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Review

Molecular imaging (SPECT and PET) in the evaluation of patients with movement disorders

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Abstract

In this article the role of molecular imaging with SPECT and PET in patients with movement disorders is reviewed. It is mentioned that SPECT and PET imaging with cocaine analogues (^{123}I-β-CIT,^{123}I-FP-CIT, ^{18}F-DOPA), radioligands labeling the presynaptic dopamine transporters, is of value for the differentiation of patients with PD or Parkinson-plus syndromes with individuals with essential tremor. In addition the clinical impact of this procedure, the role of molecular imaging in the preclinical diagnosis and in the follow-up of patients with PD, as well as, in the differential diagnosis between Alzheimer's disease and Lewy-body dementia, is evaluated. Finally, the clinical impact of ^{123}I-IBZM-SPECT imaging, a radiopharmaceutical which labels the postsynaptic D_2 receptors and the discrimination between idiopathic PD and Parkinson-plus syndromes (multiple system atrophy, progressive supranuclear palsy and corticobasal ganglia degeneration), is mentioned.

Key words: molecular imaging, movement disorders, PET, SPECT, -123-DaTSCAN, I-1Z3-IB2M

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Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by progressive damage of the nigrostriatal dopaminergic neurons in the basal ganglia. The neurons projecting to the putamen present the most severe impairment compared to those innervating caudate nucleus. The result of this process is the alteration of the neurochemical balance required for normal motor function. Clinical symptoms (tremor, rigidity and bradykinesia) occur when at least 50% of the dopaminergic cells are lost [1]. Traditionally, PD is clinically diagnosed when two at least of the above mentioned syndromes are present. Post-mortem examination in PD showed that the loss of dopaminergic cells is associated with depletion of striatal dopaminergic transporter (DAT) [2].

Parkinsonian syndromes (PS) is a broader definition that encompasses other movement disorders whose symptoms resemble PD and includes progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and corticobasal ganglia degeneration (CBGD) [3].

The diagnosis of PD remains a clinical judgment based primarily upon motor examination and the patients' response to L-dopa. Confusingly, the symptoms of PD or PS may also be experienced by individuals with essential tremor (ET), or as a result of the use of certain medications, such as antipsychotics or calcium channel blockers. ET is defined as an isolated postural/action tremor in otherwise neurological healthy person. Early differentiation between these conditions is difficult, since in many cases a six months evaluation of patients is mandatory to differentiate PD or PS from ET. Despite the fact that there are definitions between PD and ET, frequently final diagnosis is found wrong only after death. It has been mentioned that up to 25% of patients initially diagnosed as PD, later having their diagnosis changed to ET [4–7].

In recent years, techniques that allow imaging of the dopaminegric system have been developed in order to help the clinical diagnosis of PS. Such techniques are often based on assessment of DAT density as a marker for dopaminergic nigrostriatal neuron integrity [8]. Ioflupane, N-ω -fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane, also called FP-CIT, belongs to a group of compounds derived from cocaine that bind to the

dopamine transporter (DAT). Introduction of the ^{123}I radioactive label at the phenyl moiety further increased the binding affinity to the DAT, whilst the iodine-carbon bond in this position is sufficiently stable to resist deiodination in vivo. Further modifications of the cocaine molecule likewise led to improved properties for single photon emission tomography (SPET) imaging, 3–6 hours post injection of the radiopharmaceutical and increased selectivity of the DAT, relative to binding to serotonin and norepinephrine transporters [9].

Imaging of the presynaptic nigrostriatal dopaminergic system

In the early 1970's the successful application of 6-^{18}F-fluoro-L-3, 4-dihydroxyphenylalanine (^{18}F-DOPA) for PET studies of the nigrostriatal dopaminergic neurons has been reported [10]. ^{18}F-DOPA PET provides measurement of the structural as well as the biochemical integrity of the dopaminergic neurons.

In the late 1980's studies have shown the use of radioligands derived from cocaine in order to quantify nigrostriatal dopaminergic neurons by means of SPET and PET (FP-CIT, β-CIT, CFT (2β-carbomethoxy-3β-4fluorophenyl-tropane), IPT (N-3-iodopropen-2-yl-2β-carbomethoxy-3β-4-fluorophenyl-tropane), ^{123}I-altropane, ^{11}C-cocaine, ^{11}C-methylphenidate, which are specific to the binding sites [11–14]. In addition, radiotracers for the vesicular monoamine transporter derived from tetrabenazine have been introduced to visualize dopaminergic neurons [15] (Table 1).

Imaging of dopamine D_2 receptors

Dopamine acts in the central nervous system through activation of dopamine receptors, which are present in the pre- and the postsynaptic cleft. Five different subtypes of dopamine receptors have been described, but they actually fall into two classes: D_1 type (D_1, D_5) and D_2 type (D_2, D_3, D_4), with the concentration of D_1 and D_2 receptors being higher than other types (16). Attention is paid only to radiotracers for the dopamine D_2 receptors, localized in majority postsynaptically, since specific imaging studies of them have been shown to be of value for the differential diagnosis of parkinsonism. The most widely used radiotracers for imaging of these receptors for SPECT studies are the dopamine receptors antagonists iodobenzamine (I-123-IBZM) and I-123-epidepride [17, 18] and for PET studies ^{11}C-raclopride and ^{18}F-N-methylspiroperidol [19, 20] (Table 1).

Table 1. Radiopharmaceuticals commonly used for SPET and PET imaging of presynaptic dopamine transporters, vesicular transporters and post-synaptic dopamine D_2 receptors

Presynaptic dopamine transporters	Vesicular transporters	Postsynaptic dopamine D_2 receptrors
FP-CIT	Derivatives from tetrabenazine	IBZM
β-CIT		IBF
IPT		Epidepride
CFT		Raclopride
Altropane		N-methylspiroperidol
Cocaine		
Methylphenidate		

Molecular imaging in Parkinson's disease

Parkinson's disease (PD) is accounting up to 85% of all causes of parkinsonism [21]. PD is characterized by degeneration of the nigrostriatal dopaminergic projection, leading to loss of dopamine and dopamine transporters to the striatum [22].

PET studies with ^{18}F-DOPA performed in patients with PD, have shown reduction of the radiopharmaceutical uptake to the striatum, more prominent in the putamen than in the caudate nucleus [22]. In patients with early PD uptake was asymmetric (reduction more prominent to the contra-lateral of the affected site) and correlated with the disease severity [23–25].

The challenge of molecular (SPET and PET) imaging is the early (preclinical) diagnosis of PD, since that by the time clinical diagnosis has been made, about 50–60% of dopaminergic neurons projecting to the striatum have been already lost [1, 26].

Imaging with ^{123}I-β-CIT has been performed to asymptomatic relatives of PD patients with an increased risk of developing PD, selecting 25 (10%) individuals being the worst smellers [27–28]. An abnormal reduction of unilateral or bilateral dopamine transmitter binding has been found in 4 (25%) of them and two of these hyposmic PD relatives developed clinical parkinsonism. In addition, two hyposmic subjects had a unilateral reduction of putamen to caudate binding ratio and an increased putamen asymmetry index, respectively. Other clinical conditions, such as neuro-cognitive dysfunctions and visuo-motor abnormalities, often precede the onsets of the typical PD motor signs and in such cases ^{123}I-FP-CIT might represent a useful tool for detecting the dopaminergic deficit at a pre-clinical stage, so allowing the commencement of neuroprotective treatment, aimed at slowing the progressive degeneration of dopaminergic neurons [27, 29–30].

Other authors have mentioned that in early PD patients, who were drug-naïve, binding ratios were 35% for the putamen and 55% for the caudate nuclei, compared with normal individuals [31––33]. These data indicate that molecular imaging with ^{123}I-ioflupane is a sensitive marker of the degree of the dopaminergic degeneration in PD, correlated with the severity of the disease. It has also been mentioned that uptake of the radiolabelled compound in drug-naïve patients is bilaterally reduced, so this technique is able to detect PD patients in a preclinical stage [34]. Finally, a high test/ /pretest reproducibility of ^{123}I-β-CIT SPECT imaging was found [35].

In a more recent study Filippi et al. have postulated that in de novo hemi-PD patients at an early stage (Hoehn and Yahr stage I) with unilateral symptoms and preclinical dopamine transporter loss in the ipsilateral striatal binding, imaging with ^{123}I-FP-CIT detects a bilateral dopaminergic deficit [36] (Figure 1). According to these data, semi-quantitative analysis can be used to diagnose PD at an early stage and to identify individuals developing bilateral dopaminergic deficit. Similar data have been postulated by Marek et al in a small series of patients [37].

PET studies with cocaine analogues labeled with ^{11}C, allow to screen for striatal, orbitofrontal and amygdalar presynaptic dopaminergic cell loss in PD patients. It has been also mentioned that putaminal and orbitofrontal β-CFT binding levels are positively correlated with motor and mentation scores respectively, of the Unified Parkinson's Disease Rating Scale [38[. PET in PD using ^{11}C or ^{18}F-labelled CFT as a tracer for the dopamine transporter can differentiate controls from patients with mild PD [39, 40].

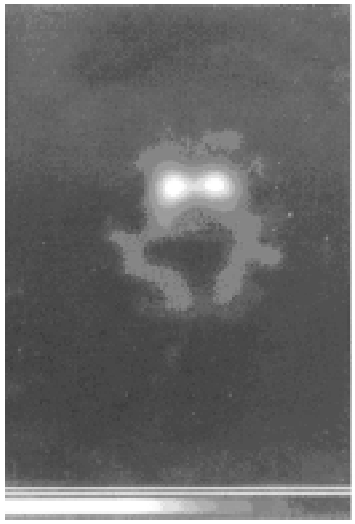

Figure1. Patient with PD (H&Y stage I).

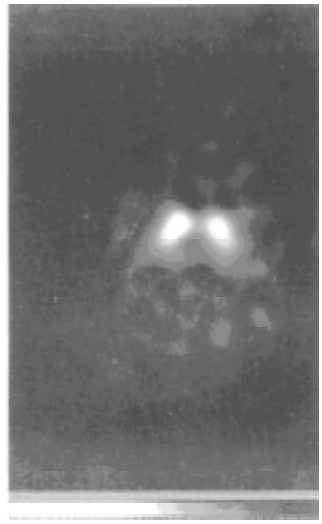

Figure 2. Patient with ET.

To study the influence of age and gender in human volunteers, Lavalaye et al have performed SPET study with ^{123}I-FP-CIT in 45 normal individuals (23 males plus 22 females). Specific to non-specific striatal binding of the radiopharmaceutical seemed to decrease with age and females were found to have significantly higher ^{123}I-FP-CIT binding ratios than males [41].

Other authors have published data according to which, specific to non-specific ratio of ^{123}I-FP-CIT is a robust measure of PD severity correlating with duration of disease. Variability in uptake values suggest that factors others than nigrostriatal degeneration may contribute to disease severity. Correlation of uptake of ^{123}I-FP-CIT with bradykinesia but not with tremor is possible to indicate an origin for tremor outwith the dopamine transporter system [42]. According to these data, ^{123}I-FP-CIT SPECT offers significant potential in defining the nigrostriatal changes in PD.

SPECT imaging with ^{123}I-β-CIT could not visualize differences of the radiopharmaceutical uptake at the level of the striatum between 113 patients with PD, 9 with MSA and 4 with PSP [43]. Interestingly, El Fakhri et al, have postulated data, concerning the differential diagnosis between PD and MSA, based on SPECT studies with ^{123}I-FP-CIT and cerebral blood flow (CBF) with Tc-99m-ECD (44). Binding potential (BP) was significantly lower in PD (53% reduction in caudate nucleus and 59% in the putamen) and MSA (26% in caudate nucleus and 20% in putamen) compared to normal controls. BP has been found to be reduced in PD compared to MSA in the caudate nucleus (36%) and putamen (49%). In addition, CBF was significantly reduced in MSA patients in caudate nucleus (28%) and nucleus lentiformis (18%), compared to normal controls, whilst there were not any significant CBF differences between PD patients and controls. Other studies of DAT uptake have shown similar differences between MSA and PD [45], whilst Messa et al have mentioned that uptake of ^{123}I-β-CIT in the head of the caudate has shown a greater reduction in 5 PSP patients compared to 13 PD cases [46]. However, between-group overlap was too large to allow differentiation between these diseases on an individual basis.

The clinical benefit of molecular imaging in movement disorders

Patients with ET present a postural tremor with or without a kinetic tremor, involving the upper limbs. PD is characterized by resting tremor, rigidity, bradykinesia and postural instability [1, 47]. Elderly individuals with ET may also present rest tremor and mild parkinsonian features and this may lead to difficulties in the differential diagnosis between ET and PD [48]. Diagnosis of PD based only on clinical assessment seems to have a limited accuracy. It has been postulated that from 402 patients initially clinically diagnosed as parkinsonism, only 299 of them (74%) were confirmed as PS after further evaluation applying recommended clinical diagnostic criteria. Of the remaining 103 subjects with a revised diagnosis, 50 (48%) of them were finally diagnosed as ET, 37 (36%) as vascular parkinsonism and 16 (16%) as Alzheimer's disease [5]. Rajput et al have reported that 24–35% of initial PD diagnoses made by general neurologists were incorrect when examined by autopsy. In the same study, it has been mentioned that when correlation between clinical impression and subsequent pathology is performed, only 75–80% agreement is achieved [49]. In a study enrolling 800 PD patients at an early (H & Y 1 or 2) stage, diagnosed by PD experts, after a 6-year follow-up, only 65 (8.1%) of them did not have PD according to the study criteria [6].

SPECT and PET studies have shown normal uptake of the radiopharamaceutical (^{123}I-β-CIT and ^{18}F-DOPA respectively) at the level of the striatum, compatible with intact nigrostriatal dopaminergic neurons in patients with ET [50, 51] (Figure 2).

A multicentre trial has been performed by the ^{123}I-FP-CIT study group across six centres in Europe in order to compare the striatal uptake of DaTSCAN in patients with PS to that in patients with benign ET. PS was defined as either PD, MSA and PSP [52]. At each of six centres the investigator assessed the acquired DaTSCAN images for their own subjects, blinded to the subject's clinical diagnosis and this process was termed as the "institutional read". Centrally standardized scans were assessed by a panel of five investigators who were also blind to the subject's clinical

diagnosis and who separately judged the scans to be visually normal or abnormal and this process was defined as the "blinded panel read". According to the "institutional read" sensitivity of the method was 97.5%, specificity 100%, positive predictive value 100% and negative predictive value 87.1%. The results for the "blinded panel read" were 95%, 93%, 99% and 76% respectively. These results reflect some differences of opinion between the two groups of readers, but overall variations from centre-to-centre were minimal and images from different SPECT instruments were deemed to be equivalent. This study demonstrates the effectiveness of DaTSCAN-SPECT in differentiating between the two patient (PS and ET) groups. Other functional imaging studies using only quantitative analysis in assessing striatal uptake, have mentioned that in 25 patients with PD, the specific:nonspecific uptake ratio of ^{123}I-β-CIT was significantly lower than in ET or healthy volunteers [53]. Booij et al using ^{123}I-FP-CIT in a group of patients with inconclusive forms of parkinsonism and performing clinical follow-up of these patients 2–4 years after imaging, have concluded that the positive predictive value of this technique is very high [54]. In another study with ^{123}I-Ioflupane SPECT imaging in 43 individuals, 95.5% (21/22) of patients were correctly diagnosed as presynaptic PS, whilst all patients (22/22) with ET were correctly evaluated with the molecular imaging method [55].

The clinical impact of dopamine transporter SPECT imaging using ^{123}I-Ioflupane, on the diagnosis and management of patients with uncertain parkinsonian syndromes has been studied by Catafau and Tolosa [56]. In 36% of patients with presynaptic PS and 54% with non-presynaptic PS, imaging results were not consistent with the initial diagnosis. Initial diagnosis was changed after SPECT study in 52% of the patients, 42% with an initial diagnosis of presynaptic PS and 54% with a diagnosis of non-presynaptic PS. After imaging, 76% of inconclusive patients (n = 19) were reclassified as presynaptic (n = 14) or non-presynaptic PS (n = 5), leaving 6 patients in the inconclusive category; 16 patients classified initially as presynaptic or non-presynaptic PS were reclassified as inconclusive after SPECT imaging review. After this review, 12 patients changed from presynaptic PS to inconclusive (75% with normal image) and 4 patients changed from non-presynaptic PS to inconclusive (75% with abnormal images). Changes to planned clinical management after ^{123}I-Ioflupane SPECT imaging were recorded in 72% of the cases, changes involving therapy in most cases (46%), mainly because new therapy was initiated. Another impact in management was either shortening or lengthening visit intervals during follow-up (21%). This study shows that ^{123}I-Ioflupane SPECT imaging had an effect in directing further investigations and therapeutic intervention in patients with uncertain parkinsonian syndromes.

Juvenile-onset dystonia that improves after levodopa administration may occur in both dopa-responsive dystonia (DRD) and juvenile parkinsonism (JP), similar conditions with different prognoses and management goals. It has been postulated that normal striatal uptake of the dopamine transporter ligand FP-CIT with the SPECT method is mentioned in a clinically atypical case of DRD, in contrast to the reduced uptake observed in JP [57].

In cases of schizophrenia, functional changes in the dopaminergic system are not likely to be reflected in a change of the dopamine transporter density and this does not seemed to be altered by anti-psychotic medication [58]. In addition, schizophrenic patients with tardive dyskinesia, studied with ^{123}I-FP-CIT SPECT, performed no change in striatal dopamine transporter density [59].

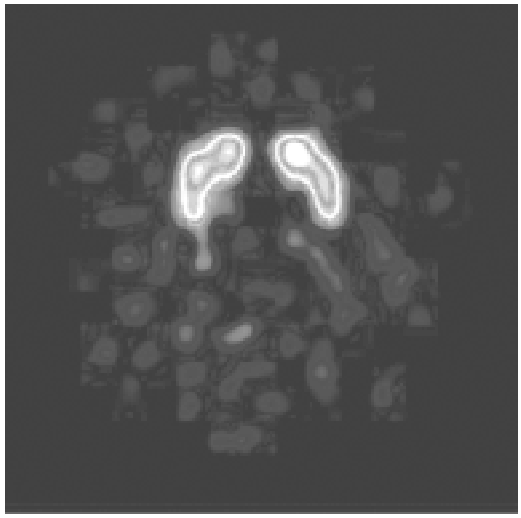

Figure 3. Normal volunteer (Dopamine transporter availability with I-123-FP-CIT) 30-year-old female.

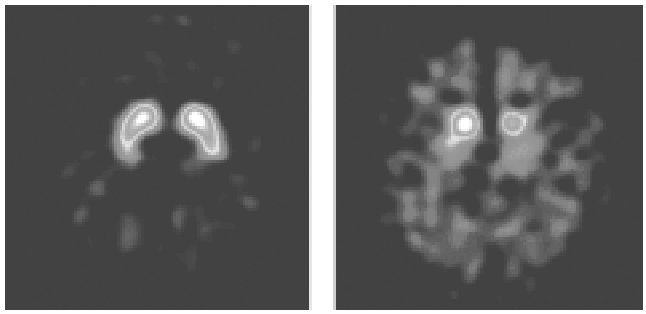

Figure 4A. Normal patient (79-year-old; **B.** Patient with PD (76-year-old men).

Costa and colleagues have shown that severe DAT loss exists in both the caudate nuclei (CN) in patients with PD and in patients with Lewy-body dementia (DLB), as well as in the putamen. DAT loss in the CN was more severe in DLB than in PD, particularly in the left hemisphere [60]. In patients with Alzheimer's disease, uptake of the radiopharmaceutical did not differ significantly from that of normal volunteers (Figure 3). The left hemisphere predominance of DAT loss in DLB subjects may explain the psychotic component of their clinical presentation and this may help to guide antipsychotic treatment. Walker et al have postulated that patients with DLB and PD showed significantly lower uptake of the radiopharmaceutical in all striatal areas than controls and patients with AD (Figure 4). There were no significant differences in binding measures between patients with AD on the ipsilateral and contralateral caudate, the ipsilateral and contralateral anterior putamen, and the ipsilateral posterior putamen, but patients with AD had lower binding than controls in the contralateral posterior putamen [61]. Similar data have published Costa et al, who have mentioned that in cases of DLB there is a marked reduction of tracer uptake in the striatum of both hemispheres

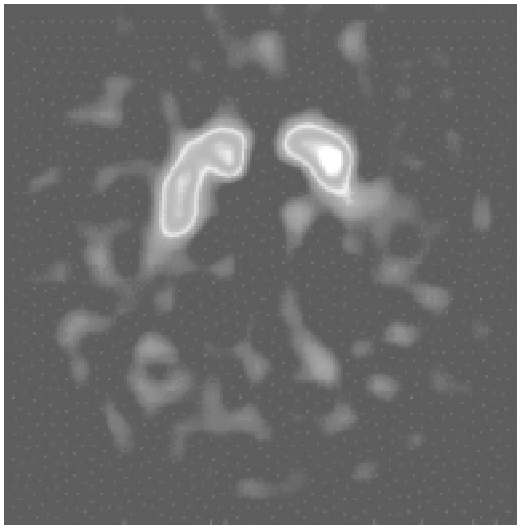

Figure 5. Patient with vascular Parkinsonism (left putamen infarct) (56-year old woman).

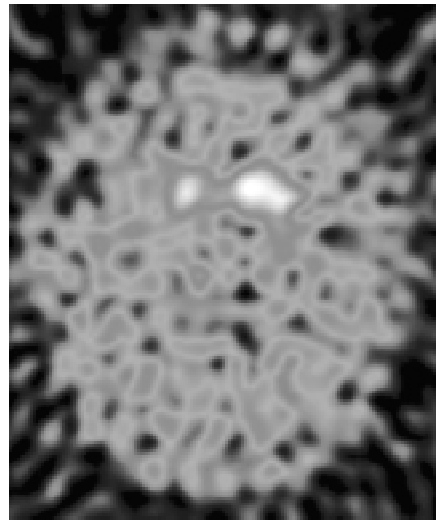

Figure 6. Dementia with Levy body (72-year-old men).

that is marked in both putamen and caudate nucleus, whereas in AD the appearance is within normal limits. The DLB appearance is similar to that of PD, however there is a trend for lower caudate uptake in DLB than PD and lower posterior/caudal putamen uptake in PD (Figure 5) than in DLB (Figure 6) [62]. Walker et al. have also shown differences PD and DLB groups in the pattern of striatal dopaminegic dysfunction. The mean caudate/putamen ratio in DLB did not differ from that of controls, whilst the mean caudate/putamen ratio of the PD group was higher than that of the control group, explaining some of the clinical differences between DLB and PD [63]. In another study it has been also suggested that functional (SPECT) imaging of the nigrostriatal dopamine pathway helps to distinguish DLB from Alzheimer's disease during life [64].

Clinically, there are difficulties in the follow-up of PD progression, since it has to be about 15–17% degradation of the presynaptic dopaminergic neurons to evaluate this [1]. Sang EK and his colleagues have examined the correlation of SPECT measures of ^{123}I-β-CIT binding to DA and 5-HT transporters with symptom severity in cases of PD. The authors found a significant correlation of SPECT measurements of ^{123}I-β-CIT binding to DA transporters with motor severity and this can serve as an in vivo indicator of disease severity in PD, with potential utility in the serial monitoring of disease progression. In contrast, the radiopharmaceutical binding to serotonin (5-HT) transporters in the hypothalamic/ /midbrain region was not correlated with measures of motor and non-motor severity [65].

In Gilles de la Tourette syndrome (GTS), which is characterized by the presence of multiple motor and one or more vocal tics and in some cases by behavioral disorders [66], a SPECT study with ^{123}I-FP-CIT in ten neuroleptic naïve patients, has shown higher striatal binding of the radiopharmaceutical in comparison with age- and gender-matched control subjects [67]. However, according to the authors, it appears that behavioral and psychiatric symptoms in GTS are not directly related measurable abnormalities in striatal DAT activity.

Differential diagnosis between Parkinson's disease and parkinsonian-plus syndromes with imaging of D_2 receptors

Post-mortem studies have practically shown no changes in numbers of striatal dopamine D_2 receptors in PD [68]. Ichise et al. have postulated up-regulation of the striatal D_2 post-synaptic receptors in L-DOPA untreated patients with PD, with ^{123}I-IBF study [69]. Other PET and SPECT studies have mentioned normal or increased dopamine D_2 dopamine receptor binding in patients with PD [70, 71]. The last study [71], was evaluating patients with de novo parkinsonism in whom imaging with I-123-IBZM was performed before the initiation of dopaminergic medication. During clinical follow-up none of the patients with reduced I-123-IBZM binding showed a positive response to dopaminergic medication and therefore, reduced I-123-IBZM binding is likely to exclude a diagnosis of PD early in the course of disease.

In another study performed by Hierholzer with ^{123}I-IBZM, specific striatal D_2 receptor binding was significantly lower in patients with parkinsonian-plus syndromes compared to patients with PD [72]. During the follow-up, patients with PD showed a constant specific striatal dopamine D_2 receptor binding, in contrast with patients with parkinsonian plus syndromes who revealed a further decline of striatal dopamine D_2 receptor binding during follow-up. In clinical practice the differential diagnosis between idiopathic PD and Parkinson-plus syndromes seems to be of value, because in the latter there is a lack of response to levodopa therapy. The presence of other, non-parkinsonian neurological signs, suggests Parkinsonian-plus syndromes, as well as, no response to levodopa therapy. Because of the similarity of the hypokinetic-rigid syndromes in PD to that in Parkinson-plus syndromes, it is difficult in some cases to discriminate between them. In early, mono-symptomatic cases with only parkinsonism present, IBZM-SPECT is helpful in this discrimination. Decreased binding of the radiopharmaceutical to the striatum, indicates striatal cell loss rendering PD unlikely and suggesting Parkinson-plus syndrome [71–74]. IBZM-SPECT cannot discriminate between the different Parkinson-plus syndromes.

It has been shown in various IBZM-SPECT studies that striatal D_2 binding is severely reduced in Huntington's disease [75, 76]. However, in these cases, IBZM-SPECT seems to play a minor role because of the major advantage of genetic diagnostic tests.

Conclusions

According to all these reviewed data, molecular imaging with SPECT and PET, seems to play a critical role in patients with movement disorders. SPECT and PET imaging with cocaine analogues (i.e.^{123}I-FP-CIT, ^{18}F-DOPA) which label the presynaptic dopamine transporters, is useful in differentiating patients with idiopathic PD or Parkinson-plus syndromes, from individuals presenting essential tremor, so unnecessary treatment with L-dopa is prevented. In addition molecular imaging plays a major role in the presymptomatic diagnosis of PD, in the clinical impact of patients with movement disorders and uncertain parkinsonian syndromes and in the follow-up of them. Imaging of the nigrostriatal presynaptic pathway is not able to discriminate patients with idiopathic PD from those with Parkinson-plus syndromes. Imaging with I-123-IBZM, a postsynaptic D_2 ligand, is of value, since normal or increased uptake of the radiopharmaceutical at the level of the striatum, is compatible with PD.

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