

## **123-I Ioflupane (Datscan®) Presynaptic Nigrostriatal Imaging in Patients with Movement Disorders**

**Angel Soriano Castrejón<sup>1\*</sup>, Ana María García Vicente<sup>1</sup>, Montserrat Cortés Romera<sup>1</sup>, Julia Vaamonde Cano<sup>2</sup>, Sonia Rodado Marina<sup>1</sup>, Victor Manuel Poblete García<sup>1</sup>, Sebastián Ruiz Solís<sup>1</sup> and María del Prado Talavera Rubio<sup>1</sup>**

<sup>1</sup>Department of Nuclear Medicine; <sup>2</sup>Department of Neurology; Ciudad Real Hospital General C/ Tomelloso s/n; Ciudad Real - Spain

### **ABSTRACT**

*123-I Ioflupane (Datscan®) presynaptic imaging has been shown to have a significant utility in the assessment of patients with movement disorders. <sup>123</sup>I Ioflupane SPECT is able to distinguish between Parkinson's disease (PD) and other forms of parkinsonism without degeneration of the nigrostriatal pathway, including a common movement disorder such as essential tremor, and to assess disease progression in PD and other neurodegenerative disorders involving the substantia nigra.*

**Key words:** 123-I Ioflupane, dopamine transporter imaging, movement disorders, Parkinson's disease

### **INTRODUCTION**

Movement disorders represent the most prevalent neurological disease after dementia (Alvarez et al., 2001). Essential tremor (ET) is the most common disorder, followed by Parkinson disease (PD), drug-induced parkinsonism, vascular pseudoparkinsonism, and parkinsonism plus disorders, among the most relevant (Salemi et al., 1994; Martí-Masso et al., 1996).

Diagnosis of these diseases is clinical, mainly based on history (family history, drug intake, cerebrovascular disease, etc.), examination, course, and treatment response. While, in theory, these conditions appear to have typical clinical and evolutionary features that may differentiate them, in practice, such features are shown not to be unique to one disease and often occur overlapped, particularly in elderly patients, which makes

differential diagnosis difficult, and years may elapse from symptoms onset to final diagnosis.

Post-mortem pathological studies have shown that up to 25% of patients diagnosed of PD do not have this disease, but it is suspected that the range of misdiagnosis in early stages by a "non specialist" is possibly greater (Rajput et al., 1991; Hughes et al., 1992).

Dopamine transporter (DAT) imaging with tropane derivatives such as FP-CIT (I-123 Ioflupane) and  $\beta$ -CIT has been developed to directly measure degeneration of dopamine (DA) presynaptic terminal and may be used to quantify changes in DAT density (Tatsch et al., 2001). Assessment of binding to presynaptic dopamine transporters is preferred over investigations of postsynaptic receptors because, in virtually all degenerative parkinsonian syndromes, presynaptic terminals are involved, while postsynaptic receptors may be preserved. In addition, it has an

\* Author for correspondence

indisputable role in confirmation or exclusion of parkinsonian syndromes when clinical symptoms are doubtful or unclear, and is able to identify patients even before they develop the definitive clinical symptoms (Innis et al., 1993).

DaTSCAN imaging may have multiple clinical applications, but the most relevant are the differential diagnosis of PD and other parkinsonian syndromes with presynaptic integrity, for early diagnosis of PD in preclinical

stages, and in longitudinal studies in PD to determine progression of dopaminergic loss. However, its significance for study and research of various conditions that will be discussed in this review is becoming evident with increased use.

### **Degenerative parkinsonisms**

Different diseases responsible for these conditions are listed in Table 1.

**Table 1** - Causes of degenerative parkinsonism:

---

Parkinson's disease
- Multisystem atrophy
Nigrostriatal degeneration
Olivopontocerebellar atrophy
Shy-Drager syndrome
- Progressive supranuclear palsy
- Diffuse Lewy body disease
- Corticobasal degeneration
- Alzheimer disease and Pick's disease.

---

### **Parkinson's disease**

PD is a progressive neurodegenerative disease affecting approximately 1% of the elderly population. While PD has a defined clinical picture, it is difficult to diagnose in its early stages because symptoms and signs are subtle, and the disease is diagnosed at a later stage (at approximately five years), when cardinal signs appear. Moreover, while its course is progressive, it is not predictable, and it is not possible to know the prognosis of a patient at disease onset. It is, therefore, important to diagnose the disease in its early stages with the help of all available diagnostic methods to rule out symptomatic parkinsonisms or parkinsonian syndromes, other than idiopathic PD, and start specific treatment.

In patients with recent onset PD or hemiparkinsonism, a 50% decrease in presynaptic transporters has been observed in the putamen contralateral to the symptomatic side, and a 30% decrease in the putamen ipsilateral to symptoms (Marek et al., 1996; Tissingh et al., 1998).

Evaluation of pre-synaptic dopaminergic integrity using 123-I Ioflupane in PD is a useful tool to: diagnose early stages, characterize disease severity and progression (Seibyl et al., 1995; Rinne et al., 1995), predict PD bilateralization in patients in a very early stage (when symptoms often involve only one side of the body) (Marek et al., 2001), assess the efficacy of agents slowing the course of

disease and, more controversially, differentiate an idiopathic disorder from other forms of parkinsonian syndromes (Innis et al., 1993).

Individual studies have shown that DAT density is reduced in neurodegenerative parkinsonisms as compared to healthy and ET subjects (Parkinson Study Group, 2000; Asenbaum et al., 1997; Messa et al., 1998; Booij et al., 2001; Vaamonde et al., 2004). Therefore, normal binding to presynaptic transporters rules out, with a high diagnostic accuracy, the presence of PD or other parkinsonian syndromes. Thus, such studies are an excellent tool for discriminating between healthy subjects, ET patients, and parkinsonian patients (Benamer et al., 2000; Catafau et al., 2004; Naumann et al., 1997; Jeon et al., 1998; Booij et al., 1999; García et al., 2004). However, some studies have shown changes in ET patients that reflect, according to different authors, a true loss of DAT. This supports the hypothesis that ET may be a syndrome overlapping with PD in a proportion of cases (Pahwa et al., 1993; Lou et al., 1991). It should also be noted that ET patients have an increased incidence of PD, which makes their diagnosis even more difficult (Gwinn et al., 1998).

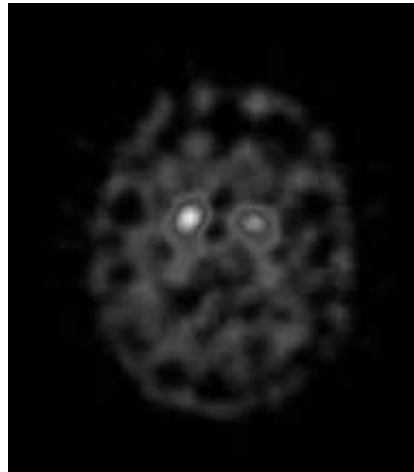
### ***Sequential studies. Assessment of disease progression in PD***

Brain SPECT of DAT provides a quantitative biomarker for progression of dopaminergic

degeneration in PD. (Nurmi et al., 2000; Staffen et al., 2000; Pirker et al., 2002). This fact is because DAT loss in PD agrees with loss of nigrostriatal dopaminergic neurons (Kaufman et al., 1991) (Fig. 1).

The progression rate of dopaminergic degeneration is faster in PD than in normal subjects (Winogrodzka et al., 2003), and a correlation appears to exist between the range of decrease in DAT binding in SPECT imaging and disease duration (Marek et al., 1997). Dopaminergic degeneration in PD appears to decrease during the

course of disease (Pirker et al., 2002). The mean progression rate of dopaminergic degeneration in the caudate is slower than in the putamen, suggesting that caudate nucleus function is relatively preserved in early stage PD (Winogrodzka et al., 2003). A relative annual decrease of approximately 5%-10% has been found in global uptake rates with 123- $\beta$ -CIT (Winogrodzka et al., 2003; Fearnley et al., 1991). In addition, DAT imaging may be of value for assessing neuroprotective therapies (Pirker et al., 2002).



**Figure 1** - Transaxial section of 123-I Ioflupane SPECT in a PD patient.

Various authors have shown that treatment with L-dopa or dopaminergic agonists in PD does not cause significant occupation or modulation in the number of striatal DAT labeled with  $\beta$ -CIT (Innis et al., 1999; Ahlskog et al., 1999). However, it should be noted that all studies are limited by the small sample size and short treatment duration. The possibility that drug effects could emerge in studies with a larger sample or longer duration is, therefore, not excluded (Winogrodzka et al., 2003).

Various cross-sectional studies have found a correlation between binding rates with  $\beta$ -CIT and the UPDRS motor scale (Seibyl et al., 1995; Tissingh et al., 1998; Asenbaum et al., 1997). However, when longitudinal studies were conducted, no correlation was shown between the annual percent change in putamen, caudate, or whole striatal body (SB) and clinical progression or severity of the disease as measured by the

UPDRS scale (Asenbaum et al., 1997; Seibyl et al., 1995).

#### **Progressive supranuclear palsy (PSP)**

Progressive supranuclear palsy accounts for 20% of all parkinsonisms. While a similar degree of presynaptic involvement was initially found in caudate and putamen (Messa et al., 1998; Kish et al., 1985), involvement may sometimes be indistinguishable from PD (Varrone et al., 2001; Brücke et al., 1997). Therefore, the diagnosis based on scintigraphic findings only is not recommended.

#### **Multisystem atrophy (MSA)**

Multisystem atrophy consists of a group of degenerative diseases affecting up to 10% of patients with parkinsonism (Quinn, 1989). A dysfunction in the nigrostriatal dopaminergic circuit exists in all of them. Response of such diseases to L-dopa is generally poor, and, in some

responding patients (up to 25%), is usually transient (Wenning et al., 1994). Its scintigraphic representation in DAT imaging is indistinguishable from PD (Eidelberg et al., 1995;

Antonini et al., 1997), and combined imaging of postsynaptic receptors with <sup>123</sup>I IBZM is sometimes required for differential diagnosis (Table 2).

**Table 2** - Scintigraphic differential diagnosis of parkinsonian syndromes

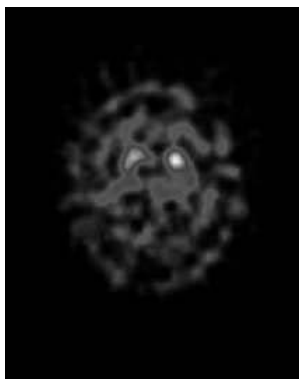
<i>Syndromes</i>	<i>DAT binding</i>	<i>DAR binding</i>
PD	decreased	preserved
MSA	decreased	decreased
PSP	decreased	decreased
CBD	decreased	decreased
Drug-induced	preserved	decreased
Dystonia	preserved	increased
DLB	decreased	decreased
ET	preserved	¿?

(CBD: corticobasal degeneration, DLB: dementia with Lewy bodies, DAR: dopamine receptors)

### **Dementia with Lewy bodies (DLB)**

Dementia with Lewy bodies is the second leading cause of dementia in the elderly after Alzheimer disease (AD) (Byrne et al., 1989). These patients usually have a picture of parkinsonism responding to L-dopa, associated with dementia with visual hallucinations and a fluctuating mental state. However, these latter signs are not specific for this condition, but may also occur in AD (Forstl et al., 1993).

In DLB, a lower activity of presynaptic DAT (Fig. 2) (Walker et al., 2002; Donnemiller et al., 1997; O'Brien et al., 2004) and postsynaptic receptors (Walker et al., 1997) has been shown in SB, unlike in AD. Moreover, Walker et al. (2004) found a consistent, non-asymmetrical decrease in uptake between caudate and putamen, an observation that could also differentiate this condition from PD.



**Figure 2** - Transaxial section of <sup>123</sup>I Ioflupane SPECT in a DLB patient.

### **Secondary parkinsonisms**

Secondary parkinsonisms are due to a known cause and account for 25% to 50% of all parkinsonisms (Martí-Massó et al., 1998; Muñoz et al., 1998). Table 3 lists their multiple causes, but we will focus on the most common conditions: drug-induced parkinsonism and the so-called vascular pseudoparkinsonism.

### **Drug-induced parkinsonism**

The frequency of drug-induced parkinsonian syndromes is variable, ranging from 20% to a little more than 50% depending on the population studied. They represent the second leading cause of parkinsonism.

**Table 3** - Causes of secondary parkinsonism:

---

- Drugs
- Toxins
MPTP, manganese, carbon monoxide, methanol
- Metabolic disorders
Hypoparathyroidism
Hypothyroidism
Acquired hepatocerebral degeneration
- Vascular
- Age-associated gait disorders
- Post-encephalitic parkinsonism and infectious diseases
- Normotensive hydrocephalus
- Post-traumatic encephalopathy
- Space-occupying lesions
Subdural hematoma, tumors, aneurysms
- Paraneoplastic

---

(MPTP: methyl-phenyl-tetrahydropyridine)

The number of drugs that may induce a parkinsonian syndrome or aggravate motor symptoms in PD is very high and increasing (Table 4), not only because of the introduction of new drugs that have this effect, but also because drugs previously used have been found to have such an effect (Van Gerpen et al., 2002; Montastruc et al., 1994).

Since the parkinsonian syndrome is biochemically characterized by a DA deficiency in the striatum, and this deficiency is subclinical until it exceeds 75%-80%, the syndrome may occur months or years after the start of the dopamine blocking agent, depending on its potency and dose. It is also dependent on the patient's age, (i.e., on his initial DA deficiency), and sex, with a greater predisposition in women because of their lower body mass and a possible estrogenic influence (Marsden et al., 1980; Gershanik et al., 1993). Patient recovery in this type of secondary parkinsonism usually occurs weeks after drug removal, but may take up to one year, and the condition may even become irreversible.

Clinical manifestations of this type of parkinsonism are often indistinguishable from PD. Until the patient is shown to be symptom-free after medication removal, it cannot be stated whether one is facing a drug-induced parkinsonism or a PD worsened by drugs. In addition, patients in the latter group will be more predisposed to experiencing iatrogenic parkinsonism because of their baseline DA deficiency. This fact would warrant use of 123-I Ioflupane SPECT, since a

normal scintigraphic study would suggest a diagnosis of drug-induced parkinsonism, while an abnormal study would suggest a PD aggravated by drugs.

**Table 4** - Drugs causing parkinsonism:

---

<i>Neuroleptics (block dopamine)</i>
Phenothiazines
Butyrophenones
Substituted benzamides (sulpiride)
<i>Anti-histamines (H1)</i>
<i>Drugs depleting DA presynaptic stores</i>
Reserpine
Tetrabenazine
<i>Calcium channel blockers</i>
Cinnarizine
Flunarizine
<i>Antiemetic drugs</i>
Domperidone
Metoclopramide (Reglan)
Triethylperazine
Metopimazine
<i>Serotonin reuptake inhibitors</i>
<i>Lithium</i>
<i>Sympathomimetics</i>
<i>Antidepressants</i>
Tricyclic antidepressants
Fluoxetine
<i>Valproic acid</i>
<i>Antiarrhythmics</i>
Amiodarone
Verapamil
Amlodipine
<i>Procholinergics</i>
<i>Chemotherapeutic</i>
<i>Amphotericin B</i>
<i>Estrogens</i>
<i>Drugs for menopausal treatment</i>
Veralipride
<i>Other</i>
Alphamethyl-dopa
Flupentixole

---

### Vascular pseudoparkinsonism (VP)

Approximately 3% to 6% of all cases of parkinsonism may have a vascular cause (Foltynie et al., 2002; De Rijk et al., 1997). In Spain, a prevalence of 2.5% of all patients with parkinsonism has been found (Benito-León et al., 2003). However, such percentages may underestimate the actual figures because of the lack of autopsy studies (Bower et al., 2002), and some reports based on clinical, neuroradiological, and pathological studies suggest that prevalence could reach 12% (Baldereshi et al., 2000; Reuck et al., 1980; Mancardi et al 1988).

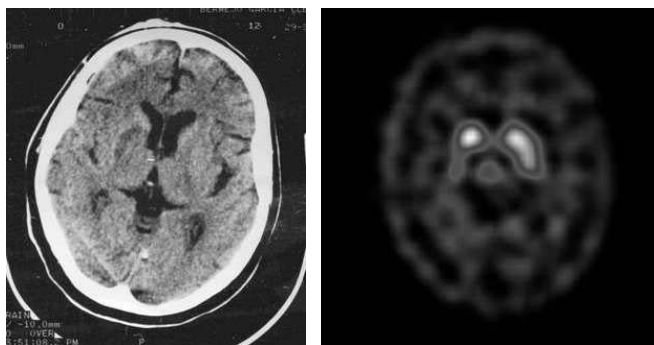
While vascular risk factors are more frequent in VP (81%) than in PD (32%) (Demirkiran et al., 2001), the presence of an increased number of risk factors in the elderly population, as well as the greater prevalence of PD in this age group, increases the possibility that both conditions may coexist. Prevalence of vascular encephalopathy in PD patients ranges from 6% to 44% according to different series (Chang et al., 1992; Sibon et al., 2004; Piccini et al., 1995; Jellinger et al., 2003), and similar prevalence rates have been found in other forms of parkinsonism, such as progressive supranuclear palsy (35%) (Dubinsky et al., 1987). In addition, the presence of vascular encephalopathy, or even the existence of vascular risk factors, may aggravate the symptomatic picture in a patient with known PD (Papapetropoulos et al., 2004).

The most relevant clinical characteristics of VP include: gait disorder, predominance in lower half of the body, postural instability, stiffness, pyramidal signs, and poor or no response to L-dopa (Tolosa et al., 1984; Trenkwalder et al., 1995), all of them occurring in a patient with evidence of cerebrovascular damage with no signs of other degenerative diseases, intake of antidopaminergic drugs, or hydrocephalus that could induce parkinsonism. Final diagnosis is made by post-mortem histological confirmation (absence of depigmentation or presence of Lewy bodies in substantia nigra) (Jellinger et al., 1996). Detection of structural lesions in a patient in the morphological image does not guarantee that these are the origin of his parkinsonism, since, while classical vascular parkinsonism involves basal ganglia, most cases show diffuse changes in the subcortical white matter (Mark et al., 1995; Sibon et al., 2004). It has also been shown that there is no correlation between the size, number, and

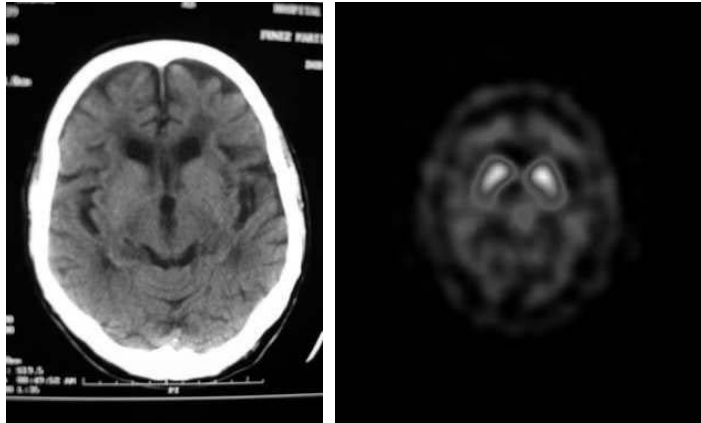
location of infarctions at both cortical and subcortical level in the white matter and clinical presentation, since many patients with cerebrovascular disease do not have signs of extrapyramidal disease.

A normal or slightly decreased striatum uptake has been found in VP with  $^{123}\text{I}$   $\beta$  CIT SPECT (Gerschlager et al., 2002; Hamano et al., 2000; Sasaki et al., 2003), and similar findings have been made with TRODAT-1 Tc-99m and DaTSCAN (Tzen et al., 2001; Lorberboym et al., 2004). This observation agrees with results from clinical and pathological studies showing sparing of the presynaptic dopaminergic circuit in VP patients (Yamanouchi et al., 1997; Jellinger KA et al., 1996).

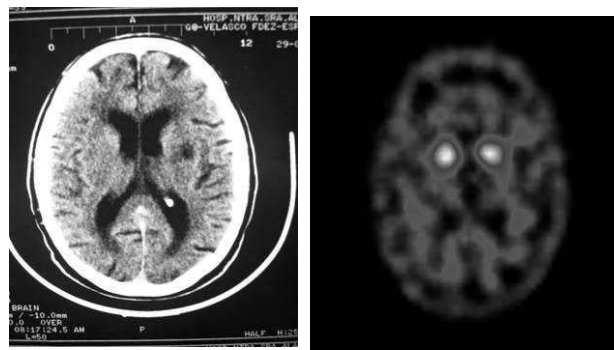
As regards VP types, different pathophysiological mechanisms may lead to different VP phenotypes as a result of its wide clinical spectrum. Zijlmans et al. (1995) proposed two types of VP, a type with an acute onset and lesion in subcortical grey nuclei (striate, globus pallidus, and thalamus), and another type with an insidious onset and diffuse lesions distributed in the white matter. Chang et al. (1992) described three anatomical patterns of brain lesions consistent with VP, each with a different prognosis. The lack of a standardized classification of the different types of VP led us to propose (Garcia et al., 2005), in a study conducted on patients with parkinsonian symptoms and cerebrovascular disease, their division into structural VP, when direct vascular lesion is found in striatum (Fig. 3), and functional VP, when vascular lesions do not affect striatum directly (which does not mean that it is less strongly affected), but functionally, through a mechanism of lesion of interconnecting pathways (Fig. 4).



**Figure 3 - Structural VP.** CT: Infarct in right striatum. Uptake defect in presynaptic DAT image corresponding to direct vascular damage.



**Figure 4 - Functional VP.** CT: Frontal atrophy and leukoaraiosis. Normal presynaptic DAT image.



**Figure 5 - Mixed VP.** CT: Lacunar infarct in left SB, near the putamen. Presynaptic DAT image showing involvement of both putamina.

This classification is considered to be methodologically adequate since, while involving pathophysiological mechanisms, it is supported by the anatomical bases of conventional radiology and functional information from nuclear medicine. Our diagnostic classification attempts to include mixed parkinsonism patients with unilateral, direct striatum vascular involvement and SPECT with more extensive involvement (bilateral) than that shown in the morphological image (Fig. 5).

Therefore, since vascular risk factors, a history of stroke, parkinsonism with atypical signs or predominating in lower limbs (without the typical resting tremor), or the lack of response to L-dopa are non-specific data, final diagnosis should be based on convergence of clinical and neuroimaging data (evidence of infarct in cortical-

subcortical motor circuits, multilacunar state, or vascular subcortical encephalopathy), and a normal DAT SPECT (Chang et al., 1992).

#### **Influence of age and sex on study interpretation**

It is estimated that dopamine transporter (DAT) concentration in the striate decreases with age by up to 65%-75%. Based on current life expectation, this means a decrease of approximately 10% per decade (Tissingh et al., 1997; De Keyser et al., 1990). Various studies have documented a decrease in DAT density with age in healthy volunteers, irrespective of the radioactive drug used for presynaptic evaluation (Mozley et al., Volkow et al., 1996; 1999; Tissingh et al., 1998). Nigrostriatal degeneration normally occurring with age may be associated with moderate parkinsonian

signs. This decrease is characteristically linear and symmetrical, with a similar involvement of caudate and putamen (De Keyser et al., 1990; Allard et al., 1989; Zelnik et al., 1986). A certain asymmetry has also been shown, with a predominant uptake in the left versus the right hemisphere (van Dyck et al., 2002; Mozley et al., 1996), that could be related to an increased volume of left basal ganglia in right-handed control subjects (Peterson et al., 1993). Because of this fact, it is very important to establish normal ranges in the different age groups, and to select an age-specific cut-off value for disease. This is highly advisable if one wants to diagnose patients in very early stages of PD, or screen high-risk populations such as relatives of parkinsonian patients (Weng et al., 2004).

When interpreting a study in an elderly patient, one must also take into account the possibility that decreased uptake may be caused by a decreased striatum size secondary to atrophy. If a symmetrical DAT involvement is seen, affecting both caudate and putamen, the functional image should be assessed together with the morphological image to rule out severe atrophy with ventriculomegaly causing a partial volume effect on striatum (Murphy et al., 1992). There are still no conclusive results regarding the influence of sex, as some authors have found a greater DAT density in women (Lavalaye et al., 2000), while others have seen a decrease compared to men (van Dyck et al., 1995).

## CONCLUSION

Functional DAT neuroimaging is a highly useful tool for diagnosis of PD in an early stage, and to differentiate PD from other parkinsonian syndromes.

## RESUMO

A imagem pré-sináptica através de 123-I Ioflupane (Datscan®) tem mostrado um papel significativo na avaliação de pacientes com distúrbios do movimento. 123-I Ioflupane SPECT é capaz de distinguir entre Mal de Parkinson (MP) e outras formas de parkinsonismo sem degenerações da via nigroestriatal incluindo um distúrbio comum

de movimento parecido com o tremor essencial e para medir a evolução da doença no Mal de Parkinson e outros distúrbios neurodegenerativos envolvendo a *substantia nigra*.

## REFERENCES

- Ahlskog, J. E. (1999), The effect of dopamine agonist therapy on dopamine transporter imaging in Parkinson's disease. *Mov Disord.*, **14**, 940-946.
- Antonini, A. (1997). Complementary PET studies of striatal neuronal function in the differential diagnosis between multiple system atrophy and Parkinson's disease. *Brain.*, **120**, 2187-2195.
- Allard, P. (1989), Age-correlated loss of dopamine uptake sites with (3H)GBR-12935 in human putamen. *Neurobiol Aging.*, **10**, 661-664.
- Alvarez, G.L. (2001), SPECT en la enfermedad de Parkinson y otros trastornos del movimiento. *Rev Mex de Neurociencia*, **2**, 169-175.
- Asenbaum, S. (1997), Imaging of dopamine transporters with iodine-123 B-CIT and SPECT in Parkinson's disease. *J Nucl Med.*, **38**, 1-6.
- Baldereschi, M. (2000), Parkinson's disease and parkinsonism in a longitudinal study. Two fold higher incidence in men. *Neurology*, **55**, 1358-63.
- Benamer, T.S. (2000), Accurate differentiation of parkinsonism and essential tremor using visual assessment of [123I]-FP-CIT SPECT imaging: the [123I]-FP-CIT study group. *Mov Disord.*, **15**, 503-510.
- Benito-León, J (2003), Prevalence of PD and other types of parkinsonism in three elderly populations of central Spain. *Mov Disord*, **18**, 267-274.
- Booij, J. (2001), The clinical benefit of imaging striatal dopamine transporters with [123I] FP-CIT SPET in differentiating patients with presynaptic parkinsonism from other forms of parkinsonism. *Eur J Nucl Med.*, **28**, 266-272.
- Booij, J. (1999), Imaging of the dopaminergic neurotransmission system using single-photon emission tomography and positron emission tomography in patients with parkinsonism. *Eur J Nucl Med.*, **26**, 171-182.
- Bower, J.H. (2002), Clinical correlates of the pathology underlying parkinsonism: a population perspective. *Mov Disor.*, **17**, 910-916.
- Brücke, T.(1997), Measurement of dopaminergic degeneration in Parkinson's disease with 123-I beta-CIT and SPECT. Correlation with clinical findings and comparison with multiple system atrophy and progressive supranuclear palsy. *J Neural Transm.*, **50**, 9-24.



- Byrne, E.J. (1989). Diffuse Lewy body disease: clinical features in 15 cases. *J Neurol Neurosurg Psychiatry*, **52**, 709-717.
- Catafau, A.M. (2004). Impact of dopamine transporter SPECT using 123I-Ioflupane on diagnosis and management of patients with clinically uncertain Parkinsonian syndromes. *Mov Disord.*, **19**, 1175-1182
- Chang, C.M. (1992), Vascular pseudoparkinsonism. *Acta Neurol Scand.*, **86**, 588-592.
- Demirkiran, M. (2001), Vascular parkinsonism: a distinct , heterogeneous clinical entity. *Acta Neurol Scand.*, **104**, 63-67.
- De Keyser, J. D. (1990), Age related changes in the human nigrostriatal dopaminergic system. *Ann Neurol.*, **27**, 157-161.
- De Rijk, M.C. (1997), Prevalence of parkinsonism and parkinson's disease in Europe: the Europarkinson Collaborative Study. *J Neurol Neurosurg Psychiatry*, **62**, 10-15.
- Donnemiller, E. (1997), Brain perfusion scintigraphy with 99mTc-HMPAO or 99mTc-ECD and 123-I beta-CIT SPECT in dementia of the Alzheimer type and diffuse Lewy body disease, *Eur J Nucl Med.*, **24**, 320-325.
- Dubinsky, R.M. (1987), Progressive supranuclear palsy and the multi-infarct state. *Neurology*, **37**, 570-576.
- Eidelberg, D. (1995), Early differential diagnosis of Parkinson's disease with 18-F FDG and positron emission tomography. *Neurology*, **45**, 1995-2004.
- Fearnley, J. (1991), Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain*, **114**, 2283-2301.
- Foltyniec, T. (2002), Vascular parkinsonism: a review of the precision and frequency of the diagnosis. *Neuroepidemiology*, **21**, 1-7.
- Forstl, H. (1993), The Lewy-body variant of Alzheimer's disease. Clinical and pathological findings. *Br J Psychiatry*, **162**, 385-392.
- García Vicente, A.M. (2004), Utilidad de la imagen de transportadores de dopamina (SPECT cerebral con Ioflupano-I-123) en la valoración de los trastornos del movimiento. *Rev Esp Med Nucl.*, **23**, 245-252.
- García Vicente, A. M. (2005), SPECT con Ioflupano I-123 en la catalogación de pacientes con síndrome parkinsoniano y vasculopatía cerebral. *Rev Esp Med Nucl.* (in press).
- Gerschlager, W. (2002), 123-I beta-CIT SPECT distinguishes vascular parkinsonism from Parkinson's disease. *Mov Disord.*, **17**, 518-523.
- Gershanik, O.S (1993), Drug-induced movement disorders. *Curr Opin Neurol Neurosurg.*, **6**, 369-76.
- Gwinn, K. (1998), The Michigan kindred: a large family with Parkinson's disease. *Mov Disord.*, **13**, 60-5.
- Hamano, T. (2000), Dopamine transporter SPECT in patients with Parkinson's disease. *Kaku Igaku.*, **37**, 125-9.
- Hughes, A. J. (1992), Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry*, **55**, 181-4.
- Innis, R. B. (1993), Single photon emission computed tomographic imaging demonstrates loss of striatal dopamine transporters in Parkinson disease. *Proc Natl Acad Sci.*, **90**, 11965-11969.
- Innis, R. B. (1999), Effect of treatment with L-dopa/carbidopa or L-selegiline on striatal dopamine transporter SPECT imaging with 123 beta CIT. *Mov Disord.*, **14**, 436-442.
- Jellinger, K.A. (2003), Prevalence of cerebrovascular lesions in Parkinson's disease. A postmortem study. *Acta Neuropathol.*, **105**, 415-419.
- Jellinger, K. A. (1996), Parkinsonism due to Binswanger's subcortical arteriosclerotic encephalopathy. *Mov Disord.*, **11**, 461- 462.
- Jeon, B.S. (1998), Dopamine transporter density measured by 123 I beta-CIT SPECT is normal in DOPA-responsive dystonia. *Ann Neurol.*, **43**, 792-800.
- Kaufman, M.J. (1991), Severe depletion of cocaine recognition sites associated with the dopamine transporter in Parkinson's diseased striatum. *Synapse*, **9**, 43-49.
- Kish, S.J. (1985), Progressive supranuclear palsy: relationship between extrapyramidal disturbances, dementia, and brain neurotransmitters markers. *Ann Neurol*, **18**, 530-536.
- Lavalaye, J. (2000), Effect of age and gender on dopamine transporter imaging with 123-I-FP-CIT SPECT in healthy volunteers. *Eur J Nucl Med*, **27**, 867-869.
- Lorberboym, M. (2004), 123I-FP-CIT SPECT imaging of dopamine transporters in patients with cerebrovascular disease and clinical diagnosis of vascular parkinsonism. *J Nucl Med.*, **45**, 1688-1693.
- Lou, J. (1991), Essential tremor: clinical correlates in 350 patients. *Neurology*, **41**, 224-238.
- Mancardi, G.L. (1988), Lacunae and cribriform cavities of the brain. Correlations with pseudobulbar palsy and parkinsonism. *Eur Neurol.*, **28**, 11-17.
- Marek, K. (1996), 123 I beta-CIT SPECT imaging demonstrates bilateral loss of dopamine transporters in hemiparkinson's disease. *Neurology*, **46**, 231-237.
- Marek, K. (1997), 123 I- beta CIT: assessment of progression in Parkinson's disease. *Neurology*, **48**, 207-208.
- Marek, K. (2001), 123 I-beta- CIT SPECT imaging assessment of the rate of Parkinson's disease progression. *Neurology*, **57**, 2089-2094.
- Mark, M.H. (1995), Binswanger's disease presenting as levo-dopa responsive parkinsonism: clinicopathologic study of three cases. *Mov Disord.*, **10**, 450-454.
- Marsden, C.D. (1980), The pathophysiology of extrapyramidal side effects of neuroleptic drugs. *Psychol Med.*, **10**, 55-72.

- Martí-Massó, J.F. (1998), Parkinsonismos secundarios. En: Jiménez-Jimenez FJ. Luquin MR, Molina JA. (eds). Tratado de los trastornos del movimiento. Madrid, 513-542.
- Martí-Massó, J.F. (1996), Drug-induced or aggravated Parkinsonism: clinical signs and the changing pattern of implicated drugs. *Neurologia*, **11**, 10-5.
- Messa, C. (1998), Differential distribution of striatal 123 I beta-CIT in Parkinson's disease and progressive supranuclear palsy, evaluated with single-photon emission tomography. *Eur J Nucl Med.*, **25**, 1270-1276.
- Montastruc, J.L. (1994), Drug-induced parkinsonism: a review. *Fundam Clin Pharmacol.*, **8**, 293-306.
- Mozley, P.D. (1996), Iodine- 123- IPT SPECT imaging of CNS dopamine transporters: nonlinear effects of normal aging on striatal uptake values. *J Nucl Med.*, **37**, 1965-1970.
- Muñoz, E (1998), Otras causas de parkinsonismo. En: Jiménez-Jimenez FJ. Luquin MR, Molina JA. (eds). Tratado de los trastornos del movimiento, Madrid; 543-564.
- Murphy, D.G.M. (1992), Age-related differences in volumes of subcortical nuclei, brain matter and cerebrospinal fluid in healthy men as measured with magnetic resonance imaging. *Arch Neurol.*, **49**, 839-845.
- Naumann, M. (1997), 123 I beta-CIT SPECT in DOPA-responsive dystonia. *Mov Disord.*, **12**, 448-451.
- Nurmi, E. (2000), Progression in Parkinson's disease: a positron emission tomography study with a dopamine transporter ligand 18-FCFT. *Ann Neurol.*, **47**, 804-808.
- O'Brien, J.T., (2004). Dopamine transporter loss visualized with FP-CIT SPECT in the differential diagnosis of dementia with Lewy bodies. *Arch Neurol.*, **61**, 919-925
- Pahwa, R. (1993), Is there a relationship between Parkinson's disease and essential tremor?. *Clin Neuropharmacol.*, **16**, 30-35.
- Papapetropoulos, S. (2004), Effect of vascular disease on late onset Parkinson's disease. *Eur J Neurol.*, **11**, 231-235.
- Parkinson Study Group. (2000), A multicenter assessment of dopamine transporter imaging with DOPASCAN/SPECT in parkinsonism. *Neurology.*, **55**, 1540-1547.
- Peterson, B.S. (1993), Human basal ganglia volume asymmetries on magnetic resonance images. *Magn Res Imaging.*, **11**, 493-498.
- Piccini, P. (1995), White matter hyperintensities in Parkinson's disease: clinical correlations. *Arch Neurol.*, **52**, 191-194.
- Pirker, W. (2002), Progression of dopaminergic degeneration in Parkinson's disease and atypical parkinsonism: a longitudinal Beta-CIT SPECT study. *Mov Disord.*, **17**, 45-53.
- Quinn, N. (1989), Multiple system atrophy-the nature of the beast. *J Neurosurg Phychiatry.*, **52**, 78-89.
- Rajput, A. H. (1991), Accuracy of clinical diagnosis in parkinsonism- a prospective study, *Can J Neurol Sci*, **18**, 275-278.
- Reuck, J. (1980), Parkinsonism in patients with cerebral infarcts. *Clin Neurol Neurosurg.*, **82**, 177-185.
- Rinne, J.O. (1995), Striatal dopamine transporters in different disability stages or Parkinson's disease studied with 123-I beta-CIT SPECT. *Parkinsonism and Related Disorders*, **22**, 47-51.
- Salemi, G. (1994), Prevalence of essential tremor: a door-to-door survey in Terrasini Sicily, Sicilian Neuro-Epidemiologic Study Group. *Neurology*, **44**, 61-64.
- Sasaki, T. (2003), SPECT imaging using 123 I beta-CIT and 123 I- IBF in extrapyramidal diseases. No To Shinkei., **55**, 57-64.
- Seibyl, J. (1995), Decreased SPECT 123 I beta-CIT striatal uptake correlates with symptom severity in idiopathic Parkinson's disease. *Ann Neurol.*, **38**, 589-598.
- Sibon, I. (2004). Parkinsonismo vascular. *J Neurology* (edición española), **2**, 253-64.
- Sibon, I. (2004), Vascular parkinsonism. *Current Opin in Neurol.*, **17**, 49-54.
- Staffen, W. (2000), Measuring the progression of idiopathic Parkinson's disease with 123 I-BetaCIT SPECT. *J Neural Transm.*, **107**, 543-552.
- Tatsch, K. (2001), Imaging of the dopaminergic system in parkinsonism with SPET. *Nucl Med Commun*, **22**, 819-827.
- Tissingh, G. (1998), Drug-naive patients with Parkinson's disease in Hoehn and Yahr stages I and II show a bilateral decrease in striatal dopamine transporters as revealed by iodine-123- I beta-CIT SPECT. *J Neurol.*, **245**, 14-20.
- Tissingh, G. (1997) Parkinson's disease reveals a smaller decline in dopamine transporters with age than in controls. *Eur J Nucl Med.*, **24**, 1171-1174.
- Tolosa, E.S. (1984), Parkinsonism and basal ganglia infarcts. *Neurology*, **34**, 1516-18.
- Trenkwalder, C. (1995), Postural stability differentiates "lower body" from idiopathic parkinsonism. *Acta Neurol Scand.*, **91**, 444-52.
- Tzen, K.Y. (2001), Differential diagnosis of Parkinson's disease and vascular parkinsonism by 99m-Tc-TRODAT-1. *J Nucl Med.*, **42**, 408-413.
- Vaamonde, J. (2004), Estudio pre y postsináptico de la vía nigroestriada mediante DATSCAN o IBZM SPECT en el diagnóstico diferencial del parkinsonismo en 75 pacientes. *Neurologia*, **19**, 292-300.
- Van Dyck, C.H. (1995), Age-related decline in striatal dopamine transporter binding with iodine-123-B CIT SPECT. *J Nucl Med.*, **36**, 1175-1181.

- Varrone, A. (2001), 123-I beta CIT SPECT imaging demonstrates reduced density of striatal dopamine transporters in Parkinson's disease and multiple system atrophy. *Mov Disorders.*, **16**, 1023-1032.
- Van Dyck, C.H. (2002), Age-related decline in dopamine transporters. *Am J Geriatr Psychiatry*, **10**, 36-43.
- Van Gerpen JA. (2002), Drug-induced parkinsonism. *Neurolog.*, **8**, 363-370.
- Volkow, N.D (1996), Dopamine transporters decrease with age. *J Nucl Med.*, **37**, 554-559.
- Walker, Z. (1997), Dementia with Lewy bodies: a study of post-synaptic dopaminergic receptors with iodine-123 iodobenzamide SPECT. *Eur J Nucl Med.*, **24**, 609-614.
- Walker, Z. (2002), Differentiation of dementia with Lewy bodies from Alzheimer's disease using a dopaminergic presynaptic ligand. *J Neurosurg Psychiatry*, **73**, 134-140.
- Walker, Z. (2004), Striatal dopamine transporter in dementia with Lewy bodies and Parkinson disease. A comparison. *Neurology*, **62**, 1568-1572.
- Weng, Y-H. (2004), Sensitivity and specificity of 99mTc-TRODAT-1 SPECT imaging in differentiating patients with idiopathic Parkinson's disease from healthy subjects. *J Nucl Med.*, **45**, 393-401.
- Wenning, G.K. (1994), Clinical features and natural history of multiple system atrophy. An analysis of 100 cases. *Brain.*, **117**, 835-845.
- Winogrodzka, A. (2003), 123 beta-CIT SPECT is a useful method for monitoring dopaminergic degeneration in early stage Parkinson's disease. *J Neurol Neurosurg Psychiatry*, **74**, 294-298.
- Yamanouchi, H. (1997), Neurological signs and frontal white matter lesions in vascular parkinsonism. *Stroke.*, **28**, 965-969.
- Zelnik, N. (1986), Decreased density of human striatal dopamine uptake sites with age. *Eur J Pharmacol.*, **126**, 175-176.
- Zijlmans, J.C.M (1995), MRI in patients with suspected vascular parkinsonism. *Neurology*, **45**, 2183-2188.

Received: July 04, 2005;  
Revised: July 14, 2005;  
Accepted: August 01, 2005.