PET findings in this atypical condition are explained in terms of deafferentation of various brain regions involved in motor control. Furthermore, they illustrate the metabolic effects related to acute focal lesions of the SN as opposed to the progressive degeneration in idiopathic PD and may serve to help unravel the complicated pathophysiology underlying these conditions.

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Key words: Secondary Parkinsonism; Vascular Parkinsonism; Substantia Nigra; Positron Emission Tomography; PET; [^{18}F]Fluorodeoxyglucose; [^{18}F]Fluorodopa

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The spectrum of movement disorders presenting with parkinsonism is known to result from either reversible specific pharmacological interference or irreversible destructive lesions in the nigrostriatal system (1). The differential diagnosis includes degenerative diseases such as Parkinson's disease (PD), Multiple system atrophy (MSA) or Progressive supranuclear palsy (PSP). The incidence of symptomatic, i.e. secondary parkinsonism is estimated to be less than 5% of all parkinsonian disorders (2). Parkinsonism in association with isolated lesions of the substantia nigra (SN) only rarely occurs (3–5). Such a condition has to date not been investigated in terms of energy metabolic or dopaminergic neurotransmitter system abnormalities.

Case report

A 71-year-old woman with a 10-year history of predominantly right sided parkinsonism of sudden onset was admitted for further diagnostic evaluation. There was no relevant history of trauma, encephalitis, cyanide or manganese intoxication, nor of hypoparathyreoidism. Risk factors for stroke included moderate hypertension, episodes of atrial fibrillation and bilateral carotid artery plaques as assessed by Doppler sonography, the latter investigation being performed exclusively in the course of her recent follow-up examination. Subsequent antistroke medication consisted of enalapril hydrogen maleate 5 mg/d and acetylsalicylate 100 mg/d. Neurological examination under L-dopa substitution identified moderate hypomimea, rigidity in upper and lower extremities, reduced arm swing, difficulties in performing rapid alternate movements as well as bradykinetic gait, corresponding to stage II of the modified Hoehn & Yahr staging (6). The symptoms and signs on the right body side were clearly more pronounced than on the left (approximately 60–70% vs 30–40%, according to clinical

evaluations by two neurologists). No tremor was observed. This was documented on several clinical follow-up examinations including a trial of intermittent withdrawal of anti-parkinsonian medication. Tendon reflexes were symmetrical, plantar responses were flexor and sensory testing was normal. Neuropsychologic testing revealed impaired mental flexibility as shown in the Wisconsin Card Sorting Test (7) and a verbal fluency test (8). No deficits in long-term memory were found. The patient had been treated with a good and stable response with 300 mg L-dopa daily since the onset of symptoms 10 years before. Medication was changed recently due to symptoms suggestive of intermittent periods of akinesia as reported by the patient. There was, however, no evidence of clinical progression according to standardized rating scales (6). Following 700 mg L-dopa plus 175 mg carbidopa daily (Nacom® 100) in combination with selegiline (Movergan®) 5 mg/day, the patient demonstrated episodes of hyperkinetic movements resembling chorea. Thereafter, medication was modified according to Nacom® 100 (5 × 1/2 daily), Nacom retard® 200 (3 × 100) daily, lisuride hydrogen maleate (Dopergin®) 0.4 mg daily, and Movergan® 5 mg/day with subsequent sustained stable response in absence of dopa-induced dyskinesias.

Methods

A cranial CT scan showed a small lesion of low density in the left SN. Additional T2-weighted MRI scans (Philips Gyroscan, 1.5-T, SE, TR/TE = 3.1 s/100 ms), performed before (18 months) and after (six months) the PET examination, depicted a circumscript area of high signal intensity at this location. A lesion of smaller size was identified in the right SN (Fig. 1). No other structural lesions were discernible in subcortical structures (basal ganglia) or cortex.

Two PET measurements were performed consecutively within two days using a four ring Siemens CTI 933/04–16 PET-scanner, allowing simultaneous acquisitions of seven contiguous sections with an in-plane transaxial resolution of 8 mm (full width at half maximum).

229 MBq [18F]Fluorodeoxyglucose (FDG), were injected intravenously over three minutes with an infusion pump. To determine the tracer input function, arterial blood samples were withdrawn from the radial artery. The scanning protocol consisted of 16 time frames with a total scan duration of 48 minutes. Regional metabolic rate of glucose was calculated on a pixel-by-pixel basis. After normalization of all images to the standard stereotactic space of Talairach and Tournoux (9) a total of 67 geometrical elliptical regions of interest (ROIs) were placed in a standard template arrangement on respective transaxial images. Fifteen healthy control subjects (mean age 57 ± 10 years) and a group of 25 patients with idiopathic PD (mean age 58 ± 10 years) were used for comparison. Data were expressed as relative values (Glucose Metabolic Index: GMI) calculated as the ratio of selected ROIs to global value.

93 MBq of 6-[18F]Fluoro-L-dopa (FDOPA), were injected intravenously over three minutes with an infusion pump. One hour prior to FDOPA administration subjects were premedicated with 2 mg/kg carbidopa orally. The scanning protocol consisted of 28 time frames with a total scan duration of 124 minutes. Arterial input, metabolite corrected, was obtained through radial artery samples. ROIs were placed on a visual display unit in a standard template arrangement on the putamen (elliptical region of 67.6 mm^2) and caudate nucleus (circular region of 33.8 mm^2) of those two planes with maximal tracer uptake. Occipital ROIs (one circular region of 612.5 mm^2 on each occipital lobe) were defined on identical planes. Data were analyzed with a multiple-time-graphical analysis (MTGA) (10–15), using the arterial input as reference. In the MTGA approach, the gradient of the linear regression of the data indicates the rate of irreversible trapping of activity, described as the influx constant Ki. Ki values for right and left putamen and caudate nucleus were calculated for the patient and compared with those obtained from healthy control subjects (n = 9; mean age 58 ± 5 years) and 20 PD patients: group H&Y I-II (n = 10; mean age 47 ± 7 years; mean disease duration 3 ± 2 years) and H&Y III-IV (n = 10; mean age 58 ± 12 years; mean disease duration 9 ± 5 years).

Results

Fig. 1 shows both SN lesions as indicated on the MRI scan and as delineated according to a neuroanatomical atlas adapted to the original MRI data. This computer-aided procedure allows an estimation of the extent of SN pars compacta and pars reticulata in relation to the brain stem lesion. For a detailed description of this procedure see (16). A quantitative analysis revealed an extension of 14.9 mm^2 (± 2 mm^2) on the left side, involving the pars compacta to approximately 47% and the pars reticulata to approximately 37%. The lesion on the right side was less homogeneous, of smaller size and mainly confined to the pars compacta segment. Quantification of its size was not possible.

PET with FDG revealed changes of GMI in several cortical and subcortical brain regions (Table 1). In the frontal cortex, putamen and cerebellum GMI was decreased by 6 to 9%. There were

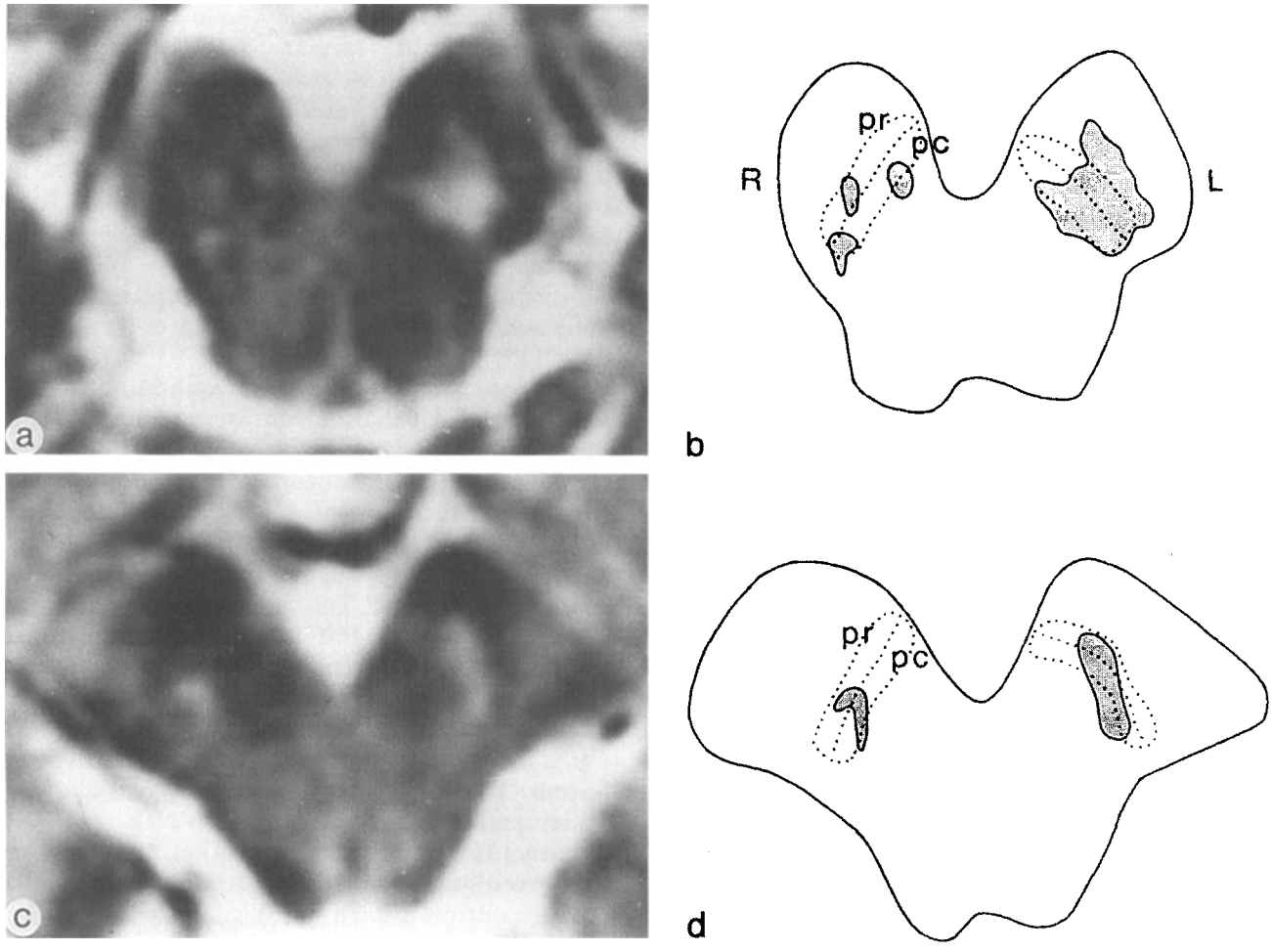

Fig. 1. a–d. MR images (SE, TR = 3.1s, TE = 100ms) of the midbrain of the patient with secondary parkinsonism due to focal substantia nigra (SN) lesions. Two sections parallel to the AC–PC line, (a) 5 mm caudal to (c). The hyperintensive lesion on the left side involves central and lateral parts of the SN pars compacta and reticulata. The lesion on the right side is less extensive, inhomogeneous and involves predominantly the SN pars compacta. The lesions and their relations to SN pars compacta and reticulata are outlined in b and d.

Table 1. Glucose metabolic index (GMI) of the patient compared with 25 PD patients and 15 control subjects

	patient	PD patients n = 25	Controls n = 15
Frontal cortex	**1.08**	1.11 ± .07	1.19 ± .06
Temporal cortex	1.03	1.00 ± .06	1.08 ± .07
Occipital cortex	1.14	1.14 ± .10	1.21 ± .09
Nucleus caudatus	1.16	1.17 ± .06	1.20 ± .08
Putamen	**1.19**	1.33 ± .08	1.28 ± .06
Cerebellum	1.08	1.17 ± .10	1.15 ± .07
White matter	0.53	0.55 ± .05	0.51 ± .05
Thalamus	**1.24**	1.13 ± .10	1.10 ± .07

The bold values of the patient's GMI are at 1.5 to 2 SD away from the control mean (see text).

no marked left-right asymmetries (0–3%). Other regions had normal or only slightly reduced GMI values. The thalamus was the only brain region showing increased glucose utilization (+13%).

FDOPA uptake in the putamen was significantly reduced on both sides, but more pronounced contralateral to the clinically more affected side (39.7% of control values contralaterally vs. 46% ipsilaterally; mean of two planes). Moderate reductions of FDOPA uptake were found in the caudate nuclei (66% contra- vs. 62% ipsilaterally; mean of two planes). Table 2 summarizes the influx constants (Ki) for FDOPA uptake of putamen and caudate nucleus in comparison to control and PD values. Figure 2 shows decreased putaminal FDOPA uptake in the patient compared with healthy control person.

Discussion

Among the heterogeneous group of secondary or symptomatic parkinsonian syndromes, focal lesions of the SN, as demonstrated in the patient described here must be considered a rare occurrence (3–5). Several features favor the diagnosis of vascular

Table 2. FDOPA influx values (Ki x 10E-3) in the patient with secondary parkinsonism due to focal substantia nigra lesions.

			PD-patients		
	Patient		H&Y I+II	H&Y III+IV	Controls
	n=1		n=10	n=10	n=9
Caudate Nucleus	Left	9.3	9.4±2.5	6.9±2.0	14.7±4.0
	Right	8.7			
Putamen	Left	5.6	6.3±1.5	4.6±1.1	14.0±3.7
	Right	6.4			

The values of the PD-patients and controls are given as means of left and right hemispheric regions.
The standard deviations given describe the intersubject variability.

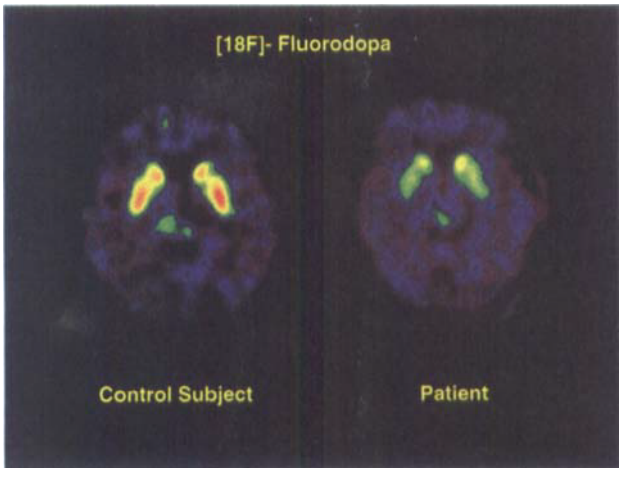

Fig. 2. Positron emission tomography (PET) scan with FDOPA uptake in the patient with secondary parkinsonism due to focal substantia nigra lesions (right image). Demonstration of decreased putaminal and caudal FDOPA uptake as compared with a normal volunteer.

parkinsonism (17) in this patient as there was a sudden clinical onset in the presence of various risk factors for stroke. Despite controversy on this issue, neuroradiologic findings in single cases support the possibility of ischemia-induced parkinsonism (4, 18–21). Our study sought to determine the extent of remote functional changes induced by focal bilateral damage to the SN.

In the patient described here, marked bilateral reductions of FDOPA uptake in striatum were a conspicuous finding. This reflects nigrostriatal dopaminergic dysfunction induced by bilateral damage of the SN pars compacta as indicated by the MRI scans. The topographical distribution of these lesions showed predominant involvement of the lateral portions of the SN. Since dopaminergic neurons in the lateral portions of the SN project primarily to the putamen, while the caudate nuclei are mainly innervated by the medial portions (22–24), highest reductions of FDOPA uptake were found in the putamen and less so in caudate nuclei. These findings are similar to those reported in idiopathic PD (15, 24–28). The stable response to L-dopa over many years in this patient may be explained by the absence, after the initial insult, of a rapidly progressive degeneration in the SN in contrast to the situation in idiopathic PD. It is hypothesized that the remaining pool of striatal dopaminergic nerve terminals was apparently sufficient to convert exogenous levodopa into dopamine and thus to restore the intrinsic dopaminergic drive (15).

The measurement of glucose utilization in this patient yielded values which are compatible with those found in patients with idiopathic PD except for the putamen. Global cortical and more selective frontal lobe decreases of rCMRG and blood flow in idiopathic PD have been reported (29–32). The patient described here showed reduced frontal lobe energy consumption. This is in agreement with her neuropsychological test scores which revealed frontal lobe deficits such as impaired flexibility in problem solving and reduced verbal fluency. A marked increase of the glucose metabolic index was found in thalamus and a moderate reduction in cerebellum. The topography of FDG-uptake changes in idiopathic PD has been extensively reported recently (31). In that communication, FDG uptake was investigated in 22 patients with PD and 20 normal controls using a statistical image covariance method. Various characteristic metabolic changes were found to be pertinent for PD: frontal cortex and cerebellar decreases in conjunction with increases in thalamus and lentiform nucleus. In our patient the metabolic changes, therefore, with the exception of the striatal value, are similar to those found in idiopathic PD and thus are assumed to be the consequence of deficient dopaminergic input from the lesioned SN pars compacta.

In idiopathic PD, striatal energy utilization is generally within the normal range, although relative and sometimes absolute increases of striatal regional cerebral blood flow, oxygen metabolism and glucose metabolism have been described (32, 33). Likewise, in animals it has been shown that neurotoxic administration of N-methyl-4-phenyl-1,2,3,6,-tetrahydropyridine (MPTP) induces increases of neostriatal and pallidal glucose metabolism reflecting striopallidal disinhibition (34).

In contrast, bilaterally decreased striatal rCMRG has been reported in other degenerative disorders, such as MSA (35) or PSP (36–37) and reflect structural cell loss in striatum in addition to dopaminergic neurotransmitter defects. The findings in this patient are unlikely due to a degenerative process involving striatal structures, given the absence of MRI changes at the level of the basal

ganglia and a protracted rather stable clinical course after a sudden onset and a continuous excellent response to levodopa therapy. It is hypothesized here that the damage by the SN lesions to the non-dopaminergic nigrostriatal neurons, which comprise approximately 20% of nigrostriatal input (38), might be responsible for the reduction of striatal synaptic activity and thus decreased energy utilization. Also, involvement of pars reticulata in the lesion as described here is likely to have different regulatory synaptic consequences compared to those resulting from degeneration of only the dopaminergic SN pars compacta neurons as is the case in PD.

Of interest is the absence of tremor in this patient. This is in accordance with the hypothesis, based on experimental monkey studies, that lesions confined to the SN do not result in tremor at rest (39). To produce tremor, midbrain lesions probably need to damage several structures including ventral parts of the superior cerebellar peduncle, the descending rubral systems and the SN. From the MRI scans in our patient it can be seen that only the SN was lesioned thus sparing the rubro-olivo-cerebellar and cerebello-thalamic pathways. In conclusion the results of this particular patient illustrate the similarities and differences of cerebral metabolic and dopaminergic neurotransmitter consequences in secondary focal SN lesions as compared to PD and may serve to help unravel the complicated pathophysiology underlying these conditions.

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