Imaging modalities in differential diagnosis of Parkinson's disease: opportunities and challenges

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Abstract

Background: Parkinson's disease (PD) diagnosis is yet largely based on the related clinical aspects. However, genetics, biomarkers, and neuroimaging studies have demonstrated a confirming role in the diagnosis, and future developments might be used in a pre-symptomatic phase of the disease.

Main text: This review provides an update on the current applications of neuroimaging modalities for PD diagnosis. A literature search was performed to find published studies that were involved on the application of different imaging modalities for PD diagnosis. An organized search of PubMed/MEDLINE, Embase, ProQuest, Scopus, Cochrane, and Google Scholar was performed based on MeSH keywords and suitable synonyms. Two researchers (TM and JPI) independently and separately performed the literature search. Our search strategy in each database was done by the following terms: ((Parkinson [Title/Abstract]) AND (("Parkinsonian syndromes "[Mesh]) OR Parkinsonism [Title/Abstract])) AND ((PET [Title/Abstract]) OR "SPECT"[Mesh]) OR ((Functional imaging, Transcranial sonography [Title/Abstract]) OR "Magnetic resonance spectroscopy "[Mesh]). Database search had no limitation in time, and our last update of search was in February 2021. To have a comprehensive search and to find possible relevant articles, a manual search was conducted on the reference list of the articles and limited to those published in English.

Conclusion: Early diagnosis of PD could be vital for early management and adequate neuroprotection. Recent neuroimaging modalities such as SPECT and PET imaging using radiolabeled tracers, MRI, and CT are used to discover the disease. By the modalities, it is possible to early diagnose dopaminergic degeneration and also to differentiate PD from others parkinsonian syndromes, to monitor the natural progression of the disease and the effect of neuroprotective treatments on the progression. In this regard, functional imaging techniques have provided critical insights and roles on PD.

Keywords: PET, SPECT, MRI, Diagnostic imaging, Parkinson's disease

Background

Parkinson's disease (PD), as the second most popular neurodegenerative disturbance, is a chronic advanced neurodegenerative disorder that causes considerable disability and reduces quality of life also with a significant impact on costs to the healthcare system as well as society [1, 2]. Two major findings when observing the

nervous system tissues of patients with PD include loss of neuronal cells as a result of death of dopamine-producing nerve cells as well as manifestation of Lewy bodies in the midbrain [3, 4].

PD diagnosis is quite challenging due to unavailability of biomarkers [5]. Yet, there is no conclusive indicative methodology for PD; hence, the analysis depends on the clinical manifestations of the diseases which is carried out by observing gradual movements (bradykinesia) with symptoms including resting tremor, muscle inflexibility, and postural flimsiness [6]. On the other hand, many

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symptoms of PD are also common within multiple system atrophy, progressive supra nuclear palsy, corticobasal degeneration, dementia with Lewy bodies, normal pressure hydrocephalus, and Alzheimer's disease to a range of condition viewpoint, and this may induce missed or misdiagnosis of the disease [7, 8].

This review provides an update on the contribution of imaging modalities in PD diagnosis.

Medical imaging approaches in PD diagnosis
Computed tomography (CT)
CT is not the preferred diagnosis imaging modality for PD because of its limited soft tissue contrast compared to magnetic resonance imaging (MRI). However, this imaging modality can effectively illustrate the patterns of regional volume loss characteristic of multiple system atrophy (MSA), corticobasal degeneration (CBD), or progressive supranuclear palsy (PSP). Although PD diagnosis by CT is nonspecific, meanwhile, it is useful in ruling out focal or regional atrophy, hidden lesions, or vascular diseases. Typically, contrast media is not indicated to the diagnosis [9].

Magnetic resonance imaging
It was shown that raised magnetic field MRI promise to more accurately distinguish healthy subjects from PD patients and also allow improved spatial resolution and increased contrast which provides better visualization of basal ganglia contours and shapes [10, 11]. In comparison to normal controls, a reduction in both magnetization transfer ratio and functional anisotropy in the substantia nigra has also been reported by MRI [12].

Although high gray/white matter contrast is accessible with conventional 3D T_1-weighted sequences for cortical and some basal ganglia constructions, there is poor contrast in many structures of interest in PD including substantia nigra (SN), subthalamic nucleus (STN), globus pallidus (GP), and red nucleus (RN) which contains high iron levels leading to shortened T_1 and the reduced contrast [13]. Iron load is considered as an advantage in T_2/T_2^*-weighted sequences so that provides an enhanced contrast due to the T_2 shortening effects [14–16].

Iron load
Physiologically, brain tissue contains iron mostly stored in the form of ferritin. In the basal ganglia (globus pallidus (GP) > putamen > caudate), ferritin accumulates as a function of age in a linear manner. Quantitative susceptibility mapping (QSM) and also iron-sensitive MRI sequences (including SWI, 3D FLAIR, T_2^*, R_2 and R_2^* relaxation) have been more and more used in PD investigation metabolism and iron content [14].

Increased iron load in PD and T_2 relaxometry have shown reduced T_2/T_2^* adiabatic $T_2\rho$ relaxation times and increased R_2/R_2^* relaxation rates [15–17].

Magnetization transfer imaging (MTI)
MTI is a technique which trusts on the transmission of energy between highly bound protons and mobile protons. The MT measure is consequently associated with myelination and axonal density degree. MT rate can be quantitatively examined by MT imaging. Reduced magnetization transfer ratio (MTR) has been observed in the SN and basal ganglia (GP, the putamen, caudate nucleus) of PD patients [18, 19].

Perfusion imaging
Arterial spin-labeled (ASL) perfusion imaging approach by MRI has been recently presented for perfusion measurements as a noninvasive option in PD [20, 21]. Arterial spin labeling (ASL) as a quantitative and functional imaging method measures tissue perfusion using magnetically labeled protons with radiofrequency (RF) waves in arterial blood water content as an endogenous tracer. ASL is non-invasive and able to quantitatively measure tissue perfusion. Recent technical advances have increased its sensitivity and also extended the potential applications [22]. In PD, it was shown a reduced perfusion in the cortex and either conserved or reduced in the basal ganglia and conserved in the sensorimotor areas [20, 21]. Several studies on ASL-MRI have consistently shown symmetrical cortical hypoperfusion in PD involving predominantly the parieto-occipital areas and the dorsolateral prefrontal cortex [20]. In PD patients with dementia, posterior perfusion deficits were found to be more striking than without dementia [23].

In a study on both FDG-PET metabolism and ASL-MRI perfusion in PD, it was found overlapping metabolic and perfusion deficits [24]. ASL-MRI has the potential to identify PD early in the PD disease course when the patients show disease-specific metabolism patterns with FDG-PET characterized by relatively increased metabolism in the globus pallidus and putamen, thalamus, cerebellum, pons, and sensorimotor cortex and relative decreases in the lateral frontal and parieto-occipital areas [25–27].

Diffusion tensor imaging
Diffusion tensor imaging (DTI) is a MRI technique which is widely applied to diagnose several neurodegenerative diseases [28, 29]. DTI provides information about the orientation and integrity of white matter tracts in vivo with the aid of anisotropic water diffusion in white matter [30–32].

DTI evaluates the degree of directionality by means of anisotropy (frequently fractional anisotropy [FA]) and

also the overall movement of molecules (mean diffusivity [MD]; trace; apparent diffusion coefficient [ADC]) as well. The measurements can either be extracted locally in predefined regions using region of interest (ROI) analysis or, alternatively, globally by voxel-based analysis (VBA) or tract-based spatial statistics (TBSS).

The most widely applied algorithm to extract related fiber data for processing DTI information is tractography [33]. In this procedure, the processed fiber data is evaluated with a connectivity analysis that lets observation of the whole brain as a complex linked network [34, 35]. Resting-state functional MRI (vs-fMRI) was used to observe defects in functional connectivity in the identical circuit [36].

Disruptions to microstructural tissue integrity, such as those seen in the neurodegeneration of parkinsonian syndromes could be affiliated with variations in anisotropy and diffusivity procedures [28, 29].

In spite of uncommon changes visible on conventional MRI imaging including narrowing or disappearance of the pars compacta of the substantia nigra (SN) on usual T_2-weighted-imaging, this sign has low sensitivity and specificity and contributes marginally to the diagnosis of PD [37].

Susceptibility weighted imaging (SWI) is a new MRI technique that can be performed on conventional MR scanners with an imaging time comparable with or lower than that of other advanced sequences. The technique is hopeful in PD diagnosis by the improved sensitivity to detect brain mineralization. There is evidence that SWI images improve visualization of the SN due to the increased sensitivity to brain iron concentration and other metals [38]. Brain iron deposition has been proposed to play a key role in the pathogenesis of Parkinson disease (PD) [39].

The iron concentration is quantitatively different in PD and atypical parkinsonian disorders. Increased iron concentration and, more importantly, impaired iron handling are assumed to cause tissue damage via oxidative stress formation of free oxygen radicals [40].

SWI sequences were considered to have a stronger and more accurate correlation with brain iron load than R_2 relaxation rate alone [38]. Studies have shown that this sequence is severely sensitive to mineralization and substances with magnetic susceptibility, hence, to be more sensitive than conventional gradient echo sequence in the detection of PD and parkinsonian syndromes [41, 42].

Diffusion-weighted MRI

Diffusion-weighted MRI (DWI) has been utilized in differentiation of PD and other parkinsonian syndromes using water apparent diffusion coefficients (ADC) [43]. ADC relies on both interactions between water molecules as well as the chemical environment and the structural barriers at cellular and subcellular level hindering their motion in vivo [44]. There are several reports on differentiation of MSA-P from PD whom demonstrated respectively high and normal putaminal ADC [40, 45, 46].

There have been a number of reports which showed that DWI method distinguished MSA-P in early stages with Parkinson's disease and also healthy volunteers on the basis of increased putaminal ADC values which was also related with disease severity [47, 48].

In an investigation by Schocke et al. [47], an expanded diffusivity was additionally found in the caudate nucleus and globus pallidus in MSA-P in contrast with Parkinson's disease patients and controls that could be reflecting the spreading neurodegeneration in the basal ganglia. Similar results were also obtained for PSP; however, MSA-P and PSP could not be isolated by DWI technique. A further report by Seppi et al. [49] on DWI in MSA with cerebellar feature patients (MSA-C) depicted an increment of the ADC in the pons, in the middle cerebellar peduncle, in the cerebellar white matter, and in the putamen.

In vivo magnetic resonance spectroscopy (MRS) is a further tool that could be used as supplementary to conventional MRI in characterization of the brain metabolism changes in patients with PD and, as an ideal imaging biomarker, has been found to meet plenty of criteria [50]. Indeed, MRS has good constancy (test-retest reliability) and, in comparison with PET and SPECT, is a non-invasive and inexpensive method [50]. Furthermore, in comparison with in vitro molecular imaging, MRS has been shown to be unrestricted to specialized centers for analysis. The metabolites recognizable with proton MRS incorporated the outstanding resonances of N-acetylaspartate (NAA), choline-containing mixes (Cho), creatine + phosphocreatine (Cr), myo-inositol (ml), lactate (Lac), and a variety of different resonances that probably would not be apparently relying upon type and nature of spectra just as on the pathological condition [51].

Studies have shown the efficacy of MRS for differentiating PD in the presence of other atypical parkinsonian disorders (APDs) [52, 53].

MRS has also been shown to be effective for delineating PD in early stage (which is even more difficult to distinguish because of overlapping syndromes of parkinsonism) [54].

Table 1 provides some clinical pointers and radiological features in parkinsonian syndromes by various imaging techniques [55].

The concentration changes of all metabolites identified by MRS could assist with assessing PD subjects with early motor symptoms, particularly in early differential diagnosis. Single-voxel proton magnetic resonance spectroscopy (1H-MRS) of striatal structures may

Table 1 Clinical pointers and radiological features in parkinsonian syndromes by various imaging techniques [55]

Syndrome	Clinical pointers	Radiological features
Multiple system atrophy	➢ May be indistinguishable from PD in early stages ➢ Jerky finger tremor related to mini-polymyoclonus ➢ "Strangulated" dysarthria ➢ Axial/craniocervical levodopa-induced dyskinesia	➢ Cerebellar atrophy ➢ T2 high signal in degenerating pontocerebellar fibers leading to "hot-cross bun" sign (Fig. 2) ➢ T2 low signal in putamen with rim of increased signal on lateral edge
Progressive supranuclear palsy	➢ Erect posture with good step size at presentation ➢ Frequent falls and injuries early in the disease course ➢ Slowed saccadic eye movements may be subtle in early disease	➢ Midbrain atrophy (with "hummingbird" sign on sagittal brainstem images, Fig. 3) ➢ 3rd ventricle dilatation
Corticobasal degeneration	➢ Markedly asymmetrical rigid/akinetic/apraxic limb with relatively normal contralateral limb in early disease	➢ Asymmetric frontoparietal atrophy on MRI
Essential tremor	➢ High-frequency tremor ➢ The tremor is postural and kinetic, and improves with rest ➢ Absent PD non-motor features ➢ Head and neck tremor ➢ May have a long and benign course	➢ DaTscan is normal
Dystonic tremor	➢ Thumb extension tremor ➢ Jerky tremor with flurries of tremor ➢ May be task-specific or task-exacerbated	➢ DaTscan is normal
Vascular parkinsonism	➢ Presents as gait disorder ➢ "Lower body" parkinsonism with mild or absent upper body parkinsonism	➢ Neuroimaging shows variable degrees of small-vessel ischemic changes

PD Parkinson's disease

discriminate PD from APDs by virtue of diminished NAA/Cr proportions in MSA but not in PD. In comparison with normal controls, in patients with PSP, CBD, and MSA, critical decrease of the NAA/Cr ratio in the frontal cortex was seen. Patients with CBD have indicated a significant decrease on the NAA/Cr ratio in the frontal cortex and putamen when contrasted with patients with PD and MSA [58]. On the other hand, patients with CBD have demonstrated clear asymmetry in the putamen when contrasted with controls and also in different patients [58].

Chougar et al. [59] figured out that patients with PSP and MSA-P had lower NAA concentrations in the pallidum, putamen, and lentiform nucleus contrasted with normal controls and patients with PD. However, different MRS reports have indicated diminished NAA/Cr and NAA/Cho proportions in the lentiform nucleus in APD, as well as in PD [60, 61].

Functional connectivity imaging
Functional magnetic resonance imaging (fMRI) was originally proposed for the detection of task-related signal changes in the brain, blood oxygen level dependent (BOLD), and in investigating functional connectivity in distant regions of the brain. Remote regions giving rise to distributed cortical and subcortical networks refer to temporal association of variations of the resting stage fMRI signal [62]. Via computational modeling, these networks are obtained from rsf-MRI data [63, 64]. Anatomical connectivity and resting state functional MRI (rsf-MRI) have been observed using tractography (Fig. 1) [65].

Rs-fMRI in PD diagnosis studies have detected irregular functional regional interactions in resting brain networks [66, 67], and hence, it was concluded that PD relates to the variations in cerebral connectivity between the basal ganglia, cortex, or cerebellum [66], and between the STN, cortical motor, and premotor areas [67]. The variations have been observed in the sensorimotor circuit associated with a reduction in functional coupling [68, 69]. Abnormal functional connectivity was also demonstrated in the default-mode network in cognitively unimpaired PD patients which may be associated with cognitive performances in memory and visuospatial tests [70]. The supplementary motor area presents a decreased signal fluctuation in drug-naïve PD patients who were not previously exposed to the therapy or treatment, while an improved functional connectivity was detected in this area with levodopa and in specific frequency band variations [71]. The variations in resting state BOLD fluctuations were successful in estimating the presence of PD, and variations in functional connectivity were distinctively related with symptoms of PD [72]. To predict motor performance, increased amplitude of low-frequency BOLD signal oscillations method was used in the premotor cortex [73]. In PSP, rsf-MRI presented connectivity disruptions among the dorsal midbrain tegmentum and the cerebellum, diencephalon, basal ganglia, and cortex which were related to more critical functional impairment [73, 74], either it was shown an interruption between thalamus and striatum, supplementary motor area, and cerebellum [75]. In general, results with fMRI in resting state refer that dopamine depletion in PD produces remapping of cerebral
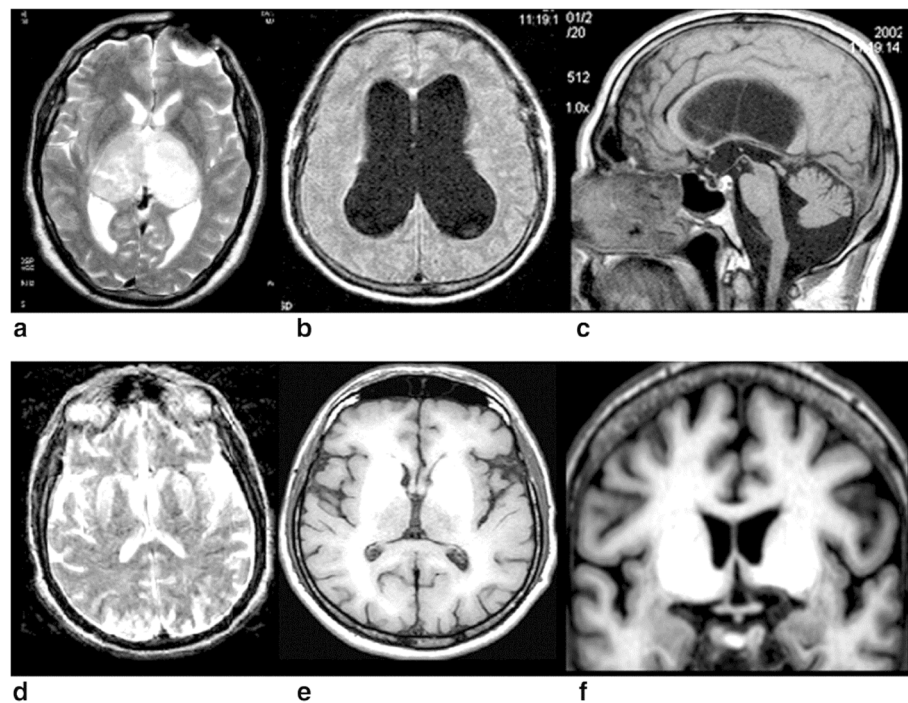
Fig. 1 MRI of nondegenerative "symptomatic" causes of parkinsonism. **a** Bilateral thalamic grade II glioma. Axial T2-weighted turbo spin echo MR image reveals two hyperintense mass lesions in the thalami. **b** Axial T2-weighted FLAIR MR image shows marked dilatation of the lateral ventricles exhibiting a ballooned shape and effacement of the cortical sulci. **c** Sagittal T_1 spin echo MR image confirms the dilatation of the lateral ventricle and reveals dilatation of the cerebral aqueduct and fourth ventricle. Note the bowing of the corpus callosum and the effacement of the cortical sulci. Both cases in **b** and **c** images have normal pressure hydrocephalus. **d** Creutzfeldt-Jakob disease. Axial T_2-weighted MR image shows symmetric hyperintensity of the putamen and head of caudate. **e** Axial T_1-weighted spin echo and coronal T_1-weighted gradient echo. **f** MR images show marked symmetric hyperintensity of the globus pallidus, putamen, and caudate [63]

connectivity which influences predominantly on sensorimotor circuit and sensorimotor integration that was affected by levodopa and differently related to motor and nonmotor symptoms [74].

Positron emission tomography (PET)

PET is a powerful and multipurpose imaging modality which allows in vivo examination of brain processes. It has made valuable contribution to neuroscience research by giving functional information as well as quantitative data of cerebral blood flow, metabolism, and receptor binding. However, its application in clinical neuroscience is confined compared to oncology due to the high costs and need for tremendous supporting facilities such as in site cyclotron, PET scanner, and radiochemical laboratories.

PET provides an impartial in vivo quantification of local radiotracer activity with a very proper sensitivity [23]. It can be used to observe cerebral blood flow and energy metabolism which are based on radiotracers [24].

An accuracy of 90% may be the highest value that can be expected with clinical assessment using current diagnostic criteria of PD [76]. Definitive diagnosis is only by demonstration of intraneuronal Lewy body inclusions in the substantia nigra compacta. PET reports have attracted an enormous recognition due to its ability to detect disease long before beginning of the symptoms [40].

^{18}F-deoxy-glucose (^{18}FDG) PET/CT brain

Despite the increasing use of FDG-PET/CT in clinics and research, its use in PD has been limited due to low spatial resolution and image quality, and high cost. FDG-PET is useful for differentiating PSP from idiopathic PD [77]. In PD-related cognitive decline, ^{18}FDG-PET has a typical template of hypometabolism chiefly affecting the posterior cortical regions [77].

^{18}FDG PET investigations can provide a measure of resting glucose metabolism and thus neuronal activity [78]. Increased glucose metabolism has been shown in the contralateral lentiform nucleus in patients with early unilateral parkinsonism [79]. Covariance investigation areas in PD patients has demonstrated hypermetabolism in the lentiform nucleus and thalamus with hypometabolism in the frontal, parietal, and parieto-occipital (Fig. 2) [56, 79].

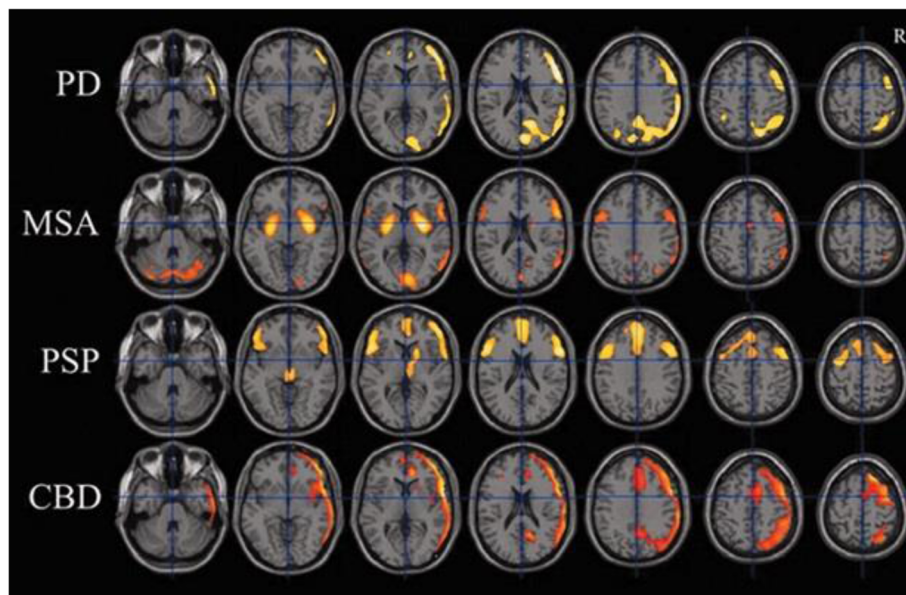Most PET ^{18}F-deoxy-glucose (FDG) studies have shown ordinary striatal metabolism in PD, thereby

Fig. 2 The administration of [18]FDG-PET for the diagnosis of Parkinson's and degenerative parkinsonism disorders. Consequences of the between-group statistical parametric mapping analysis for each diagnostic category shown in the vertical axis as follows: Parkinson's disease (PD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD), vs. healthy controls. The red and yellow colors highlighted regions superimposed on normal T_1-weighted MR templates showing areas with significantly reduced FDG uptake relative to the global mean [78]

suitable in differentiating PD from other parkinsonian syndromes including progressive supranuclear palsy (PSP) or multiple system atrophy (MSA) [80, 81]. By the technique, metabolic irregularities have been observed in a specific network in PD by investigating regional metabolic covariance patterns [82].

[18]F-Dopa PET studies

Khamis et al. [83] have shown that ^{18}F-Dopa PET is a valuable tool for identifying reduction of dopaminergic activity in PD patients at a very primary phase. But the uptake might be upregulated in early stage of the disease while expression of DATs might be downregulated.

[18]F-6-fluoro-L-dopa radiotracer uptake study indicates the dopaminergic nerve density; moreover, it expresses activity of the aromatic amino acid decarboxylase enzyme (AADC) converting dopa into dopamine and the storage of dopamine [84]. This radiotracer allows assessment of presynaptic dopaminergic system viability in the nigrostriatal as well as mesolimbic and mesocortical dopaminergic pathways. In PD, a major decline in striatal ^{18}F-Dopa uptake is usually detected, thereby indicating degeneration of dopaminergic nigrostriatal pathways [85]. The uptake reduction is well correlated with neuronal degeneration as demonstrated in pathological studies by Kroth et al. [86]. Although at the early stages of the disease, false negative cases have been observed as a

result of compensatory upregulation of AADC in preserved dopaminergic terminals [86]. The situation has been differed using dopamine transporter ligands such as Br-FECBT, due to the fact that dopamine transporter activity is not regulated as dopa decarboxylase [87]. Ribeiro et al. [88] reported higher sensitivity of DAT imaging compared to ^{18}F-Dopa in detecting dopaminergic degeneration especially in early-stage PD. At advanced stages, the upregulation diminishes. The reduction in striatal ^{18}F-Dopa uptake is not homogeneous in the striatum, and a clear anteroposterior gradient is observed when the caudate is being less affected than the anterior putamen and the anterior putamen less affected than the posterior putamen. Hence, ^{18}F-Dopa PET aids positive diagnosis of parkinsonian syndromes even at its presymptomatic stages [89].

[18]F-Dopa PET has shown that clinical expression of PD symptoms happen when about 50% of dopamine terminal function is harmed in the posterior putamen [90].

In a typical patient with unilateral parkinsonism, ^{18}F-Dopa could reveal bilaterally decreased putamen dopaminergic function with activity being the most depressed in the putamen contralateral to the affected limb/limbs [73]. Dopamine terminal dysfunction in the asymptomatic relatives of PD patients can be detected by PET [91].

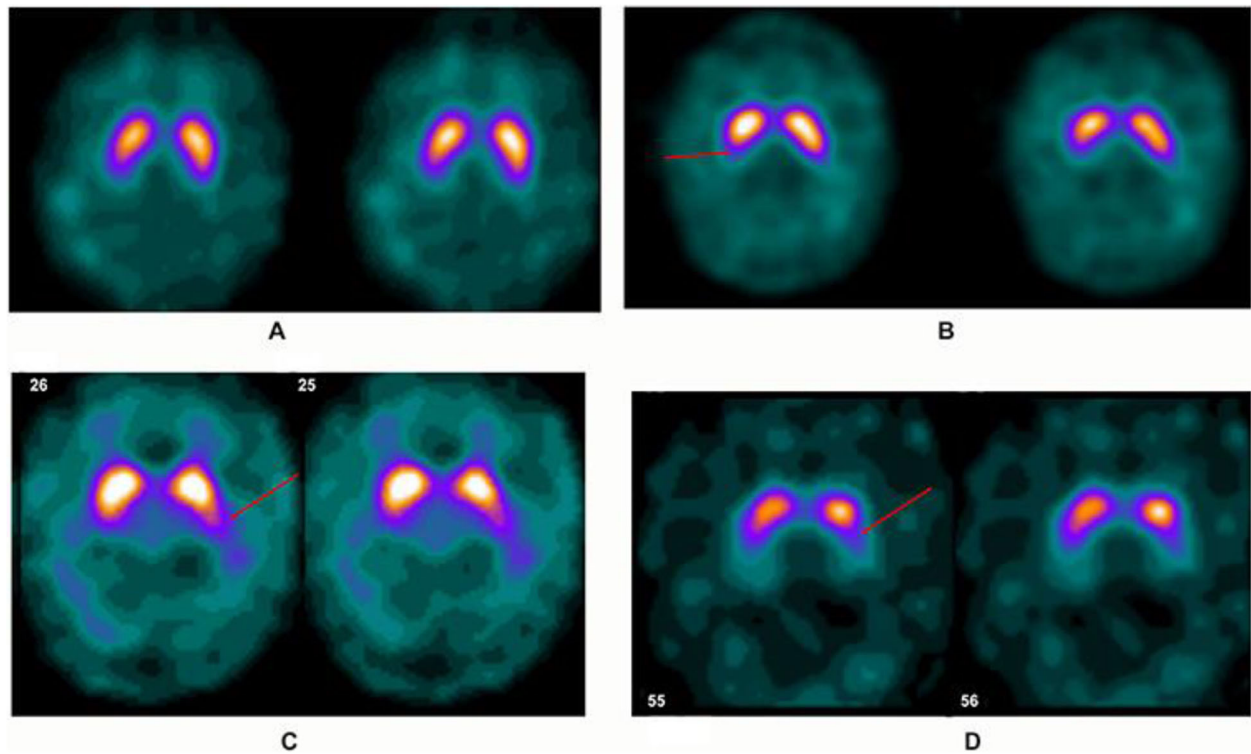[18]F-Dopa was used to study 32 members of unrelated familial kindred of which 8 showed reduced uptake in

Fig. 3 DaT scan SPECT images from four patients. Image (**a**) showing normal "comma" configuration on the striata bilaterally, with a score of 0. Mild progressive loss of dopamine transporters depicted on the right (arrow) (**b**) score of 1, moderate on the left (arrow) on image (**c**) score of 2 and severe on the left (arrow) on image (**d**) score of 3 [96]

the putamen. Interestingly, 3 out of those 8 ones developed clinical parkinsonism in a 5-year follow-up period [92].

Single photon emission tomography (SPECT)

The combined pre- and postsynaptic as well as clinical criteria using SPECT imaging method could improve the diagnosis of Parkinson's disease in early stage [93]. The fusion of presynaptic DAT and postsynaptic D2 receptor binding has shown improved diagnostic value in ruling out patients with non-idiopathic parkinsonian syndromes from PD patients [94].

Dopamine transporter scan (DaT scan)

In this test, a radiolabeled tracer, e.g., ^{123}I-ioflupane, is injected into a patient's veins, circulates around the body, and gets into the brain. When DAT and dopaminergic neurons reduce in PD and other pre-synaptic
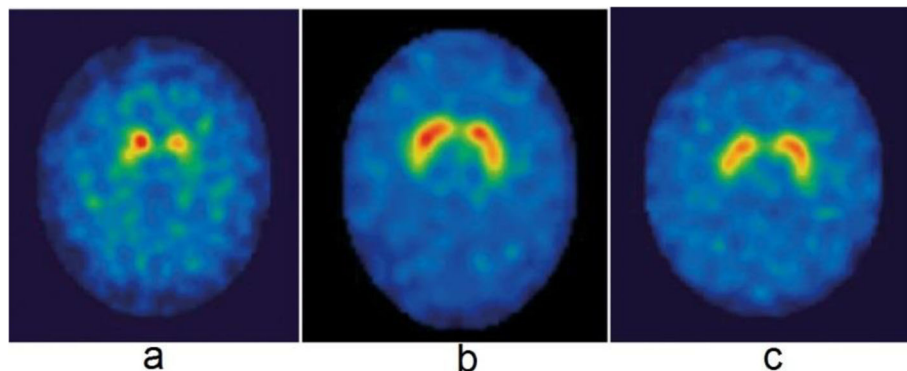

Fig. 4 Dopamine transporter imaging by administration of ^{123}I-fluopane (FP)-CIT in a patient with Parkinson's disease (**a**), an essential tremor (**b**), and a healthy control (**c**) [104]
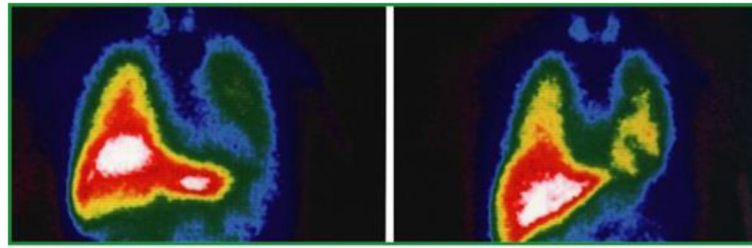
Fig. 5 The administration of iodine-123 metaiodobenzylguanidine (^{123}I-MIBG) and its uptake in Parkinson's disease (PD) (left) and multiple system atrophy (MSA) (right). Normal heart uptake in the MSA patient is seen. The image shows extensive liver uptake in both patients [104]

parkinsonism diseases, SPECT imaging should take place several hours after the tracer has been administrated. In PD, there is a smaller signal in striatum section of the brain where the ends of the dopamine neurons are meant to be [95, 96]. Indeed, the expression of this protein may reflect the functional dopaminergic neuronal density in striatum part, and its decrease in PD is presumed to be in proportion with severity of the illness (Fig. 3) [57, 97, 98].

DaTscan have no reliable results in the diseases with loss of dopaminergic nerve cells and the resultant decrease in striatal dopamine levels. So, Parkinson-plus syndromes, such as progressive supranuclear palsy (PSP), corticobasal ganglionic degeneration (CBGD), and multiple system atrophy (MSA), cannot be discriminate with DaT scan method, and hence, the mentioned cases are typically demonstrated abnormal [76].

Although DaT scan is not able to distinguish between Parkinson's disease, PSP, CBGD, and MSA from PD, but there are several reports that confirm the ability of the method to distinguish PD from drug-induced parkinsonism and vascular parkinsonism [99].

[123]I-ioflupane SPECT imaging

[123]I-ioflupane-SPECT is an important diagnostic modality for differentiating parkinsonian syndromes (PD, MSA, PSP, CBD) from ET and drug-induced parkinsonism, indicating early stage of the disease in comparison
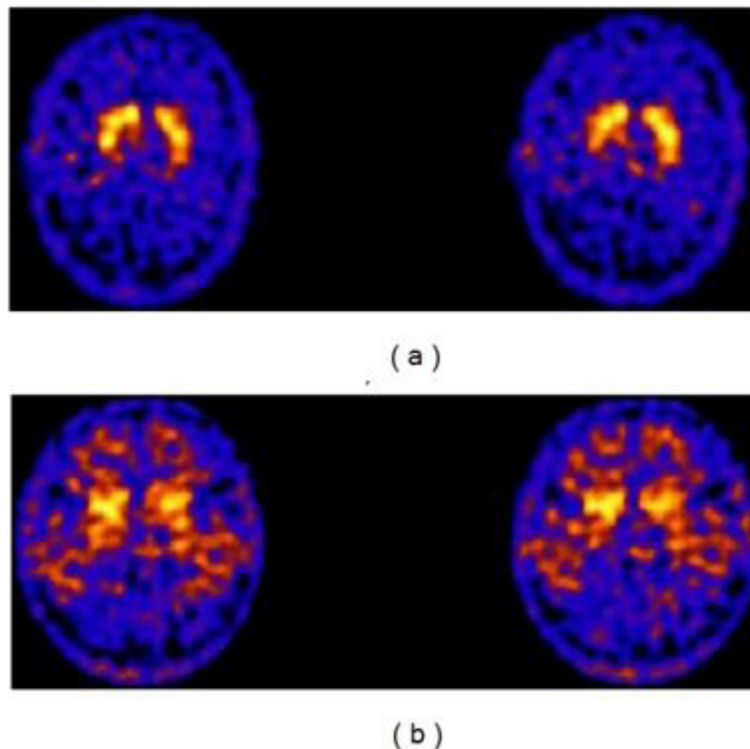

Fig. 6 SPECT imaging using ^{99m}Tc-TRODAT-1 in normal control (**a**) and patient with early PD (**b**). In the case of patient with early PD in comparison to control, images show reduced TRODAT-1 uptake in the striatum [108]

Table 2 Some radiotracers used for Parkinson's disease SPECT

Biological variable radiotracer	
Dopamine reuptake (dopamine transport)	^{123}I-β-CIT
	^{123}I-FP-β-CIT
	^{123}I-IPT (presynaptic dopamine transporter)
	^{123}I-Altropane
	^{123}I-β-PE2I
	^{99m}Tc-TRODAT-1
D2 dopamine receptor	^{123}I-Iodospiperone
	^{123}I-Iodobenzamide (123I-IBZM) (postsynaptic dopamine D2 receptor)
	^{123}I-Iodolisuride, 123I-IBF,
	^{123}I-Epidepride (extrastriatal DA receptors)

to anatomical modalities including conventional CT or MRI [100]. This approach provides valuable diagnosis based on local binding of presynaptic dopamine transporters (DaTs) with ^{123}I-ioflupane, which has been reported to have high association with progression of PD [101]. The striatum has been the focal point of most investigations making use of ^{123}I-ioflupane-SPECT. It has been shown that PD has significantly reduced dopamine transporter levels in the striatum [100].

[123]I-fluopane-CIT

[123]I-fluopane-CIT, an analog of ^{123}I-β-CIT as radiotracer in SPECT imaging, was widely used to investigate the presynaptic dopaminergic system in early diagnosis of parkinsonism and differential diagnosis of PD from ET (Fig. 4) [102, 103].

It was found that the accuracy of diagnosis was the same in both clinical exam and using DaT scan [95]. DaT scan is claimed to have enough sensitivity to discriminate changes in the nigrostriatal dopaminergic system of normal controls as well as PD patients [104].

^{123}I-MIBG scintigraphy

Iodine-123 metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy is a noninvasive and secure diagnostic strategy to recognize and assess sympathetic denervation (Fig. 5) [102]. It has reported a diminished uptake of ^{123}I-MIBG in myocardial sympathetic neurons in PD, demonstrating an impaired postganglionic sympathetic innervation in this disorder [105]. The main problem concerning ^{123}I-MIBG/SPECT is its low specificity (37.4%) in spite of its moderately high sensitivity (87.7%) [102].

^{99m}Tc-TRODAT-1

TRODAT-1, a ^{99m}Tc-labeled tropane derivative, is a cocaine analogous that can attach to the dopamine transporter (DAT) sites at presynaptic neuron membrane which is beneficial as a potential CNS dopamine

transporter imaging agent and can be labeled with ^{99m}Tc without difficulty in most nuclear medicine departments all over the world [106].

Some related researchers have discerned that DAT imaging with ^{99m}Tc-TRODAT-1 SPECT has high sensitivity particularity in differentiating PD from ET [107]. PD follows a particular pattern on DAT SPECT demonstrating more decreasing of ^{99m}Tc-TRODAT-1 binding on the contralateral to the symptomatic side and a reduction slope in tracer binding with greater/more reduction in putamen as compared to caudate nucleus (Fig. 6) [108]. ^{99m}Tc-TRODAT-1 has advantages of easy accessibility of ^{99m}Tc, lower cost, optimal energy for imaging, and faster pharmacokinetics, permitting image embodiment within a few hours [109].

Some of radiotracers used for SPECT imaging in PD diagnosis are illustrated in Table 2.

Conclusion

There are several diagnostic imaging approaches for screening of PD including PET, SPECT, MRI, and CT. Emission tomography (SPECT or PET) has an important role in PD diagnosis; however, it tends to be costly, with restricted accessibility, and needs radioactive tracers. It seems that the advanced MRI techniques as DWI, DTI, MRS, MTI, and magnetic resonance imaging-based volumetry are more delicate in separating PD from atypical parkinsonian.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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