



Editor's comment: In their review, Ba and Martin provide a very useful assessment of the utility of DAT-SPECT in clinical practice. They elegantly discuss the indications for this diagnostic modality as well as its limitations. Clinical evaluation remains the gold standard in the diagnosis of parkinsonian conditions but DAT-SPECT can be of potential assistance in a number of clinical scenarios. At this juncture, DAT-SPECT is widely available in many countries. However, its role in patient management is still limited. Thus, the authors point to the need of further assessment of DAT-SPECT utility in long-term clinical studies.

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Review

Dopamine transporter imaging as a diagnostic tool for parkinsonism and related disorders in clinical practice



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ABSTRACT

Background: Accurate diagnosis of Parkinson disease (PD) and other degenerative parkinsonian syndromes is important for management and prognostic purposes. Diagnosis can be challenging in early disease and in atypical cases.

Methods: We reviewed the literature on the application of dopamine transporter single-photon emission computed tomography (DAT-SPECT) in degenerative parkinsonism and related disorders as a diagnostic tool.

Results: The use of DAT-SPECT shows some utility in the early diagnosis of PD and differentiation from other non-degenerative parkinsonian disorders (i.e. essential tremor, dystonic tremor, drug-induced and in most cases of psychogenic parkinsonism), since it can accurately detect the presynaptic dopaminergic deficit. The test has been shown to have high sensitivity/specificity by multiple studies. DAT imaging may also have some prognostic value for disease progression. However, it has limited value in differentiating among degenerative causes of parkinsonism. DAT imaging has some limitations. In most studies, true test accuracy is unknown since the gold standard is clinical diagnosis by a movement disorders neurologist. Therefore, the sensitivity of the test cannot exceed that of the clinical diagnosis. In addition, false negative scans occur and highlight the need for clinical follow-up.

Conclusion: Clinical assessment remains the most important aspect in evaluating these patients. DAT-SPECT is a sensitive modality to detect nigrostriatal degeneration. In spite of increasing data using this technique, however, more long-term clinical studies are required to determine how DAT-SPECT scan can guide decision-making.

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1. Introduction

Dysfunction of the dopaminergic system is associated with multiple neurological conditions. Parkinson disease (PD) is one classic example. PD is common. Its estimated prevalence is close to 1% in those aged 65–69 years, and increases with age [1]. The

clinical progression of PD is heterogeneous and precise diagnosis based on clinical criteria such as those of the UK brain bank [2] can be difficult, especially in early stages. Other degenerative causes of parkinsonism, including multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and dementia with Lewy bodies (DLB) are also diagnosed primarily on the basis of their clinical features, and accurate diagnosis can be challenging. Time to reach a correct clinical diagnosis for PD can range from 2 months to 18 years depending on the clinical presentation [3]. Misdiagnosis of conditions such as essential tremor (ET), vascular parkinsonism (VP), MSA and PSP implies that 5–25%

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of patients with an initial diagnosis of PD may be inappropriately managed [4]. Accurate diagnosis is key to correct management and prognostication.

Over the past decade, neuroimaging with specific dopamine (DA)-related ligands has been used to assess function at both pre-synaptic terminals and postsynaptic binding sites. Currently, single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are widely available imaging tools. In this review, we will discuss the utility of *in vivo* presynaptic DA transporter (DAT) imaging as a diagnostic tool for degenerative parkinsonism and related movement disorders in clinical practice.

DAT is a sodium chloride dependent protein on the presynaptic membranes of the terminals of dopaminergic projections [5]. DAT plays a critical role in the regulation of the extracellular DA concentration and is considered a marker of DA terminal integrity. Degeneration of dopaminergic projections from the substantia nigra to the striatum results in loss of DAT [6]. DAT concentration closely relates to striatal DA levels [7,8], supporting its use as an imaging biomarker for PD. However, DAT imaging may underestimate true terminal density due to down-regulation of DAT in remaining dopaminergic neurons in response to the reduced levels of synaptic DA [9].

To assess presynaptic dopaminergic function, both SPECT and PET have been used as *in vivo* tools. SPECT is the more widely available of the 2 modalities due to lower cost and the availability of the tracers. Several ^{123}I and $^{99\text{m}}\text{Tc}$ -labeled DAT-SPECT imaging agents based on cocaine and other closely related tropane derivatives have been developed [10]. Examples include: [^{123}I]FP-CIT (also known as DaTSCANTM or DaTscanTM) (N- ω -fluoropropyl-2 β -carbomethoxy-3 β -(4-[^{123}I]iodophenyl) nortropane); [$^{99\text{m}}\text{Tc}$]TRODAT-1 [2-[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo[3.2.1]oct-2-yl]methyl](2-mercaptoethyl)amino]ethyl]amino]ethanethiolato(3-)-N2,N2',S2,S2']oxo-[1R-(exo-exo)]; and [^{123}I]β-CIT (2 β -carbomethoxy-3 β -(4-iodophenyl)tropane) [11]. Among these agents, [^{123}I]FP-CIT and [$^{99\text{m}}\text{Tc}$]TRODAT-1 have more rapid binding kinetics, which allow much earlier imaging (3–6 h) after administration [11]. The sensitivity and specificity of [^{123}I]FP-CIT SPECT for PD diagnosis are comparable to those of other DAT-SPECT methods [12]. Although [^{123}I]FP-CIT was not the first agent developed, it was approved by the European Medicines Agency (EMA) as DaTSCANTM in 2000 [13] with a revised guideline suggesting DaTSCANTM is indicated in patients with clinically uncertain parkinsonian syndromes (PS). The modality can help differentiate ET from conditions associated with pre-synaptic dopaminergic dysfunction, such as PD, MSA and PSP. It is also indicated for the differentiation of DLB from other dementias [14]. [^{123}I]FP-CIT (DaTscanTM) was approved by the Food and Drug Administration (FDA) for clinical use for suspected PS in 2011 [15]. FDA suggests that it be considered as an adjunct to other diagnostic evaluations when evaluating a tremor disorder. Other approved compounds include [^{123}I]β-CIT (DOPASCANTM) in Europe and Japan; [^{18}F]FP-CIT PET in Korea, and [$^{99\text{m}}\text{Tc}$]TRODAT-1 SPECT in Taiwan [12].

PET can provide higher resolution and better quantitative capacity than SPECT, but has seen relatively limited use in clinical practice due to its complex and expensive infrastructure and the lack of commercial availability of dopaminergic ligands. This review will focus on DAT-SPECT imaging given its wide potential use, and availability of the DAT ligands.

2. Diagnostic application of DAT imaging

DAT imaging allows *in vivo* assessment of presynaptic striatal dopaminergic function in patients with neurological symptoms. Image analysis is typically semi-quantitative, based on the placement of regions of interest (ROI) in the striatum and on a

background region devoid of specific binding enabling the estimation of DAT binding. There is a known gradient of dopaminergic dysfunction in PD, starting in the posterior putamen progressing anteriorly to caudate contralateral to the affected limbs, with later involvement of the putamen and caudate in the ipsilateral side as demonstrated by DAT imaging [16,17] and post-mortem pathological studies [18,19].

2.1. Early diagnosis

DAT imaging is capable of distinguishing patients with PD from normal subjects even in early disease [20,21]. A decrease in DAT binding at striatal presynaptic terminals is associated with the loss of functional neuronal activity that characterizes PD. Significant DAT changes may precede the onset of clinical symptoms [22]. Decreased striatal [^{123}I]β-CIT binding has been reported in anomic relatives of patients with PD who do not themselves have clinical evidence of parkinsonism [23]. Striatal uptake correlates with duration and severity of motor features assessed by the Unified Parkinson's Disease Rating Scale (UPDRS-III) and Hoehn and Yahr scores [7,24]. Among the motor symptoms of PD, tremor does not correlate well with striatal DAT binding, whereas bradykinesia and rigidity as well as gait, posture, facial expression and speech show a significant correlation with DAT activity [25–27].

Overall, DAT SPECT is a highly sensitive test for PD and degenerative PS. However, striatal DAT density decrease is not only seen in response to DA neuronal loss in established PD [28] but also occurs in pre-motor PD and rare cases of drug-induced parkinsonism [29], when the density of dopaminergic nerve terminals is preserved. When DAT is functionally down-regulated as a compensatory mechanism for reduced levels of synaptic DA [30], DAT SPECT can underestimate true terminal density in remaining dopaminergic neurons [9]. In contrast, ^{18}F -dopa uptake correlates more closely with the number of nigral dopaminergic neurons in humans [31]. Reduced DAT density but preserved ^{18}F -Dopa uptake was found in asymptomatic individuals with LRRK2 mutations, where compensatory changes are thought to maintain stable extracellular DA levels [30].

There is a subgroup of clinically-diagnosed PD patients that have been categorized as having scans without evidence of dopaminergic deficit (SWEDDs). The clinical presentations of these patients are consistent with PD but functional imaging fails to demonstrate DA deficiency suggesting an alternate diagnosis [16,32,33].

2.2. Diagnostic accuracy for nigrostriatal neurodegeneration

Although not specific for etiology, in clinically uncertain cases, DAT imaging can help provide evidence of presynaptic nigrostriatal pathology. However, multiple studies have revealed some limitations of the test and different sensitivity and specificity of DAT imaging in patients with uncertain parkinsonism. Representative studies are summarized in Table 1. The results of these studies indicate that abnormal DAT imaging supports the presence of a neurodegenerative presynaptic dopaminergic deficit. Patients with a clinical diagnosis of PD but normal DAT SPECT imaging are consistent in most cases with the diagnosis of conditions other than a degenerative PS [16,38,39].

False positive results have been reported in drug-induced parkinsonism [29]. [^{123}I]FP-CIT SPECT, but not ^{18}F -Dopa PET, was significantly decreased in a patient receiving chronic lithium treatment who presented with bilateral parkinsonism. DAT binding and clinical symptoms improved with the discontinuation of lithium. These observations suggest functional down-regulation of

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