Imaging beyond the striatonigral dopaminergic system in Parkinson's disease

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Abstract

Parkinson's disease (PD) is characterized by progressive loss of dopaminergic neurons in the nigrostriatal pathway, but this seems to constitute only part of the whole pathological process of the disease. Accumulating data have documented the concomitant degeneration of other dopaminergic pathways and of the serotonergic, cholinergic and noradrenergic neurotransmitter systems. In addition, pathologic process is not only restricted in the brain, since the spinal cord and the peripheral autonomic nervous system are also affected. The pathogenesis of PD remains unclear. The use of positron emission tomography and single photon emission tomography may contribute to the understanding of these aspects of the disease. This review will discuss the role of PET and SPET in imaging the extrastriatal dopaminergic system and other neurotransmitter systems as well as the imaging of microglial activation and cardiac sympathetic denervation in PD. *In conclusion*, several PET and SPET ligands can detect changes in extrastriatal dopaminergic system as well as in the serotonergic, cholinergic and noradrenergic systems in PD and also explore its possible correlation with motor and non motor symptoms. The use of PET scintigraphy allows the detection of microglial activation in PD, while ^{123}I-MIBG scintigraphy depicts cardiac sympathetic denervation in PD and is a useful imaging tool for differentiating PD from other types of parkinsonism.

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Introduction

Parkinson's disease (PD) is a slowly progressive neurodegenerative disease predominantly characterized by selective loss of dopaminergic neurons in the substantianigra pars compacta resulting in profound depletion of dopamine in striatal terminals [1]. Parkinson's disease is now considered a multisystem degenerative process, affecting not only the most targeted nigrostriatal dopaminergic system, responsible for the majority of the motor symptoms, but also other neurotransmitter systems, like cholinergic, serotoninergic, noradrenergic etc. associated with the emergence of a multitude of non motor symptoms [2-4]. Additionally, accumulating evidence suggests that pathological process affects several distinct neuronal populations not only of the brain but also of the spinal cord and the peripheral autonomic nervous system (ANS) [5-7].

Currently, the diagnosis of PD remains clinical and there is no well-established diagnostic biomarker for the disease [8, 9]. However, the most advanced imaging methods of nuclear medicine appear appealing tools, which can illustrate many different aspects of the disease process even from the premotor stage [10]. Positron emission tomography (PET) and single photon emission tomography (SPET) using various radiotracers are widely applied for the evaluation of the integrity of presynaptic dopaminergic system verifying the nigrostriatal degeneration and quantifying the loss of presynaptic dopaminergic terminals in PD [11, 12] (Fig. 1-3). Their application is continuously expanding focusing on the imaging of different aspects of PD as a multisystemic degenerative process. The aim of this article was to review the current knowledge regarding the imaging of extrastriatal dopaminergic system and of the serotonergic, noradrenergic and cholinergic neurotransmitter systems as well as the imaging of microglial activation and cardiac sympathetic denervation in PD.

Extrastriatal dopaminergic system imaging

The majority of dopaminergic neurons are located in substantianigra (SN) and the striatum is by far the main basal ganglia target of midbrain dopaminergic projections. In addition,

there is a diffuse dopaminergic output from the midbrain to other extrastriatal areas. The mesolimbic and mesocortical dopaminergic pathways arise predominantly from the ventral stegmental area and project to numerous limbic regions and cortical areas respectively [13, 14]. Apart from the nigrostriatal system, these extrastriatal dopaminergic pathways are also affected in PD to a various extent [15].

Brain [18F]-6-fluoro-L-dopa (18F-Fdopa) PET provides the measurement of the dopaminergic terminal density and the activity of the aromatic amino acid decarboxylase enzyme (AADC) [16, 17]. Fluorine-18-Fdopa PET has been used principally to assess the nigrostriatal deficit in PD [18], but also allows the study of other dopaminergic pathways.

Several studies reported increased cortical 18F-Fdopa uptake [19], particularly in the dorsolateral prefrontal cortex [20], the medial frontal cortex [19, 20] or the anterior cingulated [21] at early stage of PD as compared to advanced stage patients and normal controls [20-22]. It is likely that the increased cortical 18F-Fdopa uptake observed in early PD reflects compensatory upregulation as a result of increased activity of AADC in the remaining dopaminergic terminals. However, this upregulation may underestimate the extent of degenerative process at the early PD stages [19, 23].

Figure 1. 123I-FP-CIT SPET image from a healthy control shows normal and symmetrical radiotracer in the basal ganglia

Additionally, increased cortical 18F-Fdopa uptake seems to be preserved during the first years of PD, in contrast to striatal uptake decline, since a related study did not report significant change in cortical uptake two years after the first PET scan [23]. On the other hand, some other studies reported decreased tracer uptake even at the early stage of PD patients. Researchers have evaluated the density of dopaminergic projections including the mesocortical/mesolimbic pathway using 2-β-carbomethoxy-3β-(4-[11C]fluoro phenyl)tropane (β-CFT) PET. There was a parallel reduction in the binding levels in these extrastriatal regions namely the orbitofrontal cortex and amygdala along with the striatal reduction indicating that not only the nigrostriatal, but also the mesocortical/mesolimbic dopaminergic systems were substantially altered at the early stage of PD patients [24]. Other researchers have also reported reduced 18F-Fdopa uptake in the cortical motor areas [25].

The investigation of dopaminergic system in PD with dementia (PDD) showed additional uniform bilateral reduction in 18F-Fdopa binding in the anterior cingulate, the amygdala, the prefrontal cortex [26, 27], the ventral striatum as well as the right caudate compared with non-demented PD patients [28]. These findings support the concept that PDD is associated with impaired frontal and caudate dopaminergic function.

Investigation of the distribution of D2/D3 receptor subtypes in extrastriatal regions using PET showed that the availability of these receptors outside the striatum is affected in advanced but not in early stage PD and that this decline was present in the anterior cingulate cortex, the dorsolateral prefrontal cortex and the thalamus, but not in the limbic structures [29]. Another study of the alterations in extrastriatal dopamine D2 receptors during early stage PD showed a significant decline in the receptor availability in the left dorsolateral prefrontal cortex, the left lateral temporal cortex and left and right thalamus after a three years period, which was not associated with motor deterioration [30].

In summary, it seems that the studies mentioned above support the impairment of extrastriatal dopaminergic pathways even at early stage PD and imply association with PDD.
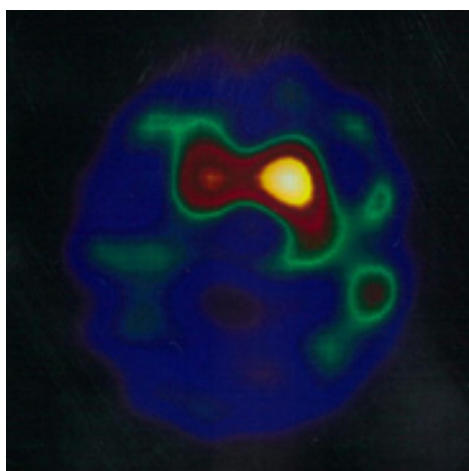

Figure 2. 123I-FP-CIT SPET image of a patient of ours with unilateral PD shows marked reduction of the radiotracer uptake in the basal ganglia contralateral to the side of motor symptoms.
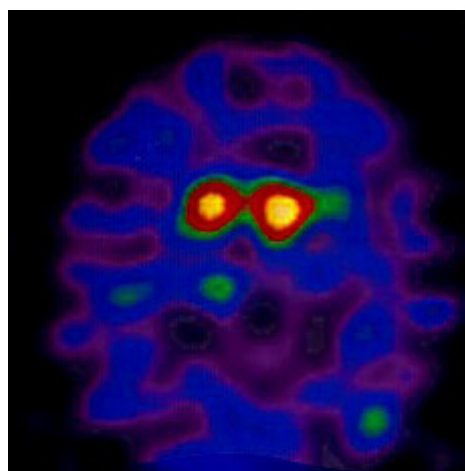

Figure 3. 123I-FP-CIT SPET image of a patient of ours with moderate stage PD and bilateral motor symptomatology shows bilateral reduction of the radiotracer uptake in the basal ganglia.

Imaging the serotonergic system

The raphe nuclei are distributed in the midline of the brainstem along its rostrocaudal extension and contain the majority of serotonergic neurons in the brain. The rostral cell groups including dorsal raphe and median nuclei project primarily to forebrain, limbic system and hypothalamus [31]. Postmortem studies in PD have shown loss of serotonergic neurons in rostral raphe complex leading to secondary reduction in serotonin levels in certain brain areas [32].

The function of serotonergic system has been investigated in PD patients with various specific PET and SPET tracers. The degeneration of serotonergic system in PD leads to alterations in serotonin transporter (SERT) levels and several studies have focused on the quantification of SERT reporting various results.

The SERT values using ^{123}I-β-CIT SPET were lower in thalamic and frontal regions in PD patients [33]. The investigation of SERT in midbrain showed mildly decreased levels of ^{123}I-FP-CIT with marked interindividual variability [34], while another study didn't reveal alterations in midbrain binding [35]. A recent paper, using of two tracers, ^{18}F-Fdopa and [^{11}C]-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile (^{11}C-DASB), revealed significantly reduced levels in raphe complex, hypothalamus and anterior cingulate cortex [36]. Other researchers have also found reduced SERT binding in PD, but the level of binding reduction was greater in forebrain than in brainstem [37]. Another study of striatal and extrastriatal serotonergic function in PD patients performed with ^{11}C-DASB PET showed widespread binding reduction in striatal, brainstem and cortical regions, which was not correlated with disease duration and motor disability [38].

Other researchers focused on the imaging of the serotonergic system in different PD stages. Studies of SERT availability in de novo PD patients showed no alterations in mesencephalic SERT binding compared with normal controls suggesting preserved serotonergic system in early PD [39, 40]. There was no correlation between midbrain SERT and striatal DAT binding, showing that midbrain SERT binding was not consistent with the dopaminergic deficit in early PD [39, 40]. Others measured the levels of SERT in subcortical and cortical brain areas of clinically advanced non-depressed PD patients. Binding of ^{11}C-DASB was significantly lower in the orbitofrontal cortex, caudate, putamen and midbrain suggesting a modest, widespread loss of brain serotonergic innervations in advanced PD [41].

Several studies were directed towards the role of serotonergic function in the emergence of depression in PD. However, the results of these studies didn't reveal a clear correlation between serotonergic dysfunction and depression in PD. Researchers showed no significant difference in SERT density measured by ^{123}I-β-CIT in the midbrain of early stage PD patients and normal controls [42]. There was no difference between depressed and non depressed patients and no correlation between radiotracer uptake and Hamilton Depression Rating Scores [42]. Thalamic SERT binding with ^{123}I-β-CIT in early drug-naive PD patients was reduced compared with controls and further reduced during follow-up. There was an association with tremor but no correlation with the Beck Depression Inventory score [43]. Another study in a small group of early

stage PD patients with concurrent depression showed a significant increase in ^{11}C-DASB binding in dorsolateral (37%) and prefrontal cortices (68%), which was correlated with depressive symptoms but not with disease severity or duration [44]. Similarly, a later study detected a significantly raised ^{11}C-DASB binding in raphe nuclei and limbic structures in antidepressant-naove PD patients with more severe depressive symptoms compared to patients with mild depressive symptoms [45]. This possibly reflects a combined effect of serotonergic terminal loss together with upregulation of SERT function and might be a feature of depression in PD.

A possible association of fatigue with serotonergic system was also examined. A recent study reported reduced ^{11}C-DASB binding in basal ganglia and limbic structures in patients with PD and fatigue, while striatal ^{18}F-Fdopa uptake was similar in fatigued and non-fatigued groups showing that fatigue in PD is associated with serotonergic dysfunction in basal ganglia and the limbic structures [46].

Imaging of the serotonergic system also included the investigation of serotonin 1_A or 5-hydroxytryptamine 1_A receptors (5-HT1$_A$). Patients with PD showed a significant reduction in midbrain raphe 5-HT1$_A$ binding with [^{11}C]N-(2-(4-(2-methoxyphenyl)-1-piperazin-1-yl)ethyl)-N-(2-pyridyl) cyclohexanecarboxamide (^{11}C-WAY 100635) as examined with PET compared with normal controls, which reduction was negatively correlated with the tremor score of the Unified Parkinson's Disease Rating Scale (UPDRS), but not with rigidity and bradykinesia [47]. Apart from the involvement of serotonergic system in the neurodegenerative process of PD, this study may also provide a clue for a possible role of serotonergic system in the origin of parkinsonian tremor. A recent study in a small number of PD patients investigated the role of postsynaptic serotonergic system in relation to depression using 4-(2′-methoxyphenyl)-1-[2′-(N-2′′-pyridinyl)-p-[^{18}F]fluorobenzamido] ethylpiperazine (^{18}F-MPPF) PET [48]. Depressed PD patients exhibited significantly reduced uptake in the limbic system as compared with non depressed PD patients indicating a possible association of depression with decreased postsynaptic 5-HT1$_A$ binding.

The serotonergic system undergoes degeneration in PD suggesting a relation between a direct role of serotonergic function with symptoms of depression.

Imaging the noradrenergic system

The locus coeruleus (LC), located in the upper pontinetegmentum is the main noradrenergic nucleus of the brain and projects extensively to forebrain, limbic system, thalamus and hypothalamus [49]. The involvement of LC in PD has been well documented neuropathologically and the coeruleus-subcoeruleus complex is involved even at the presymptomatic stage (stage 2) according to Braak's staging [50].

There are currently no selective PET and SPET tracers for the imaging of the noradrenergic system. A retrospective analysis of imaging data on early stage PD patients showed increased ^{123}I-FP-CIT binding in LC, which was negatively correlated with striatal binding. This is likely to represent a compensatory mechanism causing up-regulation of noradrenaline reuptake [51]. Increased uptake in

LC was also reported with ^{18}F-Fdopa PET studies [52, 53], which became subnormal in 3 years of follow-up [52]. However, others reported normal ^{18}F-Fdopa uptake in LC in early stage PD and the levels fell below normal in advanced stage patients [25]. The radio pharmaceutical 2β-[^{11}C] carbomethoxy-3β-(4-chlorophenyl) tropane ^{11}C-RTI-32 is an in vivo tracer of both dopamine and noradrenaline transporters and was used to detect possible differences between depressed and non-depressed patients. The depressed PD patients showed reduced [^{11}C]-RTI-32 binding in LC, the thalamus and several regions of the limbic system compared to non-depressed patients [54]. Binding of ^{11}C-RTI-32 in these regions correlated inversely with the severity of anxiety and mood disorders of these patients. The reduction in the LC and in the thalamus possibly reflects a relative loss of noradrenergic neurons, while the reduction in other limbic areas expresses mostly dopaminergic dysfunction suggesting that depression in PD is possibly associated with specific loss of both noradrenergic and dopaminergic innervations.

Imaging the cholinergic system

There are three main cholinergic sources in the brain. The basal forebrain cholinergic complex including nucleus basalis of Meynert provides the major cholinergic projections to cerebral cortex and hippocampus [55]. The pedunculopontine nucleus projects to the majority of subcortical structures and the forebrain [56], while intrinsic cholinergic neurons are located in striatum [57]. Deficits of cholinergic innervations have been identified neuropathologically in cerebral cortex and in multiple subcortical regions in PD brains being associated with neuronal loss in these cholinergic sources [15].

Iodine-123-iodobenzovesamicol (IBVM) is a biomarker of presynaptic vesicular acetylcholine transporter (VAChT) binding in cholinergic nerve terminals and consequently a biomarker of the presynaptic cholinergic terminal density [58]. In non demented PD patients IBVM binding using SPET was mildly reduced in parietal and occipital cortex, but was extensively reduced in the entire neocortex in demented PD patients [59].

Another biomarker of brain cholinergic activity is the level of acetylcholinesterase (AChE) activity, which can be assessed with the radiolabelled acetylcholine analogues, ^{11}C-N-^{11}C-methylpiperidin-4-yl acetate (^{11}C-MP4A) or ^{11}C-methylpiperidin-4-yl- propionate (^{11}C-PMP). Several studies using these radiotracers showed that the mean cortical AChE activity was severely reduced in PDD (up to 30%) and moderately reduced in PD (10%-12%) compared with controls [27, 60-62]. Interestingly, there were significant correlations of ^{11}C-PMP binding with tests of attentional and executive function [62]. Researchers showed that AchE activity was significantly decreased in cerebral cortex and especially in medial occipital cortex in PD patients, but there was no significant difference between early and advanced PD groups, indicating that brain cholinergic dysfunction occurs at an early stage, but does not progress in PD patients without dementia even in advanced stages [63]. Consistently, the authors described an even more profound reduction in cortical AchE activity in PDD, particularly in the posterior cortical regions. At the same time,

others reported a significant covariance between the cortical MP4A binding and the striatal ^{18}F-Fdopa binding in PDD patients, suggesting a parallel reduction of dopaminergic and cholinergic activity in PD [61]. A study of cholinergic innerventions in parkinsonian syndromes showed significantly decreased AChE activity in PD patients in striatum, cerebellum and thalamus with marginally significant decrease in mesencephalon, apart from the decrease in most cortical areas [64].

Radioligands have also been developed to study the brain cholinergic receptors. Muscarinic acetylcholine receptor (mAchRs) availability has been assessed in PD and the mAchR binding was significantly higher in the frontal cortex in PD patients [65, 66]. According to the authors this may reflect denervation hypersensitivity caused by loss of the ascending cholinergic input from the basal forebrain. In vivo quantification of brain nicotinic acetylcholine receptors (nAchR) has been performed and PD patients without dementia showed significant reduction of nAchRs in the cortex [67], particularly in the frontal cortex and the brainstem [68], but not significantly reduced in striatum [67, 68]. However, a more recent study using 2-[^{18}F]fluoro-A-85380 and PET showed a mild but significant reduction of the density of nAchRs in striatum in non demented PD patients but no significant decrease in cerebral cortex [69]. According to these authors, these differences may be due to methodological differences or to individual variations in different small groups of patients.

Consequently, the deficit in cholinergic innervations identified neuropathologically is supported by PET studies and it seems that the presence of dementia is associated with a more profound cholinergic dysfunction.

Imaging microglial activation

Accumulating evidence from human and animal studies has implicated neuroinflammation in the pathogenesis of PD. The key player factor in this process is the activation of microglia, which represents the brain resident macrophages and can be activated by a wide range of stimuli including neurodegeneration. A postmortem study, first reported the presence of HLA-DR positive activated microglia in the substantia nigra (SN) of PD patients [70]. Since then, many studies confirmed the presence of activated microglia in PD and the production of a variety of inflammatory mediators [71-73].

The mitochondria of reactive microglia overexpress the translocator protein (TSPO), previously known as the peripheral benzodiazepine receptor (PBR). Selective targeting of TSPO represents a way of quantifying microglial activation in vivo [74, 75]. This is particularly expressed by the radiolabelled with ^{11}C isoquinolone ligand, 1-(2-chlorophenyl)-N-methyl-N-(1-methylpropyl)-3-isoquinoline-carboxamide (PK11195), which has been used extensively as an in vivo marker of microglial activation in neurological diseases including PD.

Two combined PET studies were conducted in PD patients using ^{11}C-PK11195 to evaluate the microglial activation and a DAT ligand, [11]C-2β-carbomethoxy-3β-(4-fluorophenyl) tropane (^{11}C-CFT) [76], or ^{18}F-Fdopa [77] respectively for the study of nigrostriatal pathway. Researchers [76] studied 10 early stage drug naove PD patients and found a significant

higher binding potential of ¹¹C-PK11195 in midbrain, contralateral to the clinically most affected side, which was correlated inversely with reduced [¹¹C]-CFT binding in putamen and positively with motor severity, as measured by UPDRS scale. There was no correlation with disease duration. Four of these patients were followed-up with another PET scan 4 years later, which failed to detect any significant increase of ¹¹C-PK11195 binding in striatum [78]. Other researchers studied 18 early and late stage PD patients and reported significantly increased levels of ¹¹C-PK11195 binding in the pons, basal ganglia, frontal and temporal cortical areas, but not in SN [77]. However, this widespread [¹¹C]-PK11195 binding was not correlated with the clinical severity and ¹⁸F-Fdopa uptake in putamen. In a longitudinal examination of some of these patients over a 2 years period, the level of microglial activation remained relatively stable, despite clinical deterioration and further reduction of ¹⁸F-Fdopa uptake. These findings suggest that microglial activation occurs early at the disease process and does not follow the degeneration in the nigrostriatal pathway, but remains relatively stable.

In a more recent pilot study, a small group of PD patients showed higher binding in contralateral putamen and midbrain, which didn't reach statistical significance. After the administration of celecoxib, a COX-2 inhibitor for a short period of time, they failed to detect any effect of non-steroidal anti-inflammatory treatment on the ¹¹C-PK11195 binding [79].

The discrepancies observed in the previous results could be attributed to methodological differences. Furthermore, they emphasize the limitations in applying the ¹¹C-PK11195, which explain the scientific efforts to develop newer, highly selective TSPO ligands in order to be satisfactorily used as biomarkers of neuroinflammation [80].

Cardiac scintigraphy with ¹²³I metaiodobenzylguanidine (¹²³I-MIBG)

As already mentioned in the introduction, recent studies have implicated that the degenerative process is much more extensive affecting not only the central nervous system but also th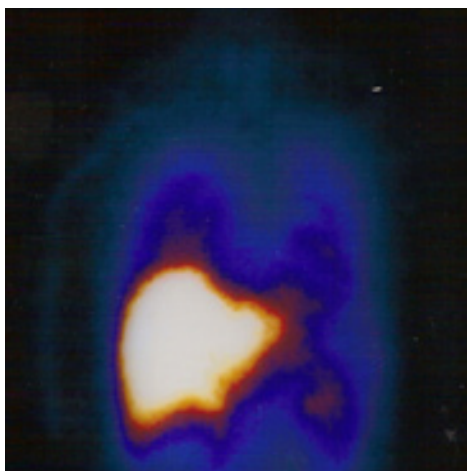e peripheral component of the ANS. Post mortem studies in PD patients confirmed the sympathetic involvement of the heart [81, 82]. The degeneration of the cardiac sympathetic nerve fibers starts early in the disease progression of PD and the a-synuclein pathology seems to be in parallel with the Braak staging [83, 84].

The planar and tomographic cardiac imaging with ¹²³I-MIBG is used for the evaluation of the sympathetic cardiac innervation in PD and may be useful for the differential diagnosis of PD from other atypical parkinsonian syndromes. Hirayama and coworkers [85] first reported a reduced cardiac uptake of ¹²³I-MIBG in PD patients compared to normal controls. Since then, multiple imaging studies showed significant reduction in myocardial ¹²³I-MIBG uptake in PD patients which reflects some degree of cardiac sympathetic dysfunction [86-92] (Fig. 4, 5). It is the loss of postganglionic sympathetic neurons which causes cardiac denervation. Reduced cardiac ¹²³I-MIBG uptake is even apparent in the early PD stages and subsequently ¹²³I-MIBG scintigraphy may contribute to the early detection of PD [87, 90, 91, 93, 94]. However, some studies reported relatively low sensitivity of ¹²³I-MIBG scintigraphy (70%-73%) in early-stage PD patients [90, 91, 95]. The diagnostic accuracy of ¹²³I-MIBG scintigraphy improves substantially if combined with other diagnostic tests, such as transcranial sonography, olfactory testing or ¹²³I-FP-CIT SPET [95-97].

The presence of correlations between parkinsonian symptoms and myocardial uptake of ¹²³I-MIBG is considered to be controversial. Several studies found no correlation between disease severity and ¹²³I-MIBG uptake [86, 94, 98-100], while other studies reported correlation with disease severity [90, 101-103] or with disease duration [89]. Comparing clinical subtypes of PD and ¹²³I-MIBG uptake, lower ¹²³I-MIBG uptake was reported in the akinetic-rigid type of the disease [104, 105].

Another important issue to be clarified is the relation between ¹²³I-MIBG uptake and the presence of autonomic dysfunction in PD. It is not yet clear whether ¹²³I-MIBG uptake is associated with symptoms and signs of dysautonomia in PD patients. Some studies found no differences in ¹²³I-MIBG uptake in relation to the presence and severity of clinical autonomic dysfunction or abnormal tests related to autonomy [86, 91, 106]. The severity of dysautonomia as measured by the scale for outcomes in PD for autonomic

Figure 4. A patient with PD studied with ¹²³I-MIBG scintigraphy. The radiotracer uptake ratio of myocardium to upper mediastinum at 15min after the injection was calculated below normal values.
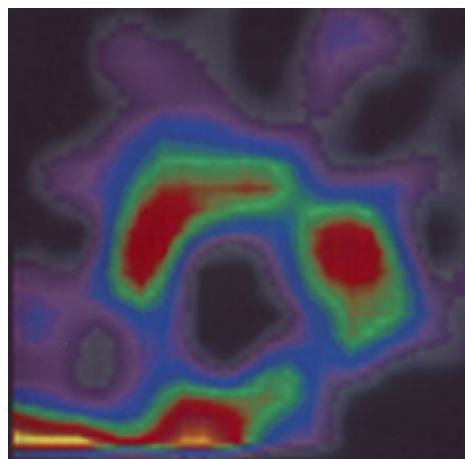

Figure 5. Image of ¹²³I-MIBG scintigraphy shows reduced radiotracer uptake in the myocardium in a patient of ours with familial PD caused by mutation in parkin (PARK2) gene.

features (SCOPA-AUT scale) was not correlated with ^{123}I-MIBG uptake [107]. However, reduced ^{123}I-MIBG uptake was present in de novo PD without clinical evidence of autonomic dysfunction suggesting that ^{123}I-MIBG scintigraphy is a sensitive method to detect latent subclinical autonomic dysfunction [94, 108, 109].

One of the scientific challenges regarding ^{123}I-MIBG scintigraphy is its ability to discriminate PD from other atypical parkinsonian syndromes. By contrast to PD, in multiple system atrophy (MSA) the ANS is mainly affected in its preganglionic structures and most MSA patients showed normal ^{123}I-MIBG uptake despite the observed symptoms and signs of autonomic dysfunction [92, 106]. However, in these studies specificity and sensitivity varied and both false positive and negative cases were reported highlighting the difficulties in differential diagnosis between PD and MSA. In progressive supra nuclear palsy (PSP) ^{123}I-MIBG uptake was reduced compared with PD patients [94, 98, 110]. Few data are recorded for other atypical parkinsonian syndromes [90, 94, 110, 111]. Various meta-analysis studies including several single-centre studies analyze the diagnostic performance of ^{123}I-MIBG scintigraphy in the differential diagnosis of PD from atypical parkinsonism. Despite the differences in methodology, these studies confirmed high specificity and sensitivity of ^{123}I-MIBG scintigraphy in differentiating PD from other types of parkinsonism, particularly MSA and PSP [112-116]. The discriminative ability of ^{123}I-MIBG scintigraphy was even higher in early PD [116]. However, false positive and negative results must be taken into account particularly when interpreting scintigraphic results [115].

In conclusion, PET and SPET studies have provided considerable insight in the comprehension and the differential diagnosis of PD [11, 12, 117]. They have detected changes in extrastriatal dopaminergic pathways and the serotonergic, cholinergic and noradrenergic neurotransmitter systems, confirmed by neuropathological studies and they implied the association of PD with motor symptoms and mainly with the presence of non-motor symptoms such as depression, fatigue and dementia. Scintigraphy by ^{123}I-MIBG can distinguish PD from other types of parkinsonism, while microglial activation imaging detects brain inflammation in PD allowing further insights into the pathophysiology of PD.

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In a recent international evaluation in Milan of all Nuclear Medicine Journals, our Journal HJNM was in the 9th position after the following Journals: J Nucl Med, EJNMMI, Semin Nucl Med, Clin Nucl Med, Nucl Med Biol, Q J Nucl Med Mol Imag, Ann Nucl Med and Nucl Med Comm. This is a great honor for us and a challenge to work harder in the future.