Special collaboration

Functional neuroimaging in the diagnosis of patients with parkinsonism: Update and recommendations for clinical use


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A B S T R A C T

Functional neuroimaging has been traditionally used in research for patients with different parkinsonian syndromes. However, the emergence of commercial radiotracers together with the availability of single-photon emission computed tomography (SPECT) and, more recently, positron emission tomography (PET) have made them available for clinical practice. Particularly, the development of clinical evidence achieved by the functional neuroimaging techniques over the past two decades have motivated a progressive inclusion of several biomarkers in the clinical diagnostic criteria for neurodegenerative diseases that occur with parkinsonism. However, the wide range of radiotracers designed to assess the involvement of different pathways in the neurodegenerative process underlying parkinsonian syndromes (dopaminergic nigrostriatal pathway integrity, basal ganglia and cortical neuronal activity, myocardial sympathetic innervation), and the different neuroimaging techniques available (scintigraphy, SPECT and PET), have generated some controversy concerning the best neuroimaging test indicated for the differential diagnosis of parkinsonism. In this article, a panel of nuclear medicine and neurology experts has evaluated the functional neuroimaging techniques emphasizing practical considerations related to the diagnosis of patients with uncertain origin parkinsonism and the assessment of Parkinson’s disease progression.

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R E S U M E N

Las técnicas de neuroimagen funcional se han utilizado tradicionalmente en la investigación de los pacientes que presentan un síndrome parkinsoniano. Sin embargo, la aparición de radiofármacos...
Introduction to the clinical problem

In recent years there has been a steady inclusion of different neuroimaging biomarkers in the criteria for clinical diagnosis of neurodegenerative diseases. Undoubtedly, this change is due to the notable progress and advances undergone by imaging techniques in the last decade. Specifically, functional techniques in nuclear medicine, such as positron emission tomography (PET) or single photon emission computed tomography (SPECT), have greatly contributed to our knowledge regarding the pathophysiology of different neurodegenerative diseases and also to diagnosis in the earliest phases of disease, when structural changes are not yet evident.

The diagnosis of neurodegenerative diseases presenting as a parkinsonian syndrome may be complex in the early phases due to the initial overlapping of symptoms between different diseases. Diagnostic accuracy improves with disease progression, when some atypical signs, incompatible with the diagnosis of idiopathic Parkinson’s disease (PD), become evident. In this scenario, the possibility of in vivo non invasive evaluation of the integrity of the dopaminergic nigrostriatal pathway, neuronal activity of the basal ganglia and cortex, as well as myocardial sympathetic innervation may be useful to complement the clinical diagnosis, thereby improving the specificity and facilitating decision making.

There is currently a great diversity of functional neuroimaging techniques with common objectives, but there is also a certain degree of controversy regarding the diagnostic capability of each technique. Therefore, it is necessary to determine the utility of each and every technique in order to establish recommendations for their use in the clinical diagnosis of patients with parkinsonism of uncertain origin. This document is the result of the consensus reached by a panel of neuroimaging experts from the Spanish Society of Nuclear Medicine and Molecular Imaging (SEMNIM) and experts in movement disorders from the Spanish Society of Neurology (SEN), following an exhaustive review of the literature.

Clinical characteristics of parkinsonian syndromes

Parkinsonism is defined as a clinical syndrome characterized by a combination of the following cardinal symptoms: resting tremor, rigidity, bradykinesia, loss of postural reflexes, gait impairment, motor blockade or freezing phenomenon. Parkinsonism can be a clinical manifestation of hereditary and nonhereditary neurodegenerative diseases but it can also be secondary to multiple causes including structural, infectious, pharmacological, toxic or traumatic events. The most frequent form of degenerative Parkinsonism is PD. In contrast to PD, other types of parkinsonism called Parkinson’s plus syndromes or atypical parkinsonism do not respond to conventional levodopa treatment or show mild and transitory response. Atypical parkinsonisms include multiple system atrophy (MSA) with its parkinsonian and cerebellar atrophy variants, progressive supranuclear palsy (PSP) and cortico basal degeneration (CBD) (Table 1).

Although PD patients may exhibit different clinical manifestations and disease progression, they present some common characteristics that can help in the differential diagnosis of the disease with other degenerative parkinsonisms. PD has an asymmetrical presentation since the beginning of the disease and remains asymmetrical throughout the evolution of the disease. The presence of resting tremor is characteristic. Despite certain differences, depending on the age of onset, progression of PD is slower than atypical parkinsonisms, and gait and balance impairment are usually present in advanced stages of PD. Motor manifestations of PD significantly improve with dopaminergic agents but most develop motor complications (motor fluctuations and dyskinesias) after 5–8 years of levodopa therapy. Non-motor symptoms are very common in PD patients, especially in advanced stages of the diseases being cognitive decline, depression, anxiety, dysautonomia, fatigue and pain the most frequent. The underlying pathology of these symptoms is unknown and, in some cases, these symptoms precede the appearance of the classical motor profile by many years.

MSA usually appears as a parkinsonism syndrome in combination with cerebellar, pyramidal and/or dysautonomic symptoms/signs. The scarce response to levodopa, the prominence and precocity of the dysautonomia, and more rapid and torpid progression differentiates MSA from PD.

PSP classically appears as a rigid-akineti symmetric syndrome with predominant axial rigidity and early alteration in balance, frequent falls, vertical supranuclear gaze palsy, bulbar syndrome and frontal cognitive dysfunction. In recent years, other phenotypes have been described including parkinsonian-type PSP in which patients initially present a parkinsonism with resting tremor and

<table>
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<th>Table 1</th>
<th>Classical clinical characteristics of degenerative parkinsonisms.</th>
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<td>Progression</td>
<td>L-DOPA response</td>
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<td>Parkinsonism</td>
<td>*</td>
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<tr>
<td>Asymmetry</td>
<td>–</td>
</tr>
<tr>
<td>Dysautonomia</td>
<td>Late</td>
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<td>Pyramidalism</td>
<td>–</td>
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<td>Cerebellar symptom</td>
<td>–</td>
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<tr>
<td>Oculomotor deficits</td>
<td>–</td>
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<tr>
<td>Apraxia in extremities</td>
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</tbody>
</table>

MSA: multiple system atrophy; CBD: cortico basal degeneration; PD: Parkinson’s disease; Mixed: with resting tremor, bradykinesia with/without rigidity; PSP: progressive supranuclear palsy; R-A: parkinsonism with rigidity and bradykinesia.
a mild response to levodopa; clinical types with gait blockade or pure akinesia; and a corticobasal syndrome or nonfluent progressive aphasia. These different phenotypes make clinical differential diagnosis difficult when dealing with PD or frontotemporal degeneration.

CBD appears with the so-called corticobasal syndrome, meaning a very symmetric akinetic-rigid syndrome, generally accompanied by dystonia of the affected extremities and cortical signs with apraxia, cortical sensitive alteration, and alien hand and myoclonus in response to stimuli.

### Evaluation of dopaminergic system by PET and SPECT

#### Striatal dopaminergic neurotransmission system

The nigrostriatal pathway originates in the dopaminergic neurons of the pars compacta of the substantia nigra and in the retrorubral field and innervates the dorsal striatum (caudate and putamen nuclei). Degeneration of this pathway is responsible for the main signs and symptoms of PD and other neurodegenerative parkinsonisms.

Dopamine is synthetized from tyrosine in the cytosol of the dopaminergic neurons. Tyrosine is metabolized to levodopa by tyrosine hydroxylase and subsequently, it is decarboxylated to dopamine by DOPA-decarboxylase. Dopamine is stored in vesicles located in the terminal part of the neuronal axon by a vesicular monoamine transporter type-2 (VMAT-2) and is released to the synaptic cleft by exocytosis. The dopamine released into the synaptic space binds to the postsynaptic dopaminergic receptors; the dopamine not bound to receptors is recaptured by the presynaptic dopaminergic nerve terminals through dopamine transporters. Dopamine transporters also recapture dopamine not bound to receptors. Dopamine is degraded by catechol-O-methytransferase (COMT). There are five types of postsynaptic dopaminergic receptors which constitute two families, type D1 (D1 and D5 receptors) and type D2 (D2, D3 and D4 receptors), both commonly related to motor activity.

Dopamine synthesis is autoregulated by the inhibition of tyrosine hydroxylase, the release of dopamine into the synaptic cleft and the density of postsynaptic dopaminergic receptors. This autoregulation system is responsible for compensating the loss of dopaminergic neurons which occurs in PD and, consequently, the delay in the appearance of PD symptoms. An increase in the number of postsynaptic D2 receptors and an increase in dopamine turnover are the two most important mechanisms induced so as to compensate for the reduction of striatal dopamine levels. The proper functioning of the compensation systems delays the appearance of PD symptoms until neural dopaminergic degeneration in the substantia nigra reaches 50–60%.

**SPECT and PET**

SPECT and PET are two nuclear medicine techniques that yield 3D images of the striatal dopaminergic system (Table 2). Both techniques require previous injection of radiotracers or radioligands (Table 2) and the significance of their striatal uptake differs depending on the radioligand used. Radioligands with affinity for molecules which participate in the synthesis of dopamine and with affinity for dopamine transporters evaluate the presynaptic or nigrostriatal neurons. The radioligands with affinity for the dopaminergic receptors assess the integrity of the postsynaptic or striato-telencephalic neurons. The information contained in the PET and SPECT images is functional (integrity of the nigrostriatal pathway) and molecular (distribution and concentration of DOPA-decarboxylase, transporters, receptors). Anatomical information of the striate body can be added using PET/MR or SPECT/MR fusion images.

#### Striatal PET imaging

A large number of PET tracers allow pre- and postsynaptic dopaminergic evaluation. With this technique we can study different aspects of the presynaptic neuron: (1) the concentration or activity of the amino acid membrane transporters, the activity of DOPA-decarboxylase and the vesicular dopaminergic

<table>
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<tr>
<th>Tracer</th>
<th>Mechanism</th>
<th>Synapsis</th>
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<tbody>
<tr>
<td>PET</td>
<td></td>
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<tr>
<td>18F-DOPA</td>
<td>Dopamine synthesis</td>
<td>Pre</td>
</tr>
<tr>
<td>11C-3T2R</td>
<td>Vesicular transporter VMAT-2</td>
<td>Pre</td>
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<tr>
<td>18F-FP-CIT</td>
<td>Dopamine transporter</td>
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<tr>
<td>11C-raclopride</td>
<td>Striatal D2/D3 antagonist</td>
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<tr>
<td>18F-falpride</td>
<td>Striatal D2/D3 antagonist</td>
<td>Post</td>
</tr>
<tr>
<td>11C-FLB-457</td>
<td>Extrastriatal D2/D3 antagonist</td>
<td>Post</td>
</tr>
<tr>
<td>11C-SCH-23390</td>
<td>Striatal D1 antagonist</td>
<td>Post</td>
</tr>
<tr>
<td>11C-MNP</td>
<td>Striatal D2 agonist</td>
<td>Post</td>
</tr>
<tr>
<td>SPECT</td>
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<tr>
<td>123I-IBZM</td>
<td>Striatal D2/D3 antagonist</td>
<td>Post</td>
</tr>
<tr>
<td>123I-epidepride</td>
<td>Striatal D2/D3 antagonist</td>
<td>Post</td>
</tr>
<tr>
<td>123I-β-CIT</td>
<td>Dopamine transporter</td>
<td>Pre</td>
</tr>
<tr>
<td>123I-FP-CIT</td>
<td>Dopamine transporter</td>
<td>Pre</td>
</tr>
<tr>
<td>99mTc-TRODAT</td>
<td>Dopamine transporter</td>
<td>Pre</td>
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</tbody>
</table>

Post: postsynaptic; Pre: presynaptic.
reserve are studied with $^{18}$F-DOPA and $^{18}$F-FMT (6-$^{18}$F-fluoro-m-tyrosine); (2) the density of the VMAT-2 transporter using $^{11}$C-DTBZ ($^{11}$C-dihydrotetrabenazine), and (3) the concentration or density of the presynaptic dopamine transporter protein using $^{1}$C-dMIP (d-threo-methylphenidate), $^{11}$C or $^{18}$F-CFT (2-$^{18}$F-carbomethoxy-3-$^{18}$F-fluoropropionic acid). $^{11}$C or $^{18}$F-PE2I, $^{18}$F-FP-CIT.

Postsynaptic neurons integrity can be evaluated using striatal dopamine D2/D3 receptor antagonist radiotracers such as $^{11}$C-raclopride or $^{11}$C-falipride; extrastriatal dopamine D2/D3 receptor antagonists such as $^{11}$C-FLB-457; striatal dopamine D1 receptor antagonists such as $^{11}$C-SCH 23390 and $^{11}$C-NNC 112; and dopamine D2 receptor agonists such as $^{11}$C-MNPA.$^{5}$

All these tracers are used almost exclusively in research. $^{18}$F-DOPA is the only radioligand used clinically in the differential diagnosis of parkinsonian syndrome of degenerative origin.

**Striatal SPECT imaging**

The number of radioligands used with SPECT is smaller than that used with PET. The most widely used presynaptic radioligand for SPECT is $^{123}$I-N-3-fluoropropyl-2-b-carbomethoxy-3b-[4-iodophenyl] nortropine ($^{123}$I-FP-CIT). $^{123}$I-IBZM, a benzamide analog of raclopride with affinity for striatal D2 receptors.$^{2}$ This analog is not registered as a radiotracer in Spain, and it is used for the differential diagnosis between PD and atypical parkinsonisms by means of a foreign medication policy.

**PET with $^{18}$F-DOPA**

$^{18}$F-DOPA is the most commonly used PET tracer in the study of PD and atypical parkinsonisms, presenting very good sensitivity and specificity values as well as good correlation with disease severity and progression, similar to cerebral SPECT with $^{123}$I-FP-CIT, but with greater spatial resolution of the striatal images because it allows separate analysis of the caudate and the putamen nuclei and identification of the **accumbens** nucleus (Fig. 1).

Discontinued use of anti-parkinsonian drugs is recommended (L-Dopa for 6–12 h, and dopaminergic antagonists for 24 h) prior to $^{18}$F-DOPA PET, and carbidopa should be administered (150 mg) 60 min before injection of $^{18}$F-DOPA. This allows inhibition of the peripheral dopadecarboxylase and thereby, improves DOPA availability in the presynaptic dopaminergic terminals.

In the clinical routine, PET images are acquired 70 min after the injection of 111–185 MBq of $^{18}$F-DOPA, and static 3D can be used with an approximate duration of 10–20 min. Ninety-minute dynamic acquisition is used in research, a requirement for absolute quantification of the decarboxylation constant ($K_d$ or $K_i$).

As in SPECT studies using $^{123}$I-FP-CIT (see below), $^{18}$F-DOPA PET can be evaluated visually by analyzing its distribution in the striatum. Quantitative analysis is performed by analyzing the uptake of regions of interest. In the case of static images, the average activity in the regions with specific uptake (striatum) and a region with non-specific uptake (occipital) is obtained, and the ratio between the two is calculated for each hemisphere (SUR). In dynamic studies, the parameter that is quantified is the decarboxylation constant ($K_i$), obtained by modeling a simplified compartmental system (Patlak plot with region of reference) from which a parametric image of the $K_i$ parameter can be created.

$^{18}$F-DOPA is currently registered and commercialized in Spain by Cis Bio International (DOPACIS®) and by Barnatrón SA (NeuroPET®).

**SPECT with $^{123}$I-FP-CIT**

$^{123}$I-FP-CIT or iodolupane (registered as DaTSCAN by GE Healthcare) is a cocaine analog that presents high affinity for the dopamine transporter ($K_i$ 3.5 nM), with good specificity (selectivity TDA/SERT of 2.8/1), and therefore, it is an excellent marker for nigrostriatal neuron viability and functionality. Uptake is concentrated in the axonal terminal of the nigrostriatal neuron where there is a high concentration of DAT, achieving maximum uptake in equilibrium at 3–6 h of endovenous administration of 150–250 MBq (normally 185 MBq).

To perform this study it is recommended that cocaine intake be discontinued 2 days prior; cessation of other drug intake is as follows: amphetamine, 7 days; methylenephedrine, 3 days; mazindol, 3 days; phentermine, 14 days; modafinil, 3 days; buspirone, 8 days and benzatropine, 5 days. In addition, lugol should be administered orally to block thyroid uptake of $^{123}$I.

Visual analysis of SPECT images is sufficient for diagnosis (Fig. 2). Complementary quantification of striatal compared to occipital uptake (SUR) can be useful for detecting significant differences with respect to healthy subjects.$^{5}$

False positives (pathologic striatal uptake with an intact nigrostriatal pathway) are infrequent and related to pharmacological interferences (drugs which block dopamine transporters) or methodological artifacts.$^{7}$ False negatives (normal striatal uptake with degeneration of the nigrostriatal pathway) are even less frequent, with the positive predictive value of SPECT being greater than 90% in almost all the series. SPECT with $^{123}$I-FP-CIT detects changes in striatal uptake in patients with premotor symptoms of PD (olfactory disorders, REM sleep phase behavior disorders) and in asymptomatic subjects who are carriers of genetic mutations in cases of familial PD.

**Evaluation of postsynaptic neuronal activity by $^{18}$FDG PET**

An increase in glutamatergic neuronal activity (excitatory synaptic activity) determines an increase of cerebral glucose metabolism through the neuron–glia metabolic unit. The 2-$^{18}$F-

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**Fig. 1. Patterns of normality and pathology of cerebral $^{18}$F-DOPA PET.** (A) Normal pattern, axial slice of $^{18}$F-DOPA PET: preserved striatal uptake in both caudate and putamen nuclei. (B) Normal pattern, coronal slice of $^{18}$F-DOPA PET: preserved striatal uptake in both caudate, putamen and accumbens. (C) Asymmetric pathologic pattern of $^{18}$F-DOPA PET: right putaminal decreased uptake and normal uptake in the left putamen nucleus and both caudate nuclei. (D) Symmetric pathologic pattern of $^{18}$F-DOPA PET: absence of uptake in both putamen nuclei and preserved uptake in the caudate nuclei.
In the case of neurodegenerative diseases, it is important to know the pattern of cerebral metabolic activity. Severe brain tissue consumption. Therefore, the studies should be carried out in previously controlled normoglycemic states. Consequently, this type of medication should be withdrawn prior to the study whenever the patient situation allows for this. In patients presenting parkinsonism, it is important to know if they are taking levodopa or dopaminergic agonists drugs because of their possible modulation of FDG uptake.

Following intravenous administration of 125–250 MBq of 18FDG (generally 150 MBq), patients are required to rest for 40 min in supine position in a quiet, dimly lit room, without talking, reading or doing any physical activity. When patients are not collaborative, and sedation is required, this should be initiated at least 30 min after tracer injection.

The acquisition protocol consists in a brain static image (10–15 min) based on the characteristics of the PET-CT scanner. The resulting images are reoriented according to the orbito-meatal angle; qualitative (visual) or quantitative analysis is performed. In visual analysis, possible areas of hypometabolism must be recognized and when a structural lesion is suspected, coregistration with the morphologic CT or MR studies is recommended. Thereafter, we should identify whether or not the findings correspond to any of the patterns described in neurodegenerative diseases (Fig. 3). Several voxel-based programs of quantitative analysis are available for complementing the visual analysis.

**Evaluation of sympathetic innervation by myocardial scintigraphy with 123I-metaiodobenzylguanidine**

Myocardial innervation scintigraphy with 123I-metaiodobenzylguanidine (123I-MIBG) shows specific neuronal noradrenergic uptake and is a functional marker of the integrity and distribution of the postganglionic presynaptic terminals. 123I-MIBG competes with NA for the uptake in the postganglionic sympathetic terminals, allowing in vivo visualization of the sympathetic innervation. 123I-MIBG does not bind to the postsynaptic receptors nor is it degraded by the COMT and MAO enzymes that fluoro-2-deoxy-d-glucose (18FDG) glucose analog is incorporated into the cells by glucose transporters. Once inside the cells, 18FDG is phosphorylated to 18FDG-6-phosphate by the hexokinase enzyme. The presence of 18F blocks its isomerization to fructose-6-phosphate, and therefore, 18FDG does not follow the glycolysis metabolic pathways or the glycogen synthesis pathways. The retention of 18FDG-6-phosphate is proportional to the glucose brain tissue consumption. Therefore, 18FDG is used for evaluating regional cerebral glycemic metabolism as a biomarker for neuronal and synaptic activity. In the case of neurodegenerative diseases accompanied by a parkinsonian syndrome, 18FDG allows evaluation of the neuronal activity in the basal ganglia. Thus, it has been suggested that 18FDG PET is a good marker for postsynaptic activity of the nigrostriatal pathway.

Patients should fast for at least 4 h before PET scanning so as to reduce the levels of glycemia (from 110 to 160 mg/dl) because elevated glycemia levels reduce the signal ratio of gray/white matter and increase the stochastic noise in the image, thereby making it more difficult to interpret the study. The use of insulin for correcting the elevated glycemia levels has not been shown to be effective and therefore, the studies should be carried out in previously controlled normoglycemic states. In addition, it is important to know the medication that the patient is taking because certain central nervous system drugs may influence cerebral glucose metabolism. Consequently, this type of medication should be withdrawn prior to the study whenever the patient situation allows for this. In patients presenting parkinsonism, it is important to know if they are taking levodopa or dopaminergic agonists drugs because of their possible modulation of 18FDG uptake.
metabolize the endogenous catecholamines. After administration of 111–370 MBq of $^{123}$I-MIBG (generally 370 MBq), there is rapid myocardial uptake with the greatest flow to the extraneuronal spaces. In the following hours, $^{123}$I-MIBG actively enters the sympathetic terminal, especially that of the left ventricle, washing out from non-neuronal tissue. Neuronal accumulation of $^{123}$I-MIBG reaches its maximum at 3–4 h, showing active neuronal uptake without passive components (Fig. 4).

Administration of $^{123}$I-MIBG is performed while resting, avoiding substances or drugs that might alter its uptake and after having performed thyroid blockade by the oral administration of a solution of lugol or 500 mg of potassium perchlorate. Thorax planar images, anterior projection, are acquired early at 15–20 min and delayed acquisition is at 3–4 h, with 10-min image duration, an energy window of 159 keV ± 20% and a matrix of 256 × 256.

The use of medium energy collimators, either all-purpose (LEAP) or high resolution (LEHR), is recommended due to the presence of photons with higher energy photopeaks in $^{123}$I than in those of $^{99m}$Tc. However, for practical reasons some centers perform the study with low energy collimators.

Regional myocardial uptake of $^{123}$I-MIBG tends to be heterogeneous, being somewhat less in the apex and inferior wall. This heterogeneity limits qualitative evaluation of the images and has led to the development of semiquantitative parameters. The heart-to-mediastinum ratio is used as an index of global $^{123}$I-MIBG uptake (heart/mediastinum (H/M) ratio). These H/M ratios are obtained by drawing regions of interest in the anterior image of the thorax and, particularly, the entire cardiac area. To obtain the H/M ratio, the mean of the counts per pixel of the myocardium is divided by the mean of the counts per pixel of the mediastinum. The washout rate is obtained as follows: (counts per pixel in the myocardium at 15 min – counts per pixel in the myocardium at 4 h)/counts per pixel in the myocardium at 15 min. The washout reflects the tone of the sympathetic nervous system and therefore, an increase in washout could be an early marker for sympathetic dysfunction, showing not only a lower number of sympathetic cardiac terminals but also an increase in spillover or a reduced capability for maintaining the NA in the sympathetic terminals. Both a reduction of the delayed H/M ratio and an increase in the rate of washout are parameters which indicate alteration of cardiac sympathetic innervation. Although some studies have reported reference values of these ratios (H/M ratio range of 1.9–2.8, with a mean of 2.2 ± 0.3), each center should adjust their ratios depending on the circumstances of their equipment and the protocols used.

**Differential diagnosis of tremor and parkinsonian syndrome**

Although PD tremor and essential tremor (ET) are not difficult to differentiate (Table 4), in some cases neither anamnesis nor clinical examination allows definite clinical diagnosis. However, in some cases patients with ET frequently develop PD. When a patient with

<table>
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<tr>
<th>Finding</th>
<th>Parkinson’s disease</th>
<th>Essential tremor</th>
</tr>
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<tbody>
<tr>
<td>Age at onset (years)</td>
<td>55–75</td>
<td>10–80</td>
</tr>
<tr>
<td>Family history</td>
<td>+/−</td>
<td>++</td>
</tr>
<tr>
<td>Frequency of tremor (Hz)</td>
<td>4–6</td>
<td>5–10</td>
</tr>
<tr>
<td>Characteristics of the tremor</td>
<td>Pronation–supination</td>
<td>Flexion–extension</td>
</tr>
</tbody>
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**Influencing factors**

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<tr>
<th></th>
<th>Parkinson’s disease</th>
<th>Essential tremor</th>
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<tbody>
<tr>
<td>Resting</td>
<td>Increases</td>
<td>Diminishes</td>
</tr>
<tr>
<td>Action</td>
<td>Diminishes</td>
<td>Increases</td>
</tr>
<tr>
<td>Concentration</td>
<td>Diminishes</td>
<td>Happy</td>
</tr>
<tr>
<td>Writing</td>
<td>Diminishes (micrography), increases (trembling)</td>
<td>Increases</td>
</tr>
<tr>
<td>Walking</td>
<td>Increases</td>
<td>Diminishes</td>
</tr>
<tr>
<td>Alcohol</td>
<td>-</td>
<td>Without latency</td>
</tr>
<tr>
<td>Postural tremor</td>
<td>Re-emerging (latency)</td>
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</tr>
<tr>
<td>Kinetic tremor</td>
<td>+/−</td>
<td></td>
</tr>
<tr>
<td>Tremor of extremities</td>
<td>Asymmetric</td>
<td>Quite symmetric</td>
</tr>
<tr>
<td>Other localizations</td>
<td>Face, jaw, lips, chin</td>
<td>Head, voice</td>
</tr>
</tbody>
</table>

Modified from Jankovic.

Fig. 3. $^{18}$F-FDG PET image of a normal subject (A) with predominant, homogeneous and symmetric activity in the basal ganglia; with PD (B) similar to the normal subject with a greater activity in the posterior region of the putamen nucleus; and with MSA-P type (C) in which a marked reduction is observed in the posterior region of the putamen in both hemispheres.

Fig. 4. Myocardial innervation study by planar scintigraphy of the anterior thorax obtained at 4 h after the administration of $^{123}$I-MIBG, (A) with normal cardiac uptake and (B) with diminished cardiac uptake in a patient with PD.
ET presents resting tremor, the added presence of PD must be ruled out. Sometimes this is a tremor of wide frequency range which is transmitted on resting when the patient is not completely relaxed. Diagnosis is further complicated if the tremor is asymmetric, if the muscle tone is increased, and if the movements of the patient are relatively slow. In this scenario, functional neuroimaging studies may be of great value in the differential diagnosis.

PET or SPECT studies of the presynaptic dopaminergic pathway have a sensitivity of 90% when differentiating between PD and patients with ET or healthy controls. However, the reference pattern for comparison is based on clinical criteria and not on pathological criteria. With this pattern, the pretest probability (the grade of clinical uncertainty) will be, at the most, equal to the post-test probability, thereby demonstrating the weakness of the diagnostic studies in this field. As pointed out by De la Fuente-Fernández, new neuropathological studies are needed for evaluating the diagnostic accuracy of the neuroimaging tests. Another interesting aspect of the neuroimaging tests is that 10–15% of patients with clinical criteria of PD, assessed by expert neurologists, show normal [18F]DOPA or [123I]-FP-CIT uptake in the striatum. These individuals have been denominated “SWEDD” (subjects without evidence of dopaminergic degeneration). These patients usually present a resting tremor phenotype which some define as dystonic tremor, and slow movement with doubtful bradykinesia. The evolution and follow-up imaging studies indicate that these patients most likely do not present PD, thereby supporting the normal results obtained from the functional neuroimaging tests.

Patients with isolated resting tremor consistently show abnormal presynaptic dopamine uptake in the striatum (Figs. 1 and 2) whereas patients with isolated postural tremor have normal uptake. Some patients diagnosed with ET show a reduction in dopaminergic uptake in the putamen nucleus, within the same range as patients with PD. This suggests early nigrostriatal dysfunction. However, there is no sufficient clinical follow-up of these patients which could confirm the development of a typical PD. A reduction in the uptake of [18F]DOPA in the putamen nucleus has also been described in asymptomatic relatives of patients with PD and in patients with isolated postural tremor who are phenomenologically identical to ET. An overlapping between PD and ET seems evident since PD is more prevalent in families with ET and vice versa.

Neuroimaging of the dopaminergic pathway is usually useful for differentiating the two entities. In fact, the technical specifications of [123I]-FP-CIT (DaTSCAN®) include the indication of differential diagnosis between ET and diseases related to PD. It is difficult to sustain a diagnosis of PD with preservation of the dopaminergic pathway. Similarly, if there were an alteration of the dopaminergic pathway, diagnosis of ET would be possible but with a high suspicion that it could evolve to PD.

### Differential diagnosis of atypical degenerative parkinsonisms

The prognosis of atypical parkinsonisms is quite different from that of PD and therefore, complementary functional neuroimaging tests may be necessary in the initial phases when there is greater diagnostic uncertainty.

#### Cerebral metabolism with [18F]FDG PET in atypical parkinsonisms

In PD, cerebral [18F]FDG PET is normal or shows an increase in uptake in the putamen nucleus while in atypical parkinsonisms, hypometabolic patterns have been described in the basal ganglia, the thalamus or cortex, depending on the causal entity (Table 5).

#### Multiple system atrophy

The most characteristic finding observed in the parkinsonian variant of MSA (MSA-P type) is a reduction in the uptake of [18F]FDG in both putamen nuclei with a rostro-caudal gradient (Fig. 3). This finding has a sensitivity of almost 95% and a specificity of 100%. In these patients, decreased uptake can also be detected in the thalamus, brainstem and in cortical areas. Thus, the second consensus for the diagnostic criteria of MSA has established that hypometabolism in the putamen nucleus, mesencephalic region and cerebellum is an additional characteristic for diagnosing a possible MSA-P type. In the study by Tang this pattern has a positive predictive value of 88% in the first 2 years of the disease and of 100% at 5 years.

In patients with cerebellar variant of MSA (MSA-C type), hypometabolism of the anterior cerebellar hemispheres and the vermis may be detected one year after symptom onset, although putaminal hypometabolism can also be observed and is common among the parkinsonian variants. The presence of this metabolic pattern is of great value for differentiating these patients from others with predominant cerebellar symptomatology such as spinocerebellar ataxias or other diseases which occur with ataxia and rigid-kinetic symptoms, and consequently, the second consensus for the diagnostic criteria of MSA established that hypometabolism in the putamen nucleus is an additional characteristic for the diagnosis of MSA-C type. Unlike patients with a parkinsonian phenotype, a cortical metabolic deficit is not detected in patients with a hereditary form of the cerebellar variant.

#### Progressive supranuclear palsy

Patients with PSP present reduced [18F]FDG uptake in the caudate, putamen (caudo-rostral pattern) and prefrontal cortex, although the earliest sign in these patients is a reduced metabolism in the brainstem. It is important to note that frontal hypometabolism is not specific of this condition because it may be observed in other neurodegenerative diseases such as the variant of frontotemporal dementia with a predominant behavioral alteration, Huntington’s disease, PD, and patients with depression. Statistical parametric analyses of [18F]FDG PET images have shown a sensitivity of 88%, a specificity of 94% and a positive predictive value of 91% for the diagnosis of MSA, which may rise to 100% in the early phases of the disease. However, the data obtained in the last longitudinal follow-up study analyzing patients suspected of having atypical parkinsonisms had a slightly lower sensitivity of 73% and a specificity of 95.2%.

#### Corticobasal degeneration

In these patients, the greatest reduction in [18F]FDG uptake is produced asymmetrically in the posterior frontal, inferior parietal and superior temporal regions, together with a more marked hypometabolism in the thalamus and striatum on the opposite side of the most affected extremities. Using voxel by voxel analysis, it is possible to differentiate the metabolic pattern of patients with CBD (greater parietal hypometabolism) from that of patients with PSP (greater mesencephalic and thalamic hypometabolism).

#### Lewy body dementia

In these patients, a symmetric hypometabolism of [18F]FDG in the association cortex, including the occipital visual cortex is the most common finding with a sensitivity of 83–90% and a specificity of 86–88%, thereby differentiating Lewy body from Alzheimer’s disease dementia. Nonetheless, this technique has not been shown to be more accurate than [123I]-FP-CIT SPECT.
Dopaminergic presynaptic functionality

PET or SPECT studies of the presynaptic dopaminergic pathway in patients with atypical parkinsonisms show decreased tracer uptake in the striatum which is similar to that of patients with PD with the same time of evolution (Table 5). However, these studies are of great value in differentiating Lewy body dementia from other dementias and therefore, they have been included among the diagnostic criteria.

Dopaminergic postsynaptic studies

123I-IBZM SPECT in patients with MSA shows reduced striatal uptake of the radioligand in the early phases of the disease; this fact contrasts with PD in which the radiotracer uptake is increased. However, this pattern is not specific of PD because it can also be observed in other atypical parkinsonisms as well as in normal subjects (Table 5). Contrary to what occurs in MSA and in PSP, 123I-IBZM SPECT is usually normal in patients with CBD. Recent studies have demonstrated the inferiority of 123I-IBZM studies compared to 18F-DG in the differential diagnosis of atypical parkinsonisms.

Cardiac scintigraphy studies

A decrease in the cardiac uptake of 123I-MIBG (Fig. 4) with a significant reduction in the H/M ratio and an increase in the washout rate has been observed in PD patients. The sensitivity of cardiac scintigraphy with 123I-MIBG in PD with less than 3 years of symptoms duration is lower than that of patients with a longer period of evolution (73% and 90% respectively). Nevertheless, the sensitivity of 123I-FP-CIT is even higher than 123I-MIBG (sensitivity 83%) in early PD. Interestingly, 123I-MIBG scintigraphy in the rigid-akinetiforms of PD is more frequently altered than in the tremor-dominant PD patients.

Although most atypical parkinsonisms do not present significant alterations in cardiac studies with 123I-MIBG, up to 30% of the cases may be pathological (especially MSA-P type) and therefore, this technique may be of greater use in cases with a cerebellar phenotype.

Finally, this technique may be of interest in the differential diagnosis for Lewy body dementia, especially in early stages of the disease.

Secondary parkinsonism

It is often difficult to differentiate the clinical manifestations of degenerative parkinsonisms from secondary parkinsonisms but from a prognostic and therapeutic point of view, their recognition gains importance. Numerous causes of secondary or symptomatic parkinsonism have been described, but the most frequent are pharmacological parkinsonism (PP) and the so-called vascular parkinsonism (VP).

Pharmacological parkinsonism

Pharmacological parkinsonism (PP) is the second most frequent cause of parkinsonian syndrome after PD. It can be due to the intake of drugs that block the dopamine receptors or to decreased levels of stored dopamine. However, these drugs may also trigger an underlying PD in a preclinical situation. The differentiation of these two clinical situations is of great importance because PP requires discontinuance of the medication responsible for the situation. Cessation of parkinsonian symptoms occurs within a time period that is quite variable (weeks, months or even years). This variability may result in an incorrect diagnosis of PD and consequently, the implementation of inadequate treatment.

The symptoms of PP are generally symmetrical but in approximately 50% of the patients with PP, asymmetry is present. Other symptoms such as postural tremor, orofacial dyskinesia, akathisia, dystonia, among others, may indicate PP, but it is actually very complex to differentiate these symptoms from those produced by PD.

In PP the dopaminergic activity reflected by 18F-DOPA PET or 123I-FP-CIT SPECT is normal in most of the cases (>90%), whereas is abnormal in patients with an underlying PD. The sensitivity of 123I-FP-CIT SPECT for differentiating these subjects is 100% with a specificity of 90.6%, making it a very useful tool for differential diagnosis.

Vascular parkinsonism

Vascular parkinsonism (VP) or lower-half parkinsonism refers to a clinical picture mainly characterized by gait disorder, bradykinesia and rigidity. It is common in aged subjects with a history of arteriosclerosis and recurrent stroke. In the past, this term was controversial, but in recent years the idea of considering VP as a proper entity has arisen. It is a heterogeneous entity which may be caused by diffuse vascular lesions of the white matter, lacunar infarcts and, less frequently, territorial infarctions.

The differentiation between VP and PD is sometimes difficult and represents a diagnostic challenge. Different clinical features have been associated with VP, including symmetric involvement of the lower extremities, gait disorder, short steps, postural instability, frequent falls and the absence of resting tremor, together
with an absence of good response to treatment with levodopa. The presentation of these symptoms varies greatly and the diagnosis of VP cannot be confirmed based exclusively on the clinical manifestations.

Structural neuroimaging (CT and MR) cannot be considered a precise method for diagnosing VP, on one hand, due to the high proportion of patients with cerebrovascular lesions who do not develop parkinsonism and on the other hand, because the presence of cerebrovascular disease is not infrequent in patients with PD.

Functional neuroimaging of the dopaminergic system using PET or SPECT is highly accurate in differentiating VP from neurodegenerative parkinsonisms. Nonetheless, the image pattern in VP varies and to a certain degree, it reflects the heterogeneity of the physiopathological mechanisms of origin: (1) normal image in one-third of the cases; (2) reduction in uptake in the striatum, with involvement being homogeneous in caudate and putamen nuclei, of variable intensity (generally mild), and without significant symmetries as in the case of degenerative parkinsonisms; (3) exclusively unilateral homogeneous decreased uptake or as an intense and well delimited focal uptake defect in any area within the striatum. When these uptake defects involve the putamen nucleus (uni- or bilaterally), VP may be mistaken with PD; in these situations, comparison of the coincidence with the image of infarction in CT or MR is required. For differentiating between VP and PD, 123I-FP-CIT SPECT presents a sensitivity of 83.7% and a specificity of 99.4%. Neuroimaging techniques evaluating the integrity of the nigrostriatal system should be considered in patients presenting a parkinsonian syndrome with some atypical characteristics such as early gait disorder and/or unsatisfactory response to dopaminergic treatment and with associated cerebrovascular disease.

**Hereditary parkinsonism (LRRK2)**

Hereditary forms of PD represent 5–10% of all cases of PD. Among these, those associated with mutations in the LRRK2 gene encoding a protein denominated dardarin are noteworthy for their frequency.

The first publications of these familial cases of PD described a clinical phenotype very similar to that of non-mutated PD. Likewise, the nigrostriatal dysfunction demonstrated by 18F-DOPA PET in patients who are carriers of some of the pathogenic mutations such as R1441Q, R1441C, Y1699C, R1441C, and G2019S is indistinguishable from that observed in the classical form of PD. Taking into account that clinical presentation and neuroimaging are similar to PD, the presence of asymptomatic carriers of these mutations allows the use of a prospective study model of disease progression from very early stages of the disease, in which the classical motor symptoms have not yet become present.

The study of the nigrostriatal pathway using PET or SPECT in this population at risk of PD can provide relevant information regarding this premotor phase, and it may help evaluate clinical and molecular markers for assessing PD evolution as well as future neuroprotective treatments for the early stages of the disease.

Studies in asymptomatic carriers have shown reduced dopamine transporter uptake (11C-methylphenidate PET) as an early subclinical sign of dopaminergic dysfunction and progression to abnormal uptake of 18F-DOPA, which is characteristic of PD. In carriers of LRRK2 mutations, PET studies with different radiotracers have been able to determine the presence of compensatory mechanisms prior to the development of the disease such as an increase in dopamine turnover, a finding which does not appear in patients already experiencing symptomatic PD.

Studies with 123I-MIBG, performed in small series of patients with genetic-based PD and carriers of R1441G and G2019S mutations in the LRRK2 gene have reported a greater or lesser involvement of cardiac innervation versus idiopathic PD. PET or SPECT studies on PD associated with LRRK2 gene mutations may be more effective than cardiac scintigraphy in both the diagnosis of the disease and in the study of preclinical stages because they are directed at areas with demonstrated neuronal degeneration which correspond with their clinical phenotype.

**Utility of the evaluation of Parkinson’s disease progression**

Neuropathological studies suggest that in PD the loss of dopaminergic neurons follows an exponentially negative course. These studies are extremely limited because they provide transversal estimations and do not take into account intra-individual variability. Longitudinal studies with functional neuroimaging techniques avoid this deficiency because they provide the possibility of in vivo evaluation of PD progression, thereby allowing the observation of both inter- and intra-individual changes.

Initial functional neuroimaging studies using presynaptic dopaminergic markers provided variable results with respect to the annual rate of PD progression, with values ranging from 2 to 10% of loss of nigrostriatal dopaminergic terminals. Differences in the technique (PET versus SPECT) as well as differences in the tracer used could account for this variability. In any case, most of the studies are concordant in that the progression of dopaminergic damage is substantially greater during the first years of the disease, thereby supporting the model of PD suggested in the previously mentioned neuropathological studies. The results of a recent longitudinal PET study confirm that progression of PD does actually follow an exponentially negative course. In this study, patients and healthy controls were followed over an 8-year period with three PET scans (at baseline and at 4 and 8 years), using three different presynaptic dopaminergic markers in each study. This was a very large study including a total of 679 PET studies, allowing the authors to develop a mathematical model for estimating the loss of nigrostriatal dopaminergic terminals, not only during the symptomatic phase of the disease but also during the presymptomatic phase. Fig. 5 shows the curve obtained for one of the tracers (dihydrotetrabenazine, 11C-DTBZ).

Consequently, the following conclusions can be made. Firstly, it appears to be quite clear that the greatest part of dopaminergic damage occurs during the presymptomatic phase of the disease and afterwards, the damage is practically 100% during the first 5–10 years of the symptomatic phase (Fig. 5). After this time, the loss of nigrostriatal dopaminergic terminals is very limited and, in fact, tends to achieve asymptotic values. As shown in Fig. 5, on the appearance of the first motor symptoms (duration of symptoms equal to 0), only 33% of the dopaminergic terminals remain preserved. Secondly, the presymptomatic phase of the disease appears to be considerably longer than suggested by neuropathological studies and some previous functional neuroimaging studies. Thus, it is estimated that in patients with an onset of motor symptoms at 53 years of age, the nigrostriatal dopaminergic damage had begun approximately 17 years before (in other words, at the age of 36). Interestingly, younger patients have a longer presymptomatic period than older patients (25 versus 10 years, respectively) and progress more slowly. And thirdly, even in the most advanced stages of the disease (meaning 30 years after the onset motor symptoms), a significant number of dopaminergic terminals still remain viable (approximately 15%).

In addition to having important conceptual implications, these findings also provide some clinical keys. On one hand, the therapeutic window for potential neuroprotective treatments is enlarged...
to 10–25 years of the presymptomatic phase of the disease. On the other hand, these findings indicate that a part of the motor complications is probably not related to PD progression itself.

**Diagnostic algorithms**

Functional neuroimaging techniques facilitate clinical diagnosis in some patients with parkinsonian syndrome, especially in those presenting initial symptoms, incomplete syndromes or in whose cases the assessment of the pharmacological response is complex. The diversity of techniques currently available in our country may generate confusion with respect to which complementary neuroimaging test may be more useful in each case. In this review, a panel of experts in nuclear medicine and neurology performed an exhaustive review of the reference literature dealing with the usefulness of functional neuroimaging techniques in differential diagnosis of parkinsonian syndrome. This review has allowed a consensus to be made of a series of practical considerations which can be used as recommendations in clinical practice.

Despite the fact that these practical recommendations are focused on functional neuroimaging techniques, neuroimaging by MR should not be "overlooked". It is undoubtedly a fundamental technique in the study of patients with neurological symptoms. The two aspects of functional neuroimaging which may contribute the most to the clinical diagnostic process are the evaluation of the presynaptic dopaminergic system and the neuronal activity of the basal ganglia, as well as of other structures such as the thalamus, mesencephalon, cerebellum and the cortex.

In the case of a patient with a parkinsonian syndrome of uncertain origin, an MR neuroimaging test with T1-weighted and T2-weighted sequences is of initial interest. This test will rule out or consider the presence of a secondary parkinsonism (Fig. 6). Regardless of the result, it may be of interest to detect the possible presence of a striatal dopaminergic deficit (123I-FP-CIT SPECT or 18F-DOPA PET) because this may help to rule out entities such as:

- Secondary Parkinson:
  - Vascular
  - Tumoral
  - Others
- Neurodegenerative parkinsonian syndrome
  - Typical pattern or good pharmacological response
  - A typical symptoms or poor pharmacological response
  - Parkinson disease
  - 18FDG PET
  - MSA, PSP, CBD

**Fig. 6.** Diagnostic algorithm proposed in patients with parkinsonian syndrome of uncertain origin.

*Modified from Brooks.*

**Fig. 5.** Curve of the progression of presynaptic dopaminergic damage according to the results obtained by 11C-DTBZ PET. The data have been normalized with respect to the normal values present during the first years of life so that the curve represents the percentage of dopaminergic terminals at each time. The straight segment in green corresponds to PD. The motor symptoms begin at time 0 (in this case at the age of 53, which was the mean age of onset in the group of patients analyzed). Figure adapted from De la Fuente-Fernández et al.
as ET, PP or VP. If a striatal dopaminergic deficit is confirmed and if the Parkinsonian syndrome has typical patterns, the most probable clinical diagnosis would be PD, especially if the patient responds to pharmacological treatment. Nonetheless, if treatment response is poor or atypical symptoms are present, the imaging test providing the most information for the differential diagnosis of Parkinsonian syndromes is 18F-FDG PET. Depending on the clinical context, cortical metabolism, the most probable cause of the clinical picture would be MSA, PSP or CBD. If the patient presents a picture of associated cognitive decline, the best test for differentiating between Lewy body dementia and Alzheimer’s disease is 123I-FP-CIT SPECT or 18F-DOPA PET. In any case, the clinical aspects should always be the core determinant of the diagnosis.

In hereditary PD, 123I-FP-CIT SPECT or 18F-DOPA PET studies can detect incipient phases of the disease with a tracer uptake pattern similar to that of idiopathic PD. This allows evaluation of clinical and molecular markers for assessing PD progression and future neuroprotective treatments for the early stages of the disease. Progression studies on striatal dopaminergic deficit have also shown that the therapeutic window for potential neuroprotective treatments is wider than previously known and may cover 10–25 years of the presymptomatic phase of the disease.

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