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Dopamine Transporter Single-Photon Emission Computerized Tomography Supports Diagnosis of Akinetic Crisis of Parkinsonism and of Neuroleptic Malignant Syndrome

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Abstract: Akinetic crisis (AC) is akin to neuroleptic malignant syndrome (NMS) and is the most severe and possibly lethal complication of parkinsonism. Diagnosis is today based only on clinical assessments yet is often marred by concomitant precipitating factors. Our purpose is to evidence that AC and NMS can be reliably evidenced by FP/CIT single-photon emission computerized tomography (SPECT) performed during the crisis.

Prospective cohort evaluation in 6 patients. In 5 patients, affected by Parkinson disease or Lewy body dementia, the crisis was categorized as AC. One was diagnosed as having NMS because of exposure to risperidone. In all FP/CIT, SPECT was performed in the acute phase. SPECT was repeated 3 to 6 months after the acute event in 5 patients. Visual assessments and semiquantitative evaluations of binding potentials (BPs) were used. To exclude the interference of emergency treatments, FP/CIT BP was also evaluated in 4 patients currently treated with apomorphine.

During AC or NMS, BP values in caudate and putamen were reduced by 95% to 80%, to noise level with a nearly complete loss of striatum dopamine transporter-binding, corresponding to the ''burst striatum'' pattern. The follow-up re-evaluation in surviving patients showed a recovery of values to the range expected for Parkinsonisms of same disease duration. No binding effects of apomorphine were observed.

By showing the outstanding binding reduction, presynaptic dopamine transporter ligand can provide instrumental evidence of AC in Parkinsonism and NMS.

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Abbreviations: AC = Akinetic Crisis, BP = binding potential, FP = Beta CIT-ioflupane, NMS = Neuroleptic malignant syndrome, PD = Parkinson's Disease.

INTRODUCTION

Around 0.3% of Parkinson disease (PD) patients per year suffer from a critical syndrome, akinetic crisis (AC) also termed malignant syndrome, acute akinesia, or Parkinson hyperpirexia syndrome,[1,2] occurring concomitantly with infectious disease, surgery, trauma, or because of drug manipulation or withdrawal.[1,2] AC is characterized by alterations of mental status, total akinesia with dysphagia, hyperthermia, dysautonomia and elevation of muscle enzymes, and by ''absent response to rescue drugs or to dopaminergic drugs that adequately reduced symptoms before occurrence of the crisis.''[2] AC symptoms are identical to symptoms of neuroleptic malignant syndrome (NMS) induced by typical and some atypical neuroleptics[2] and by dopamine depleting drugs.[1] A review of cause–effect relationship in NMS and AC[3] underlined that there is no cause–effect ratio in NMS, at contrast with the serotoninergic syndrome, evidencing that AC is indistinguishable from NMS and suggested that both represent idiosyncratic severe complications induced by heterogeneous causes with (probably) common pathophysiology.[3]

AC and NMS diagnosis is often difficult because the concomitant precipitating events (eg, septicemia, endocarditis) may confound evaluation of core symptoms.[2]

Imaging of dopamine receptor might help understanding the mechanism of these acute syndromes, by evidencing postsynaptic or presynaptic binding alterations.[5,6]

Absent postsynaptic ligand-binding (iodobenzamide) was observed in a single NMS case,[4] due to antidopaminergic drug administration. However, postsynaptic ligand-binding is extremely sensitive to interference of antidopaminergic (neuroleptics) treatment[7]; therefore, this finding was considered, by the authors of the report, expected and predictable.

Presynaptic, dopamine transporter (FP-beta CIT or ioflupane) binding instead is not modified by antidopaminergic drugs[8] and the effect of dopaminergic drugs is considered also absent or minor[9] despite some controversies.[10,11] Therefore, presynaptic dopamine transporter-binding evaluations could be potentially useful for the assessment of both, AC or NMS. Two recent reports,[12,13] describing each 2 cases of AC in hydrocephalus and in Parkinsonism, observed severe inhibition of ioflupane-binding. In our tertiary center[1,2] for movement disorders emergencies (including AC or NMS)in prospective cohort evaluation, we could evaluate FP/CIT binding by single-photon emission computerized tomography (SPECT) in 6 patients, 5 with parkinsonism and definite AC and 1 with NMS.

To exclude interference of the rescue drug (apomorphine), we performed an ancillary SPECT study in 4 PD patients without AC, who were chronically treated with apomorphine at the same doses as the ones used for emergency treatment.[14]

MATERIAL AND METHODS

Patients With AC-NMS

During 2011 to 2014, 12 patients were addressed to our clinic because of AC in Parkinsonism, and 1 patient because of NMS. In 6 patients, we could evaluate FP/CIT SPECT scan during the acute phase of the crisis. Five of the 6 patients were addressed to our tertiary center because of AC, were affected by PD according to UKBBC,[15] and were regularly followed in our clinic or in secondary clinics of the area. Table 1 summarizes clinical characteristics of patients and the precipitating factors. All patients/caregivers provided informed consent for therapy and neuroimaging, respecting the declaration of Helsinki.[16]

In 2 patients, AC was not related to withdrawal of dopaminergic drugs or administration of antidopaminergic drugs. In 1 patient, L-dopa withdrawal due to acute abdomen was the precipitating factor. One patient had NMS due to risperidone administration, but follow-up evidenced appearance of L-dopa responsive Parkinsonism despite no further exposition to antidopaminergic drugs occurred. Further details on methods are reported in online resource 1.

During AC, all patients were unresponsive to L-Dopa at the same drug regime that adequately corrected symptoms before the appearance of akinesia and were unresponsive to administration of dopaminergic rescue drug.[1,2] Clinical signs were characterized by fever (>39°C), severe akinesia (UPDRS III 56.0 ± 9.1) dysphagia, labile blood pressure, confusional state and high serum levels of CPK (827.7 ± 124.8 IU/L), and myoglobuline (696.1 ± 139.9 ng/mL) (online resource 1). All vital parameters were constantly followed during the crisis.

During AC, all patients were treated with L-Dopa administered with nasogastric tube, according to prior drug regimens, and methyprednisolone 1 g/day, heparin, hydration. Four patients received continuous apomorfine infusion subcutaneously (rescue drug) with an electronic pump releasing 3.5 to 14 mg/h of apomorphine, for a total dose of 50 to 200 mg/24 h -day, for 2–4 days before SPECT acquisition. All Parkinsonian treatments were withdrawn 12 hours before ligand administration and were re-introduced only after imaging acquisition. Two patients received apomorphine immediately after SPECT acquisition. Five patients recovered completely or partially from AC in 5 to 12 days and returned to proper L-dopa regimens according to our treatment protocols and previous literature.[1,2,14] The fourth patient died on day 22 because of ventricular tachyarrhythmia

Effect of Apomophine in Non-AC-PD Patients

A possible effect of apomorphine on FP/CIT SPECT-binding potential (BP) was postulated in experimental studies on L-Dopa and dopamineagonists,[17–19] although several studies did not evidence BP reduction induced by these drugs.[20,21] To corroborate our findings, we tested the effect of apomorphine in 4 patients not affected by AC. Apomorphine, in continuous subcutaneous infusion, is currently used for the treatment of PD patients experiencing severe motor fluctuations, at the dose of 50 to 200 mg/day subcutaneously.[14,22] Apomorphine is also indicated as a supportive, rescue treatment for AC and NMS[14,22] at the same doses as used in chronic treatment.

Four patients, matched for age and disese duration with the 6 AC-NMS patients, all affected by PD according to UKBBC,[15] all regularly treated with continuous subcutaneous apomorphine 100 to 200 mg/day (7–14 mg/h) because of severe motor fluctuations, underwent FP/CIT SPECT. All patients/caregivers provided informed consent for therapy and neuroimaging, respecting the declaration of Helsinki.[16]

The patients had undergone a first neuroimaging FP/CIT SPECT acquisition 5 ± 1 years before the last evaluation (Figure 1). All patients were also treated with L-Dopa. None of them presented with AC. All dopaminergic drugs were withdrawn 12 hours prior to scanning. Brain scanning was performed 4 hours after the infusion of 166.5 Bq of ^{123}I-FP/Cit, performed according to SPECT scan methods and analyses as described in the following paragraph.

TABLE 1. Demographics, Clinical Characteristics and Precipitating Factors

	Pt 1†	Pt 2	Pt 3	Pt 4*	Pt 5	Pt 6†
Diagnosis	AC in PD	AC in PD	AC in PD	AC in DLB	AC in PD	NMS†
Age/sex	70/F	69/M	69/M	72/F	74/M	74/M
Disease duration, y	7	9	4	6	7	—
H/Y	2	3	2	3	2.5	—
UPDRS before AC	21	32–46	22	25	34	—
UPDRS during AC	73	86	64	67–80	57	86
UPDRS post-AC	42	36–48	27	—	33	36
PE	pneumonia	Surgery, femoral fracture	Flu-like syndrome	Acute abdomen	Gall bladder inflammation	risperidone
Temperature during AC	40°C	39.7°C	38.8°C	40.1°C	39°C	40.9°C
CPK, IU/L	745	805	322	987	315	752
Myoglobin, μg/mL	654	599	189	895	201	578
AC duration, d	5	12	10	—	8	12
Treatment during AC/day	A 150–200 mg	A 50 mg	L-D 600 mg	A 100–200 mg	L-D 400 mg	A 70–150 mg

Demographics, clinical characteristic and precipitating factors in 6 patients with AC/NMS. A = apomorphine, AC = akinetic crisis, H/Y = Hoehn/Yahr, L-D = L-Dopa, NMS = neuroleptic malignant syndrome, PD = Parkinson disease, PE = precipitating event, SPECT = single-photon emission computerized tomography, UPDRS = Unified Parkinson disease Rating Scale part III, yrs = years.

* Patient represented in Figure 1.

† Patients represented in Figure 2.

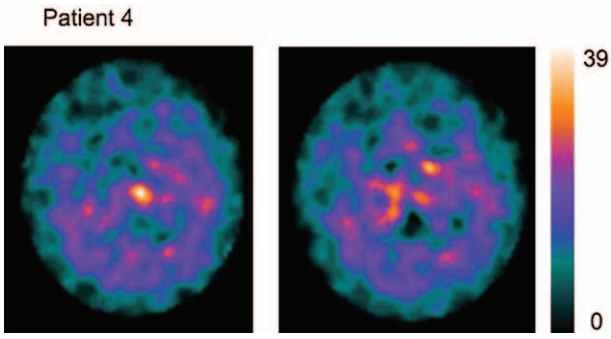

FIGURE 1. FP/CIT SPECT acquisition in patient 4, who died during AC. SPECT is plotted at the maximum saturation level: notice residual activity in areas corresponding to caudate, and the widespread distribution of the ligand, appearing with low levels in extrastiatal areas. Notice that the saturation level of the scale is 1/4 of scales reported in Figure 3, and a 1/5 to 1/4 of Figure 1. Binding uptake shows the typical pattern ''burst striatum,'' a severe bilateral reduction with almost no uptake in either the putamen or caudate with increased background uptake.[28,31]. AC = akinetic crisis, SPECT = single-photon emission computerized tomography.

DAT Acquisition and Analyses

123-I FP-CIT SPECTs were performed in all patients 48 to 72 hours after onset of the AC (Figures 2 and 3A) and 95 ± 2.8 days after recovery in survivors (Figure 3B), with GE, INFINIA double head gamma camera and evaluated according EANM procedure guidelines[23,24] by Nuclear Medicine specialists blinded to diagnosis. All patients/caregivers gave informed consent before SPECT acquisition. This observational study received approval by our local ethical committee, according to the declaration of Helsinki and subsequent revisions.

Brain SPECTs were acquired according to standard procedures.[24–26] 166.5 Bq of 123-I-FP-CIT (DatSCAN Amerham Health, Amsterdam) was injected intravenously 60 min after administration of oral potassium iodide (Lugol solution) to block thyroid uptake of free radioactive iodide. Patients underwent imaging 4 hours after the injection, by means of a dedicated double head gamma camera equipped with ultrahigh-resolution collimators, matrix size 128×128, 120 frames, 40 s/frame, angular 3 degree, zoom 1.5. Slices (5.89-mm thick) were transversal, coronal, and sagittal canthomeatal-orientated Chang's[26] correction with a coefficient of 0.11 cm. Two SPECT evaluation methods were used: semiquantitative analyses of cumulative dopamine transporter bindings[23] by regions of interest (ROI) density evaluation (Table 2), a visual classification comparing color scale intensity of basal ganglia versus background/occipital areas and semiquantitative BasGanV2-assisted evaluation[27–29] by an automated volume if interest (VOI) measurement (Figure 4), assessing total binding density in basal ganglia.

For ROI analysis, 2 adjacent transaxial slices with the highest radiotracer uptake in the basal ganglia were summed (total thickness 11.78 mm) for semiquantitative analysis of caudate and putamen DAT-binding fixed ROIs (ROIs: 1 pixel $2.9 \times 2.9\,mm^2$) were drawn over the putamen, elliptical, 35 pixel, and the caudate, circular, 30 pixel, and an irregular occipital area of 265 pixel. The trace uptake was calculated, analyzing both sides, as: (count density target ROI) − (count density occipital ROI)/(count density occipital ROI) × 100.

For the second semiquantitative measurement, SPECT images were evaluated by a Basal Ganglia software

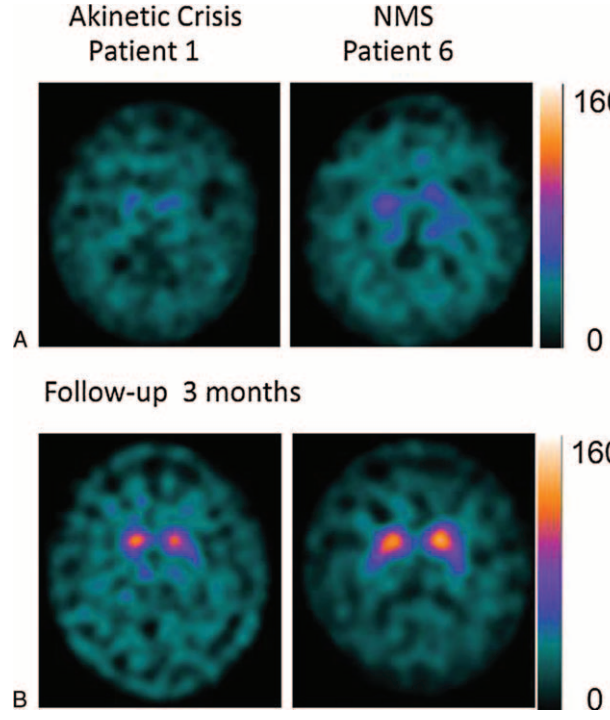

FIGURE 2. FP/CIT SPECT acquisition during AC/NMS, and after recovery, in patient 1 and 6. Notice almost complete disappearance of binding during the crises (''burst striatum'') and recovery (A), 3 months after the crises (B), with appearance of an ''egg shape'' pattern in patient 1 and a ''mixed type'' pattern in patient 6. Notice that saturation level scales are 4 times higher than the scales reported in figure 1. AC = akinetic crisis, NMS = neuroleptic malignant syndrome, SPECT = single-photon emission computerized tomography.

(BasGanV2)[29,30]-assisted evaluation BasGanV2, a PC-based free software (http://aimn.it/struttura/gruppi/gs_neuro.php), which can be used for the analysis of DICOM images after transaxial reconstruction, a D operator-independent technique. The software draws automatically a 3D VOI) for each basal nucleus and provides background VOI; it determines the uptake/binding-potential values in the basal ganglia, and it compares the values obtained in each nucleus with reference to a database of 96 healthy subjects to determine age-adjusted values.[27,29] The binding ratio for ^{123}I-FP-CIT was calculated for putamen and caudate by ([mean counts of the target Tomean counts of background VOI]/[mean counts of the background VOI]). Wilcoxon signed-rank tests were used to assess statistical significance of BP recovery after AC-NMS in the 5 surviving patients. No statistical comparisons were performed in the ancillary study because of the time elapsed from first assessment and because the ancillary study was only designed to understand whether apomorphine-induced changes are comparable with alterations observed during AC-NMS.

The visual assessment method[32] for 123-I-FP-CIT SPECT was also used, to provide simple descriptive evaluation. This method is based on the visual assessment grading system[32] and categorizes tracer capture in 5 patterns.[28–30] Pattern 1 is normal uptake, pattern 2 ''eagle wing'' shows discrete reduction prevalent in the mesial putamen, creating the shape of a wing (Figure 1, left, patient B), pattern 3 ''mixed type'' is asymmetric uptake reduction (Figure 1, left, patient D), the pattern 4, ''egg

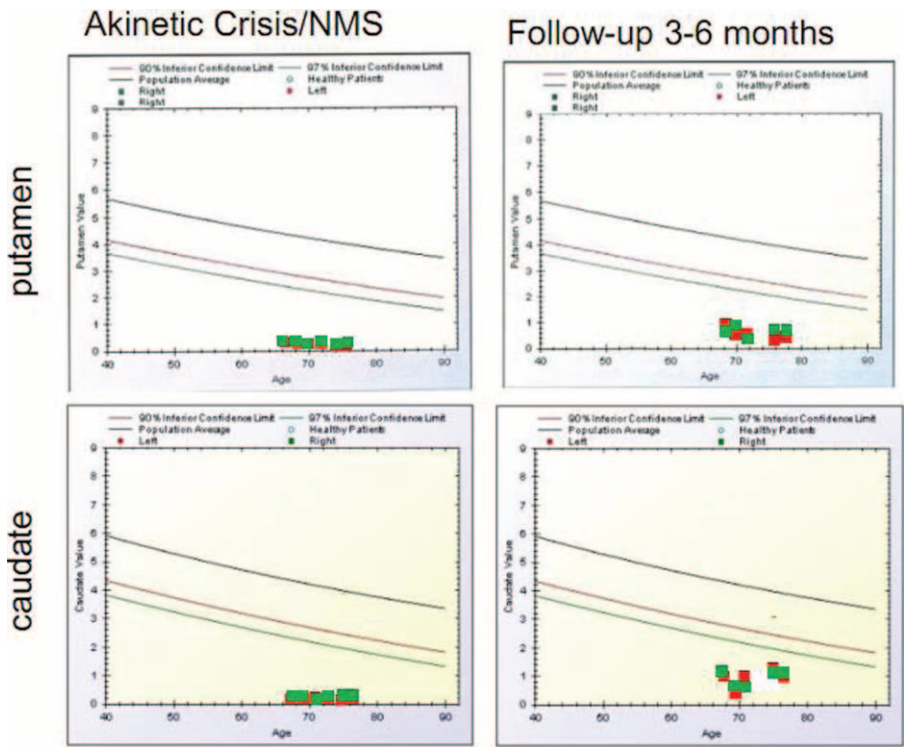

FIGURE 3. BasGan V2 analyses during AC/NMS in 6 patients and at the follow-up 3 to 6 months in the 5 surviving patients. Red dots indicate left putamen/caudate, and green dots indicate right putamen/caudate. AC = akinetic crisis, NMS = neuroleptic malignant syndrome.

shape'' indicates no uptake in the putamen and preserved uptake in the caudate, resulting in an oval, egg shape of the caudate (Figure 3B, Figure 1, right, patient B), and the pattern 5 ''burst striatum'' indicates no uptake in the putamen and the striatum (Figures 2 and 3).

RESULTS

Patients During and After AC

Table 1 summarizes the characteristics of the 5 PD/DLB patients affected by AC and of 1 patient affected by NMS. No evidence of Parkinsonism was reported in patient 6 before the occurrence of NMS due to risperidone administration. During NMS, the patient presented with severe akinesia of the same severity as akinesia in PD/DLB patients, in which the precipiting causes were infections and bone trauma. Despite recovery, this patient at the 6-month follow-up presented a bilateral Parkinsonism (Hahn/Yahr stage 2) with an UPDRS score of 16.

During AC, FP/CIT scans showed in all patients reduced/absent uptake in the putamen and severely reduced or no uptake in the caudate of the patients. The visual analysis of SPECT acquisition evidenced aspects of ''burst striatum'' pattern 5[28,31]

TABLE 2. ROI Measurements in Patients With AC/NMS and Follow-up

FP-CIT SPECT ROI[1,2]	Pt 1*		Pt 2		Pt 3		Pt 4**		Pt 5		Pt 6*		P AC vs P-AC	Typical Normal Value ± SD
	AC	P-AC	AC	P-AC	AC	P-AC	AC	P-AC	AC	P-AC	AC	P-AC		
Striato-L/Occ	0.84	2.33	0.65	1.74	0.86	1.84	0.31	—	0.42	1.94	1.12	1.66	0.003	(4 ± 0.5*)
Striato-R/Occ	0.79	1.90	0.89	2.15	0.85	1.76	0.39	—	0.31	1.76	0.94	1.97	0.002	
Caud-L/Occ	0.99	2.31	0.95	1.46	0.99	1.96	0.36	—	0.48	1.99	1.09	1.53	0.016	(4 ± 0.5*)
Caud-R/Occ	0.91	1.91	1.02	1.84	0.98	1.89	0.48	—	0.37	1.83	1.29	1.95	0.005	
Put-L/Occ	0.69	2.35	0.35	2.01	0.73	1.71	0.26	—	0.35	1.89	0.78	1.78	0.003	(4 ± 0.5*)
Put-R/Occ	0.67	1.89	0.76	2.45	0.71	1.62	0.30	—	0.25	1.68	0.96	1.98	0.004	
Put-L/Caud-L	0.69	1.01	0.37	1.43	0.73	0.87	0.72	—	0.72	0.94	0.71	1.16	0.132	(0.75 ± 0.07)
Put-R/Caud-L	0.74	0.98	0.74	1.33	0.72	0.85	0.62	—	0.67	0.91	0.74	1.20	0.058	
Pattern*	5	4	5	3	5	4	5	—	5	4	5	3		

AC = akinetic crisis, BP = binding potential, L = left, NMS = neuroleptic malignant syndrome, P-AC = post-AC, R = right, ROI = regions of interest ([count density target ROI]—[count density occipital ROI])/[count density occipital ROI] × 100), SD = standard deviation, SPECT = single-photon emission computerized tomography. Pattern * 5 = burst striatum, 4 = egg shape, 3 mixed type. [1]Figure patients 1*, 6* ROI analyses, [2] Figure 2 4** ROI analysis.

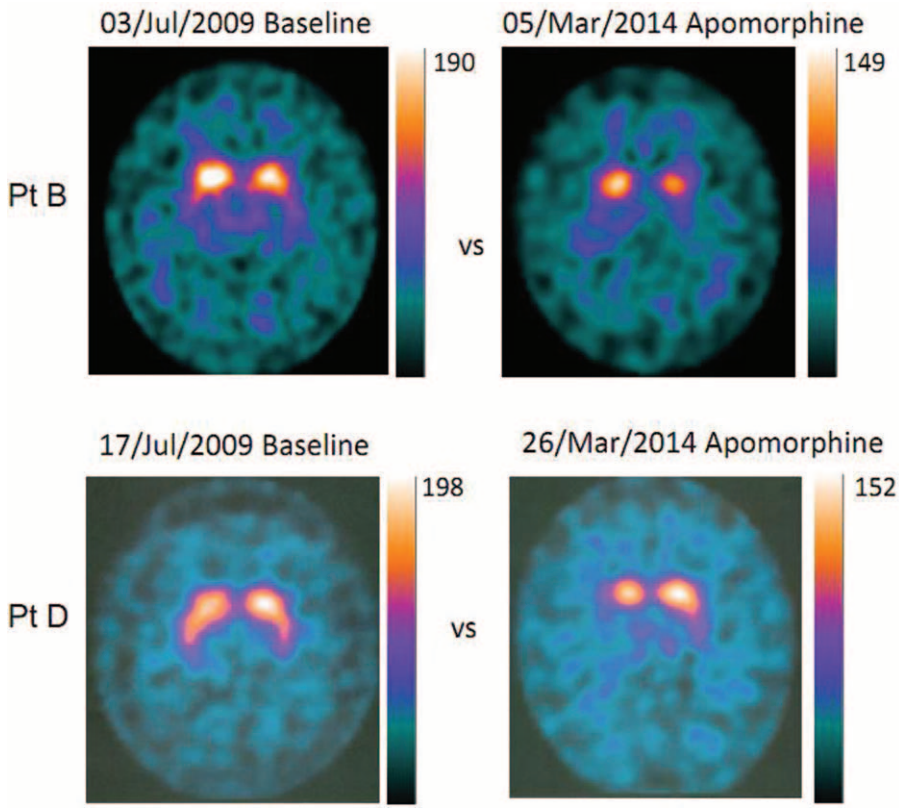

FIGURE 4. FP/CIT SPECT acquisition in two patients (PtB, PtD) chronically treated with apomorphine. Baseline SPECTs were acquired 6 years before, second acquisitions were obtained during chronic treatment. Notice that BP decay is in the range (Table 3) expected for the time lapsed from first acquisition, and the BP values are multiples of values (4–5 times) observed during AC (Figures 1 and 2). AC = akinetic crisis, BP = binding potential, SPECT = single-photon emission computerized tomography.

in all patients. Figure 2 shows FP/CIT acquisition plotted at the maximum saturation level, in patient 4, who died 2 weeks after onset of symptoms. In the 4 PD patients who recovered from AC and in the patient with NMS, a second SPECT acquisition performed 3 to 6 months after recovery showed recovery of FP/CIT BP mostly evident in the caudate, same as expected for Parkinsonism with the same UPDRS score and disease duration, with pattern 3 ''mixed type'' and pattern 4 ''egg shape'' of visual categorization.

Figure 3 shows examples of FP/CIT SPECT acquisitions in 1 PD patient with AC and in the patient with NMS during the crisis and 3 to 6 months after recovery. Figure 4 shows the BasGanV2 VOIs plots from putamen and caudate in the 6 patients during AC/NMS and the follow-up at 3 to 6 months in the 5 surviving patients.[27,29]

The ROIs semiquantitative analysis is reported in Table 2. As shown in Table 2, during AC or NMS, BP was reduced to less than 1/6 to 1/10 of the age-matched control mean values. In recovering patients, BP increased in the caudate by 250% to 500% and in the putamen by 230% to 650% in comparison with acquisition during the crisis. Wilcoxon signed-rank tests evidenced that BP recovery in caudate areas was significant at $P < 0.01$, whereas recovery in putamen was significant at $P < 0.05$.

Apomorphine Effect Assessment in Non-AC Patients

Figure 1 shows examples of FP/CIT SPECT acquisition in 2 patients who were regularly treated with apomorphine. For a comparison, SPECT acquisitions obtained several years before, at onset of motor fluctuations, are matched with SPECT acquisitions obtained during apomorphine treatment. No aspects of ''burst striatum'' were observed. FP/CIT SPECT BP during apomorphine treatment was in the range expected from PD patients of the same disease duration and severity.[33–35] According to literature, presenting only ROI semiquantitative measurements, in PD patients, BP decay is by an annual rate of 5% to 10% in the putamen and by 3% to 6% in the caudate on an average.[28–36] Table 3 shows comparisons of baseline measurements and actual measurements during apomorphine treatment, and a comparison with the decay expected from literature data, in the time elapsed from baseline to acquisition during apomorphine treatment. The VOIs' measurements in Figure 5 and the ROIs' measurements reported in Table 3 show that the values measured in the 4 patients corresponded to a decay of <5% year for all patients. The BP values during apomorphine treatment were 2.5 to 7.5 times higher than in the AC-PD/NMS patients.

DISCUSSION

Our findings offer the unprecedented evidence that FP/CIT uptake is absent/extremely reduced in AC and NMS, and that instrumental assessment with SPECT might help the identification of these challenging and possibly lethal syndromes.

During AC and NMS, FP/CIT SPECT showed in all patients reduced/absent uptake in the putamen bilaterally, yet more interesting was the finding of extremely reduced activity

TABLE 3. ROI Measurements in Patients Without AC at Onset of Severe Symptoms With Fluctuation and 5 ± 1 years After, During Chronic Apomorphine Administration

FP-CIT SPECT ROI (Disease Duration)	Pt A (5 Years)			Pt B* (6 Years)			Pt C (4 Years)			Pt D* (6 Years)			Typical Normal Value ± SD
	B	Apo	ED	B	Apo	ED	B	Apo	ED	B	Apo	ED	
Striato-L/Occ	2.72	2.50	2.50	2.86	2.63	2.58	3.36	3.11	3.14	2.64	2.38	2.38	(4 ± 0.5*)
Striato-R/Occ	2.91	2.70	2.67	2.33	2.14	2.10	3.27	3.12	3.06	2.85	2.63	2.57	
Caud-L/Occ	3.14	3.11	2.88	3.04	2.99	2.74	4.16	3.85	3.89	3.48	3.25	3.14	(4 ± 0.5*)
Caud-R/Occ	3.48	3.26	3.20	2.54	2.48	2.29	4.06	3.95	3.80	3.57	3.33	3.22	
Put-L/Occ	2.35	1.88	2.16	2.69	2.27	2.05	2.68	2.37	2.50	1.79	1.52	1.61	(4 ± 0.5*)
Put-R/Occ	2.44	2.19	2.24	2.13	1.80	1.92	2.61	2.29	2.44	2.23	1.03	2.01	
Put-L/Caud-L	0.75	0.60	0.69	0.88	0.60	0.79	0.65	0.61	0.60	0.51	0.56	0.46	(0.75 ± 0.07)
Put-R/Caud-L	0.70	0.67	0.64	0.84	0.72	0.75	0.64	0.57	0.59	0.63	0.57	0.56	

Apo = apomorphine, B = baseline/disease onset, Caud = caudate, ED = expected decay, L = left, Occ = occipital, Pts B, D* = Figure 4, 5, Put = Putamen, R = right, SD = Standard Deviation.

in the caudate nucleus (Figures 1 and 2), resulting in the feature of ''burst striatum'' with disappearance of the oval-shaped images corresponding to caudate. Semiquantitative evaluations showed uptake reductions to noise level of scales (Figure 3, Table 2).

During follow-up, repeated scans showed increment of FP/CIT uptake, with resumption of the typical patterns observed in progression of Parkinsonism.[32–35] These findings suggest that during AC or NMS, dopamine presynaptic transporter activity is inefficient and that this dysfunction may recover during follow-up in surviving patients. Two previous case reports,[12,13] describing 2 patients each, showed also severe suppression of FP/CIT uptake in patients with AC. Only 2 patients survived the crisis, in one recovery of BP was observed, in the other instead, despite clinical recovery, no improvement in FP/CIT uptake was reported, even though SPECT figures showed a ''burst striatum'' pattern during AC and an ''oval shape'' (caudate activity) after recovery. We suggest that the utilization of 2 semiquantitative evaluations and of the visual categorization methods, in our study, gave proper evidence of functional recovery, by allowing to overcome difficulties due to low level of uptakes in Parkinsonian conditions.

During the progressive course of Parkinsonism, FP/CIT SPECT alterations appear because of reduction of BP. These alterations are mostly evidenced in the putamen, initially in the mesial part and in the more severe cases in the entire putamen, with the appearance of ''eagle wing'' and ''egg shape'' patterns of visual assessment categorization.[27,29,32] Uptake in the caudate is relatively preserved (eg, ''egg shape'' is due to the preservation of the oval, caudate, shape and disappearance of the ''wing'' representing the putamen). The ''burst striatum'' pattern designs disappearance of uptake in the caudate areas. This pattern appears in severe Parkinsonism, and as shown in our results during AC and NMS.[27,29]

For this reason, we suggest that extreme reduction/disappearance of caudate activity might constitute a tentative operational indication for AC identification. Visual assessment of a ''burst striatum'' pattern, with disappearance of caudate uptake in patients with moderately severe Parkinsonism before the crisis, could identify the presence of AC, and could evidence NMS.

Semiquantitative evaluations (Table 2, Figure 3) suggest that reduction of caudate FP/CIT BP to less than 1/5 of the value corresponding to the 97% inferior confidence limit for age-matched control could also suggest a diagnosis of AC/NMS. To make, of the proposed SPECT instrumental assessment of AC-NMS, a definite diagnostic tool, our study fosters further studies correlating PD severity duration with SPECT findings and establishing unequivocal measurement methods. At present, only 4 studies are available.[4,7,12,13]

The attempt to understand the mechanism underlying the observed dopamine transporter suppression during AC and NMS requires further considerations.

First, as AC and NMS are life-threatening conditions, urge to treat (with putative rescue drugs) made it impossible to withdraw treatments, until ligands were available for SPECT acquisition, in 4 patients. Thus, it might be argued that the observed alterations are due to drug effects, that is, effect of risperidone in the NMS case and effect of L-Dopa or apomorphine in the NMS and AC cases. Despite several previous studies evidenced that dopamine agonists (DAs), L-dopa, and neuroleptics do not alter dopamine transporter-binding,[4,8,9] fewer studies challenged these evidences.[5,10,11] Theoretical considerations suggest that DAs may upregulate, whereas L-dopa may downregulate dopamine transporter-binding.[31,36] Other clinical experimental studies showed instead uptake reductions induced by L-Dopa or DAs, in the range of 3% to 22%.[11]

Several of our findings challenge the treatment effect hypothesis: first, reductions of presynaptic dopamine transporter binding to noise level during AC, increments by 230% to 650% (caudate) in recovering patients, as observed in our patients, are of a magnitude incompatible with predictions resulting from studies showing drugs effects on DAT-binding.[10,11,31,36]

Second, 2 of the patients of the present case series were not treated with apomorphine. The patients, with AC and FP/CIT SPECT uptake reduction in the 2 previous case reports,[12,13] were not treated.

Third, the L-Dopa doses administered to our patients were in the range commonly used in PD patients undergoing SPECT assessment. Apomorhine doses were also in the standard treatment range[1,2,14] and apomorphine was withdrawn from the night before assessment. Apomorphine has a half-life of 45 min; therefore, it is unlikely that the finding, in the 4 AC patients who received apomorphine as a rescue drug, is dependent on drug interactions, as apomorphine and all other treatments were withdrawn 12 hours before SPECT acquisition. According to half life[22,37] apomorphine should have disappeared at the time of SPECT acquisition.

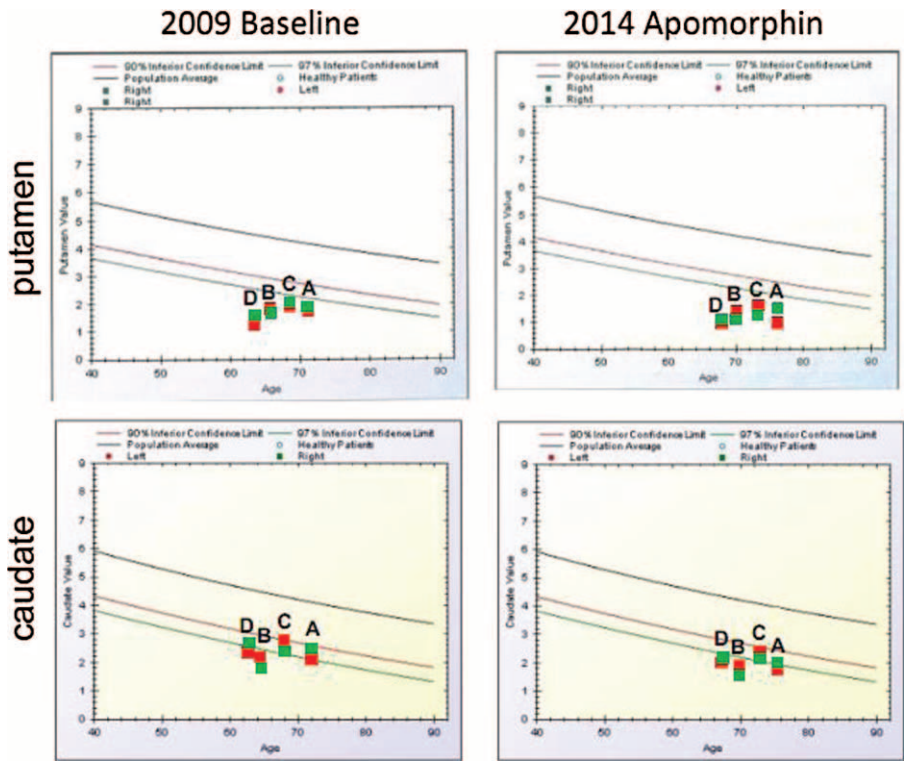

FIGURE 5. BasGan V2 analyses in 4 patients at baseline and 5 ± 1 years after during chronic treatment with apomorphine. Red dots indicate left putamen/caudate, and green dots indicate right putamen/caudate.

Fourth, in the ancillary SPECT study performed in 4 Parkinsonian patients, age- and disease duration-matched, who were not affected by AC but who were regularly treated with apomorphine, the FP/CIT BP was evidently above the levels observed in AC and NMS patients; in the range expected for Parkinsonisms with similar progression,[32–35] no ''burst striatum'' patterns were observed.

As an alternative hypothesis to drug effect, we suggest that the explanation for our finding could be that AC is due to altered energetic state, same as NMS, wherein mitochondrial complex I activity inhibition was observed.[38,39]

According to this hypothesis, a recent study[40] evidenced that AC is more frequent in monogenic PD due to mitochondrial dysfunction than in ''idiopathic'' parkinsonism's. In POLG mutations, a pathology due to mitochondrial DNA mutations[41] FP/CIT BP is severely reduced, even in absence of Parkinsonism.[42]

Mitochondrial dysfunction and altered energetic state would alter the proton adenosine triphosphatase pump needed for dopamine transporter activity,[36] leading to dopamine transporter suppression, and would also alter synaptic dopamine release. Because of the reduced dopamine release, due to the energetic failure, also dopamine transporter expression would furtherly be depressed, in the compensatory attempt to maintain dopamine concentration in the synapse.[36] This hypothesis may explain the unprecedented finding, observed in the present study, of the almost complete suppression of FP-CIT-binding during AC and NMS.

Therefore, our conclusion is that FP-CIT SPECT, by evidencing severe BP reduction with the ''burst striatum'' pattern, in both putamen and caudate can be used to assess both AC and NMS.

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