Published in final edited form as:

Mov Disord. 2016 March ; 31(3): 405–409. doi:10.1002/mds.26450.

A Scan Without Evidence Is Not Evidence of Absence: Scans Without Evidence of Dopaminergic Deficit in a Symptomatic Leucine-Rich repeat Kinase 2 Mutation Carrier

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Abstract

Introduction—The basis for SWEDD is unclear, with most cases representing PD mimics but some later developing PD with a dopaminergic deficit.

Methods—We studied a patient initially diagnosed with SWEDD (based on ¹⁸F-dopa PET) who developed unequivocal PD associated with a leucine-rich repeat kinase 2 p.G2019S mutation. Repeat multitracer PET was performed at 17 years' disease duration, including (+) [11C]dihydrotetrabenazine, [11C](N,N-dimethyl-2-(2-amino-4-cyanophenylthio) benzylamine (which binds the serotonin transporter), and ¹⁸F-dopa.

Results—The patient showed bilateral striatal dopaminergic denervation (right putamen 28% of age-matched normal, left putamen 33%). ¹⁸F-dopa uptake was decreased, particularly on the left (mean 31% of normal vs. 45% on the more affected right side). Serotonin transporter binding was relatively preserved in the putamen (right mean 90% of normal, left 81%) and several cortical regions.

Conclusions—SWEDD can occur in genetically determined PD and may, in some cases, be the result of compensatory nondopaminergic mechanisms operating in early disease.

Keywords

SWEDD; LRRK2; Parkinson's disease

Some patients diagnosed with Parkinson's disease (PD) have intact dopaminergic function by PET or single-photon emission computed tomography (SPECT) imaging, most notably in four large trials using PET with 6-[¹⁸F]-fluoro-L-dopa (¹⁸F-dopa)¹ or SPECT with [¹²³I] β-

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Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

CIT,²⁻⁴ where it occurred in 5% to 15% of studied patients; this phenomenon has been called scans without evidence of dopaminergic deficit (SWEDD). The basis for SWEDD is controversial and could in theory be the result of imaging error, clinical (diagnostic) error, or occurrence of a different process clinically similar to PD; true PD presenting without dopaminergic deficit has not been favored as an explanation, given that symptoms of disease generally emerge only after substantial loss of nigral dopamine neurons and striatal dopamine.^{5,6}

Longitudinal studies of patients with SWEDD have shown that the majority of these patients do not develop a dopaminergic deficit^{7,8}; final diagnoses include other tremor syndromes (essential tremor, dystonic tremor, and fragile X tremor ataxia syndrome) and other causes of parkinsonism (other degenerative causes, vascular, medication induced, and psychogenic).⁹ However, a minority of patients with SWEDD subsequently do develop dopaminergic deficits—2 of 16 patients in one report,⁸ 4 of 30 in another,⁹ and 6 of 72 in the PRECEPT study.⁷ In 248 patients with unclassified parkinsonism studied with [¹²³I] β-CIT scans at baseline and followed for a mean 18 months, 22 of 112 eventually diagnosed with PD had SWEDD.¹⁰ Furthermore, SWEDD has been associated with a higher than expected frequency of nonmotor features of PD, including depression, sleep disorders, autonomic dysfunction, and hyposmia.¹¹ The basis for SWEDD is therefore varied, with most representing PD mimics, but rare cases may, for unclear reasons, represent early PD.

Patients and Methods

Patient Description

A 61-year-old female presented to our clinic in 1998 with several months' resting tremor affecting the left hand and leg, associated with slight ipsilateral bradykinesia (reduced arm swing). In 1999, she agreed to participate in the REAL-PET study,¹ in which untreated patients with recently diagnosed PD were randomly assigned to receive ropinirole or levodopa; ¹⁸F-dopa PET uptake was measured at study entry and at 2 years (or after at least 12 months if patients withdrew, as our patient did at 14 months for personal reasons). Her initial scan was one of 21 in REAL-PET deemed to be a SWEDD, with striatal ¹⁸F-dopa PET uptake within 2 standard deviations (SDs) of age-matched healthy controls, and without an anteroposterior gradient of decreased uptake (Fig. 1A). A follow-up scan at 14 months as part of the study protocol was again a SWEDD by the same criteria (Fig. 1B).

Over the subsequent 14 years, her disease progressed, with gradually worsening asymmetric L-dopa-responsive parkinsonism and emergence of peak dose dyskinesias, which responded partially to amantadine. She maintained normal cognition (Montreal Cognitive Assessment Score 27/30 in 2014). In 2014, she agreed to participate in a genetics research study and, despite a lack of identifiable family history, was unexpectedly found to have a leucine-rich repeat kinase 2 (LRRK2) p.G2019S mutation, suggesting that, in fact, her tremor had been the earliest manifestation of LRRK2-associated PD.

The patient agreed to further study with multitracers PET using (+)[¹¹C]dihydrotetrabenazine (DTBZ), [¹¹C] (N,N-dimethyl-2-(2-amino-4-cyanophenylthio) benzylamine (DASB), and ¹⁸F-dopa, as well as a brain MRI scan. DTBZ labels the vesicular monoamine

transporter type 2 and its uptake in striatum predominantly represents dopaminergic nerve terminal density. DTBZ uptake is less subject than ^{18}F -dopa PET to compensatory regulatory changes.¹² DASB labels the serotonin transporter (SERT).

Scanning was completed over 2 days, with dopaminergic medications held at least 12 hours before scanning, and lack of exposure to drugs with affinity for the SERT was confirmed. Radiotracer was administered by intravenous injection over 60 seconds using a Harvard infusion pump (185 MBq in 10 mL of saline for DTBZ, 190 MBq for ^{18}F -dopa, and 555 MBq for DASB). One hour before the ^{18}F -dopa scan, the patient received 200 mg of carbidopa orally. An acquisition time of 60 minutes for DTBZ and 90 minutes for ^{18}F -dopa and DASB was used. DTBZ and ^{18}F -dopa studies were performed on a GE Advance tomograph (GE Healthcare, Little Chalfont, UK) with in-plane resolution of 4 mm. DASB images were obtained on a high-resolution research tomograph with an in-plane resolution of 2.3 mm.

A region of interest (ROI) template was developed in Montreal Neurological Institute (MNI) space using MRI and DASB PET data from healthy controls. Subjects' PET images were coregistered to the corresponding subjects' MRI anatomical image. This MRI image was then warped to the MNI image template to obtain an image transformation matrix. The inverse transformation was then applied to the MNI-defined ROIs before placing the ROI template on the original PET data. DTBZ and DASB tissue input binding potentials (BP_{ND}) were determined using a Logan analysis (DTBZ) or simplified reference tissue model (DASB) with occipital cortex (DTBZ) or cerebellum (DASB) as reference regions. ROI placement on the DTBZ and F-dopa (FD) images has previously been described in detail.¹³ BP_{ND} was compared with age-matched control values. The tissue input Patlak graphical method¹⁴ was used to obtain the ^{18}F -dopa uptake rate constant (K_{occ} , min^{-1}) with the occipital cortex used as reference region. K_{occ} values were also expressed as a fraction of age-matched control values.

The study was approved by the institutional research ethics board of the University of British Columbia (Vancouver, BC, Canada).

Results

Results of ^{18}F -dopa PET from previous studies were reviewed. In 1999, at 1-year disease duration, ^{18}F -dopa uptake in the right caudate was 122% of normal, in the left caudate 128%, the right putamen 103%, and the left putamen 119% (Fig. 1A). At 2 years' duration, uptake in the right caudate was 88% of normal, in the left caudate 105%, in the right putamen 94%, and in the left putamen 122% (Fig. 1B).

At 17 years' duration, DTBZ PET showed bilateral striatal dopaminergic denervation (right putamen: 28% of age-matched normal; $t = 5.58$; $P < 0.01$; left putamen: 33% of age-matched normal; $t = 4.34$; $P < 0.01$). Although DTBZ binding was lower in the side of onset (the right putamen), the repeat ^{18}F -dopa uptake was now higher on this side, though both sides now showed significantly reduced uptake compared to healthy controls (right side mean: 45% of normal; $t = 6.16$; $P < 0.01$ vs. 31% on the left; $t = 6.17$; $P < 0.01$; Fig. 1C).

DASB binding was relatively preserved compared to age-matched controls in the putamen (particularly on the right; mean 90%, left 81%), caudate (85%, 82%), ventral striatum (96%, 82%), as well as several cortical regions (anterior cingulate right 99%, left 81%, dorsolateral prefrontal right 90%, left 108%, orbitofrontal cortex right 101%, and left 86%), but reduced in thalamus (right 67%, left 64%; Fig. 1D).

Discussion

How could a symptomatic patient genetically predisposed to PD initially have a normal ^{18}F -dopa PET scan? ^{18}F -dopa uptake may be normal in early disease, particularly if aromatic amino acid decarboxylase activity is upregulated, and has been shown to lag behind changes in dopamine transporter binding in patients with LRRK2-associated PD.¹⁵ Indeed, our patient's original studies show elevated ^{18}F -dopa uptake in the less clinically affected left putamen (~120% of age-matched controls) and normal (~100% of age-matched controls) uptake on the right. The second study, though still within 2 SDs of normal, does show an asymmetric overall reduction in ^{18}F -dopa uptake in the right putamen compared with baseline (~94% of normal whereas the left remained 122% of normal), suggesting that the scans captured the gradual expected disease-related decline in ^{18}F -dopa uptake, even though uptake values were substantially greater than expected for sporadic PD of comparable duration (Fig. 2).

It is particularly interesting that our patient currently shows relative preservation of DASB binding and ^{18}F -dopa uptake in the now overtly dopamine denervated striatum, particularly on the right where DTBZ binding is lower. By contrast, in the original studies performed close to disease onset, ^{18}F -dopa uptake was higher in the left striatum, but ultimately declined to the level expected for disease duration. We speculate that compensatory upregulation of serotonergic nerve terminals may have been sufficient to result in relative preservation of ^{18}F -dopa uptake, but nevertheless insufficient to maintain normal dopaminergic function (particularly in the absence of exogenous L-dopa), causing symptoms to appear in the setting of a "normal" (but likely falling) ^{18}F -dopa uptake.

At autopsy, patients with PD have reduced immuno-reactivity to SERT protein and other serotonergic markers in striatum, but changes are less prominent than those in the dopaminergic system, and some patients have normal levels.¹⁶ DASB binding in striatum, brainstem, and multiple cortical areas is diffusely reduced in PD at approximately 3 to 14 years' duration, without correlating to disease duration or clinical scores¹⁷; however, other researchers have found preservation of DASB binding in 9 patients with very early PD (within mean 2.1 months of diagnosis), and an inverse correlation of striatal DASB and DAT binding in that cohort suggested that a possible compensatory upregulation of the serotonin system might operate in early stages of disease.¹⁸

Serotonin neurons express aromatic amino acid decarboxylase and can produce and release dopamine in response to L-dopa (and thus ^{18}F -dopa), though in an unregulated fashion because their presynaptic terminals lack dopamine autoreceptors and they do not express a dopamine transporter.^{19,20} In the dopamine denervated PD striatum, this may have a significant impact on synaptic dopamine levels and has been shown to correlate with L-

dopa-induced dyskinesias,²¹ which our patient also exhibits. ¹⁸F-dopa uptake reflects decarboxylation of L-dopa and vesicular trapping of dopamine, and elevation of this marker could therefore reflect, at least in part, decarboxylation within serotonergic neurons.²² DASB measures the density of the SERT, and relative increases may theoretically represent upregulated SERT expression in existing serotonin terminals or sprouting of new terminals, but either mechanism could contribute to false apparent elevation of ¹⁸F-dopa uptake.

Could serotonin neurons play a compensatory role in the earliest stages of PD? Our single-patient study is limited by the lack of DASB and DTBZ imaging at the time of the original ¹⁸F-dopa study, and the differences in PET equipment and technique between the recent and remote scans; we have therefore necessarily made a number of inferences. However, there is corroborative evidence from animal studies, showing sprouting of serotonergic fibers after 6-hydroxydopamine lesions in neonatal, but not adult, mice.²³ In genetic forms of PD, such as our case, where the degenerative process presumably occurs over prolonged periods, compensatory changes could develop gradually over many years. If such mechanisms are active, they may contribute to the risk of L-dopa-induced dyskinesias and could also cause striatal ¹⁸F-dopa uptake to appear normal early in the course of manifest disease, providing one explanation for SWEDD.

Acknowledgments

Funding agencies: This work was funded by the Michael J. Fox Foundation for Parkinson's Research, Canadian Institute of Health Research, and Parkinson Society Canada.

The authors wish to acknowledge the generosity of our patient, as well as the staff at TRIUMF and the PET imaging department including Carolyn English and Siobhan McCormick.

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FIG. 1.
(A–C) Evolution of ^{18}F -dopa PET uptake (Kocc) at 1, 2, and 17 years from motor onset. (D)
At 17 years from motor onset, DASB binding (Bq/ μL) in the same patient is preserved in
striatum.

FIG. 2.

Comparison of ^{18}F -dopa (FD) uptake (blue) and DTBZ binding (red) in the current case (“x”) with that observed in sporadic PD (lines, with upper and lower ranges ± 2 standard error). Values are expressed as a ratio of age-matched healthy controls (modified from Nandhagopal and colleagues, 2008, with permission, to compare with sporadic PD with age of onset 61). In the more affected right putamen, our patient has FD uptake comparable to healthy controls at 1 and 2 years when scans were identified as SWEDD; much later in disease, FD uptake remains elevated compared to values expected for disease duration on this side, although DTBZ binding is in keeping with expected values; in the less affected left putamen, FD is elevated above that of healthy controls early in disease course and later is reduced to a degree comparable to that observed with DTBZ and is in keeping with expected values.