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Molecular imaging in Parkinsonism: the essential for clinical practice and future perspectives

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Molecular imaging in parkinsonism: the essential for clinical practice and future perspectives

Key words: SPECT, single positron emission tomography, PET, positron emission tomography, parkinsonism, atypical parkinsonism

Abstract: Nuclear medicine with positron emission tomography (PET) and single photon emission computed tomography (SPECT) develops powerful tools in molecular imaging to help clinicians in the challenging diagnosis of parkinsonism. These techniques can provide biomarkers for neurodegenerative parkinsonism and to distinguish Parkinson disease (PD) from atypical parkinsonism. This review summarizes the main SPECT and PET contributions to the diagnosis of parkinsonism. We will also discuss new technologies in the field of nuclear imaging and their potential contribution to the diagnosis of parkinsonian syndromes.

Introduction: understanding nuclear medicine imaging and its use

Nuclear medicine imaging includes single photon emission computed tomography (SPECT) and positron emission tomography (PET), depending on the type of radioactivity used respectively gamma rays or positrons. The principle is the same: a radioactive tracer is injected to the patient and its radioactivity is then detected by a camera to get images. Some radiotracers are commonly used in routine and others are still under research.

Nuclear medicine examinations are increasingly used in the field of parkinsonism, especially since their integration in some diagnostic criteria of atypical parkinsonism [1]. They can provide helpful biomarkers in the diagnosis of neurodegenerative parkinsonism, as each entity can show specific imaging features [2]. Neurologists must have a good understanding of these routine examinations to ensure appropriate prescription and proper interpretation of the results, avoiding interpretation pitfalls. On the other hand, there is a growing tendency to group together different diseases according to the underlying pathophysiology, as corresponding treatments are being developed. Identifying tauopathies and α -synucleinopathies using PET could help this process. Developing radiopharmaceuticals isn't the only field of research in nuclear medicine; impressive advances in image acquisition technology and analyses have also been made. This short review is a summary of the main nuclear medicine examinations and their expected results that contribute to the diagnosis of parkinsonism. Major advances in this field will also be discussed.

1) Investigating striatal dopaminergic denervation using presynaptic dopaminergic SPECT or PET

Presynaptic dopaminergic imaging can show striatal dopaminergic denervation as observed in neurodegenerative parkinsonism. Two examinations are commonly used in routine: DaTSCAN® or Striascan, which uses ^{123}I -labeled dopamine active transporters (DAT) for SPECT imaging, and ^{18}F -fluorodopa PET that visualizes dopa-decarboxylase activity. Drug interactions can be observed in both modalities and need to be specified (see Table 1), but only ^{18}F -fluorodopa requires stopping anti-parkinsonian drugs before examination, usually for 24h [3]. The normal aspect is a homogenous fixation of the caudate and the putamen, with a 'semicolon' aspect (Fig 1.a). In case of neurodegenerative parkinsonism, one observes a decrease in radiotracer uptake of the striatum, whereas a normal aspect is observed in the following cases: essential tremor; drug-induced parkinsonism; psychogenic tremor. In case of

vascular parkinsonism, destruction of dopaminergic neurons by vascular lesions can also lead to a decrease of radiotracer uptake wherever there is a lesion, hence any vascular lesion on dopaminergic pathways should be noted and compared to the magnetic resonance imaging (MRI) findings. It is interesting to point out that atypical parkinsonism usually has a more severe dopaminergic denervation than Parkinson disease (PD), but the different denervation patterns do not allow to distinguish between the different degenerative parkinsonian syndromes [3].

2) Characterizing the type of degenerative parkinsonism

¹⁸F-FDG PET features of atypical parkinsonism and PD

¹⁸F-fluorodeoxyglucose (FDG) is the most widely used PET tracer. It evaluates glucose metabolism. Each neurodegenerative disease presents a different metabolic brain pattern (Fig.2 and Table 2) allowing differentiation with good sensitivity and specificity [4-6].

¹²³I-meta-iodobenzylguanidine (MIB) cardiac scintigraphy to distinguish Lewy body diseases from other degenerative parkinsonism

¹²³I-MIBG cardiac scintigraphy is a reflect of postganglionic sympathetic cardiac innervation, since MIBG is a norepinephrine catecholamine analog. In progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and multiple system atrophy (MSA): no cardiac noradrenergic denervation is found [7]. In PD, even at early stage, and dementia with Lewy bodies (DLB): cardiac noradrenergic denervation is observed with 94.1% sensitivity and 80.2% specificity (Fig. 3). It is important to notify any heart disease treatment as examination results can be affected [8].

3) Advances and research in radiopharmaceuticals:

Developing radiotracers is an active field in radiopharmaceutical research, with different aims.

Shorter and more comfortable examination, with better image quality

DaTSCAN SPECT and ¹⁸F-fluorodopa are used in routine to evaluate dopaminergic denervation. They both have inconveniences described in Table 3.

New PET radiotracers are in development [9] with dopamine-active transporters as a target. They have the advantage of a shorter acquisition time (10 minutes, 30 minutes after injection)

whereas DaTSCAN SPECT takes 40 minutes to acquire the images four hours after tracer administration.

Targeting new proteins of interest

Atypical parkinsonism is characterized by early onset (within the first five years) of symptoms that are unusual for PD [10]. The diagnosis of a parkinsonian syndrome is based on clinical and para-clinical diagnostic criteria but remains probabilistic. Post-mortem brain analysis is still the only way to confirm the type of the disease based on the study of the proteinopathy related to the cerebral degeneration [1].

Therapeutic advances in parkinsonian syndromes require the rapid development of more convenient and specific diagnostic tools for each disease, or at least, the ability to differentiate Lewy body diseases (related to α -synucleinopathy: PD, MSA and DLB) from tau diseases (PSP and DCB). Indeed, therapeutic trials are underway for example to evaluate the efficacy of anti- α -synuclein antibodies (PADOVA trial, NCT04777331 with intravenous prasinezumab) or microparticles that may prevent α -synuclein misfolding (ORCHESTRA study, NCT04658186 with oral UCB0599) with the hope of a clinical improvement and/or a lower disease progression. For PSP, several trials are also ongoing (for example, NCT04539041 with intrathecal injections of NIO752; NCT04993768 with TPN-101; NCT04008355 with AZP2006 oral solution).

Radiopharmaceuticals are under development with tau PET radiotracers that are close to being validated. PSP and DCB are mainly 4R tauopathies, while Alzheimer disease (AD) is associated with 3R and 4R deposits. Tau PET can show specific patterns of tau brain accumulation in PSP and DCB, and none in PD and DLB [11]. However, it yields inconsistent results, and especially differentiating non-AD tau from AD tau [12].

While tau PET is promising, α -synuclein PET imaging is still in a research stage because of difficulties in developing a tracer that can cross the blood-brain barrier and target α -synuclein specifically [13]. Similarly, imaging of post-synaptic D2 receptors is limited by several factors especially drug interactions and interpretation difficulties [3].

Targeting neuroinflammation and serotonergic pathways

Neuroinflammation which may be secondary to microglial activation in the nigrostriatal pathway have been reported in neurodegenerative parkinsonism and linked to dopaminergic terminal loss [14]. Some proteins related to neuroinflammation, for example translocator

protein ligands, can be labeled by PET radiotracers. These mitochondrial membrane proteins are expressed in activated macrophages and microglial cells. It thus allows to image glial neuroinflammation and to better understand implication of microglial changes early in the degeneration process [14]. A better understanding of this neuroinflammation might lead to the development of specific neuroprotective drugs.

Serotonergic dysfunction has also been suspected as a potential mechanism of degeneration in parkinsonism with a disturbed serotonergic signaling from raphe nuclei in subcortical and cortical regions revealed with ^{11}C -MADAM PET [15]. An association between serotonergic receptors availability in the raphe and UPDRS total and rest tremor scores was found in PD patients thanks to serotonergic receptors 5-HT(1A) PET tracer [16]. Furthermore, serotonergic dysfunction in other structures involved in motor circuitries have been reported with reductions of ^{11}C -DASB PET tracer in caudate and putamen significantly correlated with posture and action tremor severity in PD patients [17].

Further studies focusing on the relationship between serotonergic and dopaminergic systems in parkinsonism are necessary, as regulating serotonergic disturbance might improve tremor.

Radiopharmaceuticals aren't the only field of development in nuclear medicine, their detection, and analysis also are.

4) Advances in image acquisition technology and image analyses

Image acquisition

Injected radiotracers are composed of a tracer, distributed according to its target, and a radioactive isotope, detected by a camera. Detection is complicated by attenuation caused by several layers of tissues. Time of acquisition and image quality (spatial and energy resolution) is dependent camera detector performance. More powerful SPECT detectors are now available using 3D ring detectors versus planar detectors or using new CZT (cadmium–zinc–telluride) detector compounds [18].

For PET, a 3D detector is the rule. Improvements have been constant, but the major advance was the ability to acquire dynamic images in routine practice. PET imaging for the brain volume generally takes 10 to 15 minutes for acquisition, usually 30 to 60 minutes after injection, depending on the radiotracer used. Digital PET cameras can record several images per minute, starting after injection in a what is called dynamic acquisition. In addition,

dynamic acquisition enables recording many useful parameters, for example a constant on ^{18}F -fluorodopa PET reflecting its decarboxylation rate constants [2].

Image analyses

Nuclear medicine physicians usually work with two types of images: the first one from the radiotracer detected and the second one from a low-dose computed tomography that is perfunctory. The two types of images are coupled for anatomical interpretation. For a better interpretation, images of the radiotracer may be fused with brain MRI. This fusion could be achieved immediately by hybrid PET/MRI cameras registering PET and MRI images at the same time, but these machines are expensive and poorly available. Alternatively, the physician may fuse images acquired on a regular PET/SPECT machine with images from a prior MRI. This is essential when interpreting presynaptic dopaminergic examinations, for example in the context of vascular lesions.

Beyond morphologic or metabolic examination, connectivity can be studied. Functional MRI evaluates the blood-oxygen-level dependent signal that is an indirect reflect of neuron activation, but this signal is sensitive to many parameters and is delayed compared to metabolic rate of glucose changes. Metabolic connectivity has been studied using ^{18}F -FDG PET imaging in normal subjects and neurodegenerative parkinsonism and even applied to dopaminergic imaging [19]. Studying the brain as an interconnected system will help to better understand the pathophysiology of parkinsonism, and remote effects of any local change.

Conclusion

Nuclear medicine routine examinations are powerful tools to help the clinician establish the diagnosis of neurodegenerative parkinsonism. Presynaptic dopaminergic imaging coupled with MRI (to exclude lesions) enables the positive diagnosis of degenerative parkinsonism, which can then be characterized with ^{18}F -FDG brain PET and ^{123}I -MIBG cardiac scintigraphy (atypical parkinsonism versus PD; type of atypical parkinsonism). Many radiopharmaceuticals are under development, with new targets such as tau or α -synuclein proteins, and techniques of image acquisition and analysis are rapidly evolving. In the future, combining clinical evaluation and specific protein-PET (tau, α -synuclein) will probably be one of the most robust means to diagnose the underlying pathophysiology early in the disease course. Thus, patients will be able to benefit from a specific treatment as soon as possible in the hope of preventing neuronal degeneration. In addition, the development of radiotracers targeting neuroinflammation or other neurotransmitters such as serotonin dysfunction may

contribute to a better understanding of neurodegeneration as a global process with many interactions between various biological systems.

Disclosure of interest

The authors declare no conflict of interest.

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Dopaminergic presynaptic exam	Interaction	Recommendations
DATSCAN SPECT	Cocaine, amphetamines, modafinil, anticholinergic drugs, fentanyl, anesthetics, antidepressants, SSRI, lithium	Whenever possible, stop medications for at least 5 half-lives
¹⁸F-FLUORODOPA PET	Anti-parkinsonian drug	12h minimal L-DOPA stop
	Neuroleptics	Note neuroleptic intake
	Amino acid-containing foods	Avoid food 4h prior to examination

Table 1: Main interactions with dopaminergic presynaptic examinations and recommendations. SSRI=selective serotonin reuptake inhibitors.

DISEASE	CORTEX	STRIATUM	CEREBELLUM
PD	normal, or parietal hypometabolism	hypermetabolism	normal/hypermetabolism
DLB	posterior, occipital predominant hypometabolism with cingulate island sign*	hypermetabolism	normal/hypermetabolism
MSA	mainly normal	putamen hypometabolism	hypometabolism
CBD	asymmetrical hypometabolism	asymmetrical hypometabolism of basal ganglia, same side as striatum	asymmetrical hypometabolism, opposite side to cortico- striatal hypometabolism
PSP	frontal midline hypometabolism	caudate hypometabolism	normal

*Table 2 : Neurodegenerative parkinsonism and the main ¹⁸F-FDG PET metabolic anomalies : DLB=dementia with Lewy bodies; MSA=multiple system atrophy; CBD=corticobasal degeneration; PSP=progressive supranuclear palsy. * Cingulate island sign defined as sparing of posterior cingulate cortex (PCC) relative to precuneus and cuneus*

Dopaminergic denervation imaging	Inconveniences	Advances
¹⁸F-fluorodopa PET	Compensation phenomenon at early stage of degenerative parkinsonism leading to a lower sensitivity than SPECT	New PET tracers could target dopamine-active transporters, Shorter examination and higher spatial resolution are expected, no compensation phenomenon
DaTSCAN SPECT	Long completion time, lower spatial resolution than PET	

Table 3: Inconveniences of current radiotracers for dopaminergic denervation imaging, and new radiotracers for this purpose.

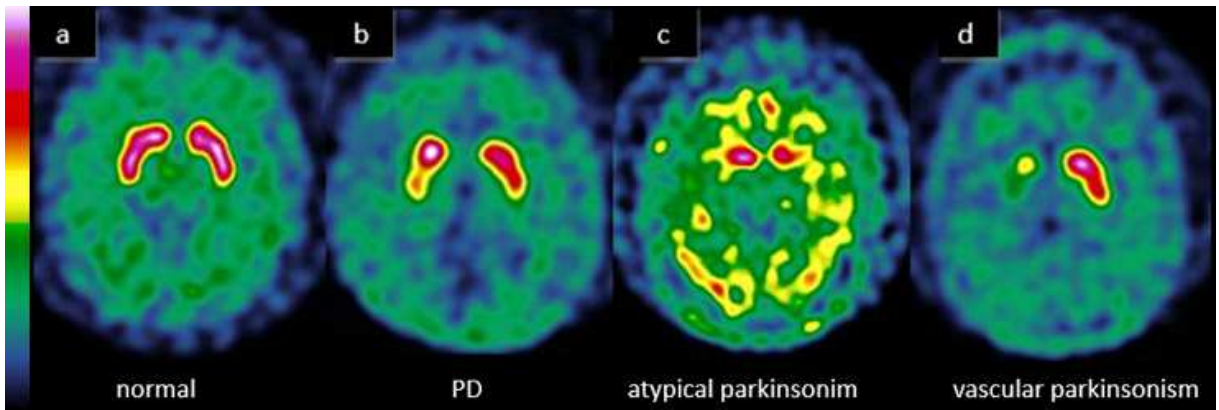


Figure 1 : Axial images of DaTSCAN showing: (a) normal examination; (b) asymmetrical right denervation of the putamen as often seen in PD; (c) bilateral diffuse striatal denervation with background increase as often seen in atypical parkinsonism; (d) amputation of the right striatum due to an ischemic sequelae of a sylvian ischemic stroke.

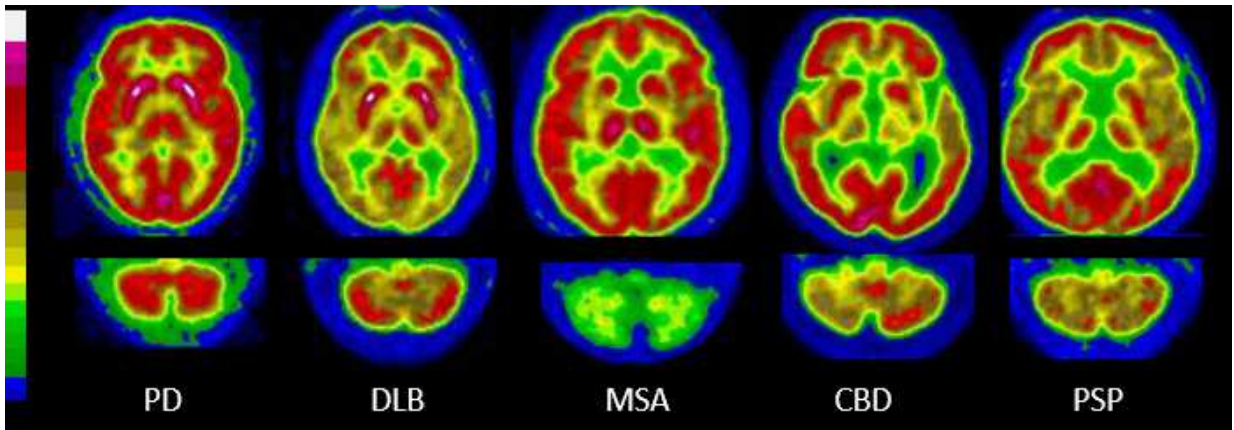


Figure 2 : Axial ^{18}F -FDG PET at the level of the striatum (top row) and the cerebellum (bottom row) showing different metabolic patterns in PD and atypical parkinsonism.

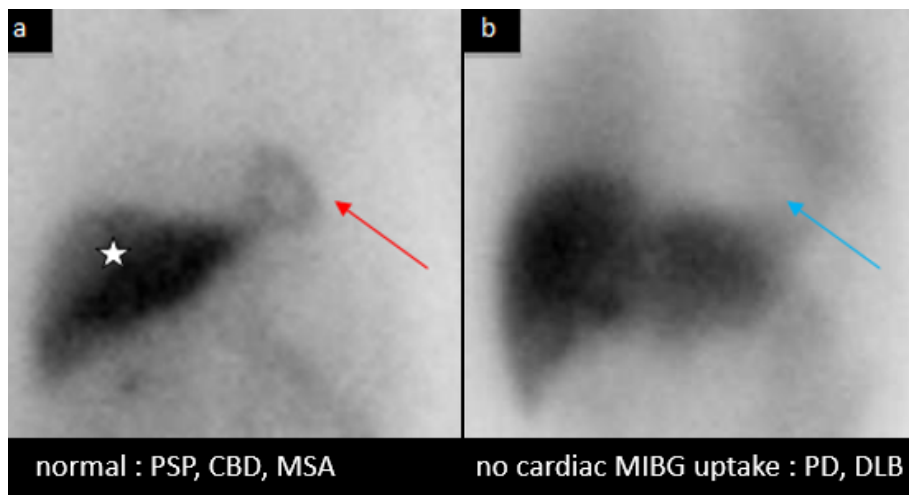


Figure 3: ¹²³I-MIBG scintigraphy - planar anterior image showing (a) physiologic uptake in the liver (white star) and normal cardiac uptake (red arrow) as seen in PSP, CBD, or MSA; (b) no cardiac uptake (blue arrow) as observed in PD or DLB.