Movement Disorders
CLINICAL PRACTICE

CASE SERIES

Negative DAT-SPECT in Old Onset Parkinson's Disease: An Additional Pitfall?

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ABSTRACT: Background: Scans without evidence of dopaminergic deficit (SWEDDs) refer to patients clinically diagnosed with Parkinson's disease (PD), but showing normal findings on dopamine transporter single-photon emission computed tomography (DAT-SPECT). This entity remains highly debated, but recent findings suggesting that DAT-SPECT does not reflect either nigral cell bodies or striatal fibers of dopaminergic nigrostriatal neurons could improve our understanding of SWEDDs. Notably, compensatory downregulation of DAT in the early stages of PD seems to be less efficient in older-onset than in young-onset patients.
Cases: We report eight patients with old-onset clinical parkinsonism and a positive response to levodopa in which DAT-SPECT was normal both visually and semiquantitatively. Two subjects demonstrated an abnormal scan when repeated later.
Conclusions: We suggest that old-onset patients may truly have dopaminergic degeneration despite normal imaging results, presumably because they are diagnosed in the early stages confirming less efficient striatal compensatory strategies in old-age onset PD.

Parkinson's disease (PD) is a common neurodegenerative disorder in which the diagnosis still rests on the observation of typical clinical features such as bradykinesia, rest tremor, and rigidity, which are attributed mostly to dopaminergic cell loss in the substantia nigra. Dopamine transporter single-photon emission computed tomography (DAT-SPECT) is a sensitive method to establish nigrostriatal dopaminergic dysfunction assisting in the early diagnosis of PD. However, the negative predictive value of dopaminergic imaging is not 100% in the early phase of PD.[1] Notably, patients with parkinsonism and normal DAT-SPECT imaging have been reported to both have abnormal scans on follow-up and respond well to dopaminergic therapy.[2] Emerging data increasingly indicate that striatal dopamine transporter (DAT) should not be considered a faithful measure of the severity of nigrostriatal degeneration.[3,4] Moreover, DAT availability may even reflect early disease-induced compensatory mechanisms[5] and recent evidence supports the presence of age-related differences in striatal compensatory changes in PD patients.[6] How do these findings affect our understanding of some patients with scans without evidence for dopaminergic deficit (SWEDDs)?

Case Series

From the movement disorders clinic at the Neurology Unit of Pisa University, we clinically reviewed data of PD patients seen between April 2008 and December 2011 included in our de novo database. In a sample of 232 patients, baseline DAT-SPECT scans were normal in a total of 28 (3.4%). All subjects fulfilled the United Kingdom (UK) Parkinson's Disease Society Brain Bank diagnostic criteria for idiopathic PD. We focused on patients who had a clinical follow-up in our clinic for at least 5 years, a clinical confirmation of PD and who had performed at the time of first observation a DAT-SPECT scanning using [^{123}I]-FP-CIT SPECT.

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TABLE 1 *Demographic and clinical features of patients, before and after dopaminergic treatment*

Patients	Age at onset, y	Age at DAT-SPECT, y	Sex	Motor phenotype	Predominantly affected side	Predominantly affected putamen	UPDRS III baseline	UPDRS III asymmetry index baseline	MMSE baseline	LEDD 2 y follow-up	UPDRS III 2 y follow-up	UPDRS III Asymmetry Index 2 y follow-up	MMSE 2 y follow-up
Case 1	78	79	M	AD	R	L	15	+1.33	27	400 mg	10	1.25	27
Case 2	79	80	F	AD	L	L	19	−1.71	27	400 mg	13	1.5	26
Case 3	83	84	M	AD	R	L	20	+1.85	26	450 mg	14	1.75	27
Case 4	78	78	M	AD	R	R	18	+1.83	28	350 mg	12	1.2	28
Case 5	83	83	F	TD	L	R	13	−1.2	30	300 mg	9	1.25	29
Case 6	86	87	M	AD	R	R	16	+1.14	29	400 mg	9	1.66	28
Case 7	79	79	F	TD	R	L	11	+1.25	30	300 mg	7	1.33	30
Case 8	81	81	F	AD	L	L	17	−1.6	27	350 mg	11	1.25	27

Abbreviations: AD, akinetic-dominant; DAT-SPECT, dopamine transporter single-photon emission computed tomography; F, female; MMSE, Mini Mental State Examination; LEDD, levodopa equivalent daily dose; L, left; M, male; R, right; TD, tremor-dominant; UPDRS, Unified Parkinson's Disease Rating Scale (positive [+] and negative [−] symptom asymmetry index indicate right and left dominant motor symptom, respectively).

TABLE 2 *Results of semi-quantitative FP-CIT SPECT image analysis (DaTQUANT, GE Healthcare)*

Patients	Striatum right SBR	Striatum left SBR	Putamen right SBR	Putamen left SBR	Caudatus right SBR	Caudatus left SBR	Putamen to caudatus right ratio	Putamen to caudatus left ratio
Case 1	+2.11	+2.01	+2.10	+2.03	+2.11	+1.98	+1.00	+1.02
Case 2	+1.64	+1.61	+1.48	+1.43	+2.02	+1.96	+0.82	+0.82
Case 3	+1.79	+1.67	+1.76	+1.71	+1.84	+1.60	+0.94	+1.04
Case 4	+1.56	+1.86	+1.52	+1.79	+1.65	+1.99	+0.95	+0.93
Case 5	+2.67	+2.71	+2.69	+2.79	+2.62	+2.55	+1.02	+1.07
Case 6	+2.21	+2.30	+1.90	+1.99	+2.94	+2.90	+0.74	+0.77
Case 7	+2.17	+1.99	+2.21	+2.08	+2.09	+1.81	+1.04	+1.10
Case 8	+2.55	+2.38	+2.69	+2.50	+2.22	+2.16	+1.15	+1.11

Abbreviations: DAT-SPECT, dopamine transporter single-photon emission computed tomography; SBR, striatal binding ratio.

Of 28, we found and here report 8 patients (Table 1) with a clinical diagnosis of PD on a follow-up over 5 years and a positive response to levodopa in which the baseline FP-CIT-SPECT was normal both visually and semiquantitatively (Table 2). Mean age at onset was 80.8 ± 2.9 years, with 4 males and 4 females. Mean duration of symptoms was 10.25 ± 5.41 months (range, 4–17), and mean follow-up was 5.9 ± 0.7 years. Longitudinal independent reassessments by experts confirmed the PD diagnosis. Interestingly, all patients met the novel Movement Disorders Society diagnostic criteria for clinically established PD, when applied retrospectively. All patients started levodopa soon after the diagnosis with a mean daily levodopa equivalent daily dose at 2 years follow up of 368.75 ± 53.03 mg. Most showed clinical progression along with a documented clinical improvement on Unified Parkinson's Disease Rating Scale (UPDRS) from levodopa treatment and in two of eight at the 5 year follow-up motor fluctuations (wearing-off) were present. In addition, all patients reported subjective hyposmia. A repeated DAT-SPECT after 3 years in two of our patients (case 1 and 2) became positive (transaxial DAT-SPECT images of case 1 elaborated by using the DaTQUANT software, GE Healthcare, Waukesha, WI, USA are shown in Fig. 1). No patients were on neuroleptic drugs or had a magnetic resonance imaging (MRI) brain showing extensive leukoaraiosis, especially in the basal ganglia. The study was approved by the local ethical committee, and all subjects gave written informed consent.

Discussion

A normal functional neuroimaging of the presynaptic dopaminergic system has been included among the absolute exclusion criteria in the new diagnostic criteria for PD.[7] However, the value of DAT-SPECT for clinical decision-making remains unclear. DAT uptake does not distinguish different degenerative parkinsonisms, but, even more, there is possibility of false negatives in subjects with clinical evidence of parkinsonism, also

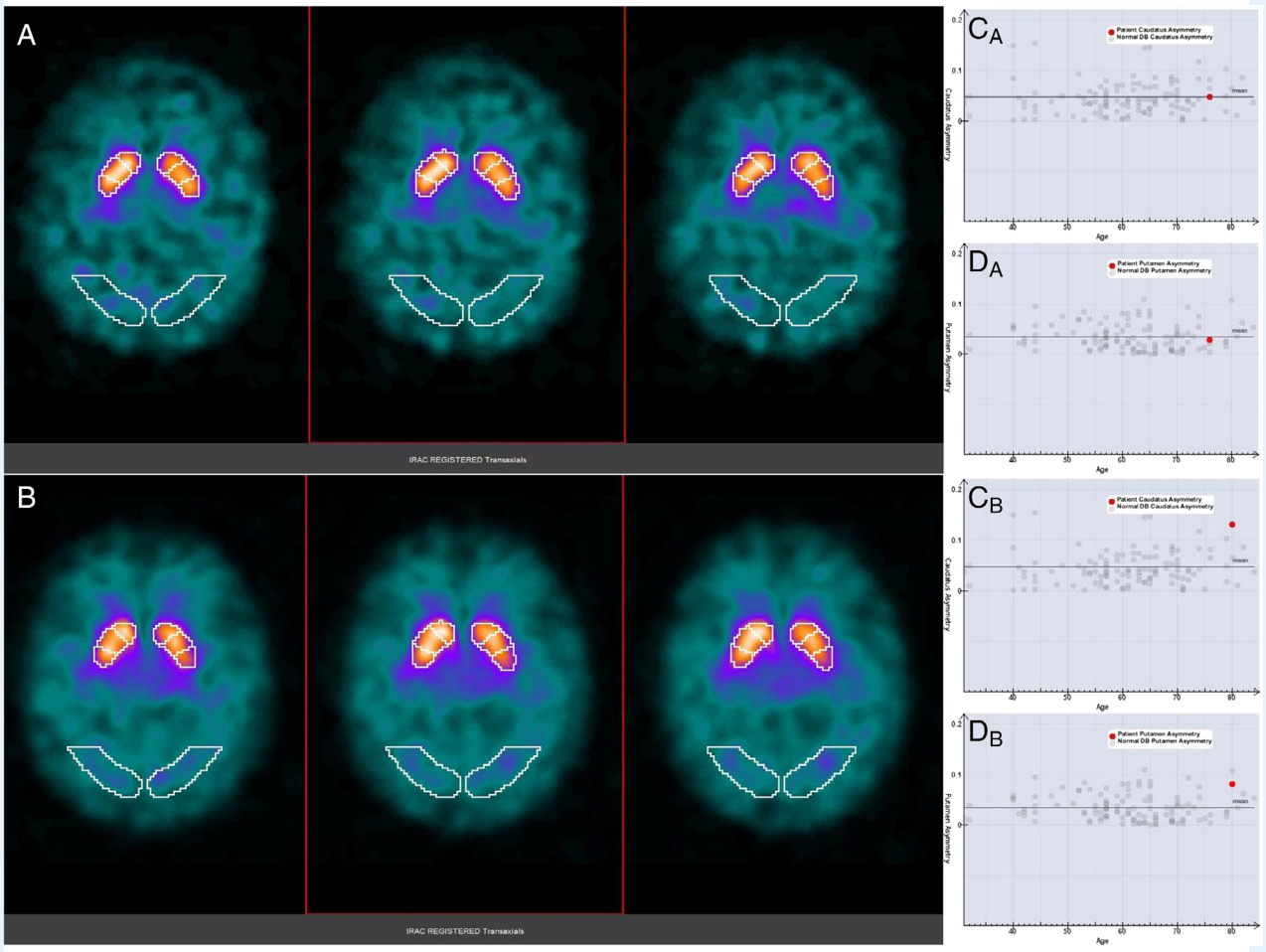

FIG. 1. Left: [^{123}I]FP-CIT SPECT (transverse slices) of case 1 acquired at baseline (**A**) and after 3 years (**B**). Right: scatter-plots showing asymmetry indices (right/left) for caudate (C_A-C_B) and putamen (D_A-D_B), with a mild reduction in left striatal uptake over time.

known as SWEDDs. Notably, among patients with PD enrolled in trials or imaging studies, 4%–15% have been found to have normal DAT-SPECT.[8] Although most patients with SWEDDs represent a clinical misdiagnosis of PD, a handful of such cases might truly have degenerative presynaptic nigrostriatal parkinsonism. Our understanding of the SWEDDs phenomenon relies heavily on the seemingly incontrovertible correlation between striatal DAT binding and nigral cell counts,[2] but recent findings suggest that nerve terminal DAT may not reflect what is happening in the cell bodies or striatal fibers of dopaminergic nigrostriatal neurons.[3,4] In particular, DAT may be subject to downregulation as a result of compensatory mechanisms, which are deemed responsible for minimizing the effects of dopaminergic deficit in early disease.[9] PD is not a uniform disorder and there are different subtypes of PD, with age at onset as a critical variable. Evidences from molecular imaging studies show a different pattern of DAT depletion between old-onset PD and young-onset PD patients.[10] Disease-specific and age-related factors are hard to disentangle in vivo, but, recently, we proposed that a different availability of DAT between PD patients with young and old onset, as the result of age-related differences in early striatal compensatory mechanisms, could account, at least in part, for age-at-onset-dependent differences in PD.[6] Therefore, we might speculate that some old patients in early PD stages may have a normal or near-normal DAT-SPECT imaging as a result of initial nigral degeneration combined with inefficient presynaptic compensatory mechanisms, as suggested by the tendency of older patients to have a reduced pre-symptomatic phase and a faster PD progression compared with younger subjects.[5] It is likely that with progressive nigral cell loss subjects with SWEDD later convert to an abnormal result, as confirmed in two of our patients who were the only ones to agree to repeat DAT-SPECT. Underreporting of SWEDDs in old patients may arise because of they are generally excluded from clinical trials and because of the reluctance to use DAT-SPECT as adjunctive tool in elderly with suspected parkinsonism. It is worth noting that because there are no pathological confirmations in these patients, their true diagnosis remains to be determined. DAT imaging results have a strong diagnostic and therapeutic influence in uncertain parkinsonisms. According to our report, we support the notion that DAT-SPECT should not definitively rule out the diagnosis of PD in an individual case as well as it should not affect treatment to a meaningful degree. Notably, PD remains a clinical diagnosis and a trial with levodopa should be started anyway in patients clinically presumed to have PD. Normal DAT-SPECT in old patients could represent false-negative imaging cases in the initial stage of the disease, presumably attributable to less efficient striatal compensatory strategies. Hence, old onset SWEDD patients might be more likely to truly have dopaminergic degeneration despite normal imaging results, simply because they are diagnosed in the early stages. Because elderly patients represent a growing population of subjects with parkinsonism, neurologists should be careful regarding the interpretation of DAT-SPECT in this population. Moreover, we reinforce the concept that some SWEDDs could be actually in early stage of nigrostriatal dysfunction, reinforcing the importance of a thoughtful clinical evaluation and indicating the need of clinical follow-up. Diagnosing the older patients with PD can be challenging and further studies addressing both the pattern and degree of dopaminergic dysfunction in old onset PD and the age effect on striatal compensatory strategies are warranted.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

G.P.: 1A, 1B, 1C, 2A, 2C, 3A
S.G.: 1B, 1C, 2A, 2C, 3A
T.D.: 2A, 3A
D.F.: 2A, 2C, 3B
D.V.: 2C, 3B
G.S.: 3B
U.B.: 1A, 3B
R.C.: 1B, 1A, 2C, 3B

Disclosures

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