Abstract.—Objective. To determine the diagnostic accuracy of FP-CIT SPECT in entities with and without presynaptic involvement of the nigral-striatal dopaminergic pathway in a large group of patients with movement disorders, evaluating the usefulness of quantitative analysis.

Materials and methods. A group of 183 consecutive patients clinically diagnosed as either having or not having degenerative Parkinsonism. These results were then contrasted with those of FP-CIT SPECT to determine the diagnostic accuracy of the procedure. The specific binding index was evaluated with ROC curves.

Results. FP-CIT SPECT was highly accurate in the diagnosis of neurodegenerative Parkinsonism (sensitivity: 95%, specificity: 90%). Most of the false positive results arose in patients with vascular Parkinsonism and the false negative results in patients with Parkinson disease. ROC curve analysis of semiquantitative evaluation had a sensitivity of 83% and specificity of 82% with an optimal cut-off of 1.44. The area under the curve was not significantly different between patients ≤ 60 and > 60 years (0.899 vs 0.884).

Conclusions: FP-CIT SPECT has a high degree of diagnostic accuracy for striatal dopaminergic involvement. No significant changes in diagnostic accuracy were seen with respect to patient age.

KEY WORDS: Parkinsonism, SPECT, dopamine transporter.

INTRODUCTION

Parkinsonian syndrome (PS) or Parkinsonism is characterised by the presence of hypokinesia associated with rest tremor and/or rigidity and/or postural instability. The condition which presents with most frequency in this syndrome from a clinical point of view is Parkinson’s disease (PD). PD is neurodegenerative and originates due to the progressive loss of dopaminergic neurons of the nigrostriatal pathway.

Although PD is the most representative pathology of PS, there are other pictures which, though they differ clinically from this, are also expressed by this set of symptoms. Worth noting are multisystem atrophy, clinical la existencia o no de parkinsonismo degenerativo y se confronta con el resultado de la tomogammagrafía (SPECT) con FP-CIT, estableciendo la validez diagnóstica de dicho procedimiento. El índice de captación específica se valoró mediante curvas ROC.

Resultados. Considerados de forma global se obtuvo una exactitud diagnóstica del 93% para el diagnóstico de un parkinsonismo de origen neurodegenerativo. La mayor parte de resultados falsos positivos se obtuvieron a partir de pacientes con parkinson vascular (PV) y la de falsos negativos a partir de sujetos con enfermedad de Parkinson (EP). El análisis mediante curva ROC de la valoración semicuantitativa apor-tó una sensibilidad del 83% y una especificidad del 82%, con un punto de corte óptimo de 1,44. El área bajo la curva no se modificó de forma significativa en pacientes ≥ 60 y > 60 años (0,899 frente a 0,884).

Conclusiones. El estudio tomográfico con FP-CIT permite poner de manifiesto, con elevada seguridad diagnóstica, la afectación de la vía dopaminérgica nigroestriada en pacientes afectos de un trastorno del movimiento. No se obtuvieron cambios significativos en pacientes ancia-nos.

PALABRAS CLAVE: parkinsonismo, SPECT, transportadores de dopamina.

Diagnosis accuracy of FP-CIT SPECT in patients with Parkinsonism

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Originals

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Concluding a significantly lower specificity in patients under 55 years, this purpose. In this context, Eerola et al. which question the usefulness of FP-CIT SPECT for patients distributed as shown in Table 1.

(MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), in which unlike PD, as well as involvement of the presynaptic terminal there is involvement at the post-synaptic level of the nigrostriatal pathway.

Similar symptoms may appear without there necessarily being degeneration of the dopaminergic neurons, which project from the mesencephalic black substance to striated, something which occurs in conditions such as essential tremor (ET), vascular Parkinsonism (VP), drug-induced Parkinsonism (DIP) or in Alzheimer’s disease (AD). At this point it is worth mentioning the importance of correct delimitation of those patients in whom the symptoms have their origin in the degeneration of the nigrostriatal pathway, since it has significant implications regarding the course, treatment and prognosis of the disease.

The differentiation between PD, other forms of Parkinsonism and pictures with similar symptoms, at the expense of clinical criteria, may be difficult, particularly in the initial phase of the disease in which the symptomatology may be mild, manifesting not clearly or atypically. In this respect, the diagnostic accuracy of the clinical criteria for the diagnosis of PD is variable, varying in range between 76% and 90%, basically depending on parameters such as the level of specialisation of the clinician and the population studied.

The dopamine transporters are proteins situated at the presynaptic terminal of dopaminergic neurons which are responsible for the reuptake of dopamine. Measurement of the density of these transporters using tomographic techniques, either SPECT or positron emission tomography (PET), using specific ligands, provides us with a direct measurement in vivo of the integrity of these presynaptic terminals. Various tracers derived from tropane and cocaine analogs have been used for this purpose, among others Ioflupane or FP-CIT-I-123 (N-\(\beta\)-fluoropropyl-2\(\beta\)-carbomethoxy-3\(\beta\)-[4-Iodophenyl] nortropane). The use of this radiopharmaceutical agent, and of the other tracers utilised for this purpose, has shown to be a suitable method for delimiting patients with and without involvement of the dopaminergic system in various studies.

However, some studies have recently been published which question the usefulness of FP-CIT SPECT for this purpose. In this context, Eerola et al. limit the usefulness of this technique to patients under 55 years, concluding a significantly lower specificity in patients over that age.

Thus the objective of this study was to state our experience regarding the usefulness of tomographic study with FP-CIT in a large series, in order to establish the differential diagnosis between conditions which progress with presynaptic impairment of the nigrostriatal dopaminergic pathway with respect to others which do not have this alteration, including analysis using ROC curves of the specific uptake index extracted from the semi-quantitative evaluation for this purpose.

**MATERIALS AND METHODS**

**Patients**

183 patients (94 men and 89 women) recruited consecutively in the movement disorders clinic of our hospital from January 2003 to December 2004 were included. This was a group of patients who had been referred to our Department in order to perform an FP-CIT tomographic study, in whom there was suspicion of involvement of the nigrostriatal pathway according on the clinical history and neurological examination. Patients on treatment with drugs which have an effect, known or suspected, by a direct competitive mechanism at the level of dopaminergic transporters were excluded. Specifically, two subjects on prolonged treatment with sertraline were not included; the possibility of its withdrawal was ruled out, in agreement with the neurology team, due to the severity of the depressive symptoms. Antiparkinsonian therapy was not suspended, so the possible pharmacological interference of this at striatal level was not assessed.

The mean age of the patients at the time of their first visit was 65.3 years (30-88) with a standard deviation of 11.29 years. 51.4% (94/183) of patients studied were men and 48.6% (89/183) were women.

All patients underwent clinical follow-up, a period after which they were classified, basically by taking into account the existence or not of presynaptic impairment. This follow-up was carried out by the team of neurology specialists in the movement disorders clinic of our centre and consisted of an initial visit and six-monthly reviews. After the initial clinical impression and analysis of the set of complementary examinations, excluding FP-CIT SPECT, the specialist clinician established a first diagnostic approach, with patients distributed as shown in Table 1.

After a variable period (although never less than 18 months), the specialist reached a provisional
diagnosis using specific clinical criteria and distributed as follows:
1. PD (87/183), 47.5%.
2. Parkinson plus disorders (PP), (25/183), 15.8%, where patients with MSA (10), PSP (4), CBD (2) and Lewy body dementia (LBD) were included.
4. ET symptoms (27/183), 14.8%.
5. SP (40/183), 21.9%, vascular (VP) and pharmacological origin.

Method
Only the normal/abnormal criterion was assessed, i.e. whether the FP-CIT SPECT allowed differentiation of a group of conditions with presynaptic involvement from others in which their integrity is assumed, without trying to assign them to different clinical groups within the set of pathological studies.

The images were obtained after a period of between 3 and 4 hours after the intravenous injection of 185 MBq (5 mCi) of Ioflupane–I-123, with prior thyroid blocking with Lugol’s solution. The tomographic study (SPECT) with Ioflupane/FP-CIT-I-123 was performed using a General Electric gamma camera, Millennium model, equipped with a dual head and general purpose collimator. A 360° circular orbit was made around the cranium, at 3° intervals, 60 images with a duration of 35 seconds per interval, 128 x 128 matrix. Image reconstruction was carried out using filtered back-projection algorithms without attenuation correction, application of a Hanning filter (frequency 0.7) and images were obtained with transaxial cuts.

The images were interpreted by three Nuclear Medicine specialists, with masking of the clinical orientation. Visual assessment was established by exclusively considering the normal/abnormal criterion and after arriving at a consensus report between the three specialists. A study was considered to be normal when bilateral, symmetrical uptake appeared in caudate and putamen nuclei, and abnormal when there were areas of significant reduced uptake in any of the striatal structures. Quantitative evaluation was not regarded for image assessment.

Data analysis
Analysis of diagnostic validity and calculation of the sensitivity (Se: percentage of patients in whom FP-CIT SPECT was considered as pathological in subjects with clinical diagnosis of degenerative Parkinsonism), specificity (Sp: percentage of patients in whom FP-CIT SPECT was considered normal in subjects without clinical diagnosis of degenerative Parkinsonism), positive predictive value (PPV: percentage of patients with clinical diagnosis of degenerative Parkinsonism in whom FP-CIT SPECT was considered as pathological) and negative predictive value (NPV: percentage of patients without clinical diagnosis of degenerative Parkinsonism in whom FP-CIT SPECT was considered normal) were carried out by comparison of the results from the FP-CIT SPECT with the certainty criteria (clinical follow-up) following the conventional method, by establishing the ratios of true positive (TP), false positive (FP), true negative (TN) and false negative (FN) results of the procedure in question.

The quantitative evaluation was made by establishing uptake indices between the areas of specific activity (binding to dopaminergic transporters) and areas of non-specific activity (vascular activity) by obtaining regions of interest (ROI) on both striates (mean counts, 250 pixel rectangular ROI) and mean uptake on the occipital lobe (350 pixel ROI with rectangular morphology) in the result of the sum of the 6 images most representative of striatal activity (thickness of cut: 3.39 mm; total thickness examined: 20.34 mm). The arithmetic mean of the index of both hemispheres was calculated with the object of obtaining an overall assessment of the state of the nigrostriatal pathway.
The aforementioned quantitative evaluation index was calculated as follows:

\[ UI = \frac{\text{specific activity in striatal ROI}}{\text{non-specific activity in occipital ROI}}. \]

**Statistical analysis**

The data were analysed using the SPSS statistical program (version 11.5). Central and dispersion measurements, 95% confidence intervals and ROC curve analysis were used to describe the quantitative variables. The ANOVA test was used for comparison of means of a factor. A level of significance was considered for \( p < 0.05 \).

**RESULTS**

Once the results had been considered globally, 35% (64/183) of the studies were considered as normal. On the contrary, 65% (119/183) showed alterations according to the assessment made by the group of Nuclear Medicine specialists. The FP-CIT results in the different groups after the clinical follow-up period are shown in table 2.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>4</td>
<td>83</td>
<td>87</td>
</tr>
<tr>
<td>PP</td>
<td>2</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>ET</td>
<td>26</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>SP</td>
<td>34</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>HD</td>
<td>0</td>
<td>4</td>
<td>4</td>
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</table>

Total: 66 117 183


**DISCUSSION**

Recently, various articles have been published which question the usefulness of FP-CIT SPECT in being...
able to show the existence of presynaptic involvement in patients with movement disorders. Thus, Ravina et al.\textsuperscript{16} carried out a review on the role of diagnostic imaging techniques based on the use of radiopharmaceutical agents, in different assumptions applied to PD. In the assumption on the diagnostic and prognostic usefulness of these techniques, in the clinical context which concerns us, although B-CIT SPECT provides Se values over 95% and a Sp between 83 and 100% for differentiating between a clinically probable PD and an ET picture, most studies, according to these authors, were conducted with small populations. In this same context Eerola et al.\textsuperscript{7} concluded a limited Sp (68.5%) for ruling out presynaptic involvement in a heterogeneous group of patients, a fact determined by the impossibility of correctly delimiting the physiological dopaminergic loss, of the loss caused by a neurodegenerative change with involvement of the nigrostriatal pathway.

Table 3

<table>
<thead>
<tr>
<th>Result</th>
<th>N</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDP</td>
<td>67</td>
<td>1.6195</td>
<td>0.16279</td>
<td>1.57-1.66</td>
</tr>
<tr>
<td>DP</td>
<td>116</td>
<td>1.2769</td>
<td>0.17071</td>
<td>1.24-1.30</td>
</tr>
</tbody>
</table>

NDP: non-degenerative Parkinsonism; DP: degenerative Parkinsonism

FIG. 2.—Semi-quantitative analysis. ROC curve. Area below the curve: 0.870; CI 95%: 0.813-0.935.

FIG. 3.—Semi-quantitative analysis. ROC curve in 60 year old patients. Area below the curve: 0.899; CI 95%: 0.796-0.961.

FIG. 4.—Semi-quantitative analysis. ROC curve in patients > 60 years. Area below the curve: 0.884; CI 95%: 0.812-0.935.

This study shows high diagnostic accuracy for the diagnosis of degenerative Parkinsonism, based on a large series. In our study, the patient’s age was not a factor which conditioned the diagnostic accuracy of the procedure, as analysis of the ROC curves in ≤ 60 year old patients and those > 60 years shows (0.899 versus 0.884) shows. Although the age and the physiological deficit that it brings as regards neuronal loss may occasionally cause diagnostic queries, the different pattern of striatal neuronal involvement in the senile subject, and especially in the PD patient, usually guides towards the origin of that loss. Thus, Fearnley et al.17 analysed the different pattern of involvement of the black substance in healthy controls stratified by age and in patients with PD. In the case of PD, the ventrolateral layers, which project towards the posterior putamen, were affected preferentially, unlike that which occurs in normal aging, with greater involvement of the dorsomedial layers which project towards the caudate. Therefore, in PD clearly selective involvement towards the putamen region with respect to the caudate takes place (fig. 5).

However, we found greater diagnostic difficulties, in this same context, for making a correct differential diagnosis with SP symptoms of vascular origin. The involvement of the presynaptic terminal in VP has been considered in some publications and rejected in others.18,19 Theoretically, the vascular impairment of the basal ganglia does not have to affect the uptake of FP-CIT, since the post-synaptic neuron is located at this level. Cases have been described, nevertheless, of deficiency of uptake in focal and extensive infarcts of the basal ganglia,20 which in any case would give rise to a different impairment pattern, at least to that seen in PD, although the possibility of PD and VP coexisting in the same patient should be taken into account, made on the other hand difficult to delimit.

The majority of studies interpreted erroneously as negative corresponded to patients diagnosed with PD after the clinical follow-up period. In this respect, various studies have shown contradictions between the result of the study with presynaptic markers, which were normal, and patients clinically diagnosed with PD (fig. 6). In some series, these discrepant cases known as SWEDD (Scans Without Evidence of Dopaminergic Deficit) constitute up to 14% of patients.21 There is currently no explanation for this fact, and at least until there is, it is proposed to consider the basal dopaminergic image as an inclusion criterion for future studies in which patients with PD in initial phases are evaluated.22

Another cause of FN was extracted from a patient clinically diagnosed with LBD with a FP-CIT study without apparent changes. An explanation for these

<table>
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<th>Table 4</th>
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<tbody>
<tr>
<td><strong>DIAGNOSTIC ERRORS</strong></td>
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<tr>
<td>Patient</td>
</tr>
<tr>
<td>18</td>
</tr>
<tr>
<td>30</td>
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<td>65</td>
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<td>143</td>
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<td>172</td>
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</tbody>
</table>

ID: initial diagnosis; DF: diagnosis after follow-up; TF: time of follow-up; VAL: diagnostic validation; PS: Parkinsonian syndrome; PD: Parkinson’s disease; LBD: Lewy body dementia; PP: Parkinson plus; ET: essential tremor; SP: secondary Parkinsonism; CBD: corticobasal degeneration; VP: vascular Parkinsonism; FN: false negative; FP: false positive; Sstr/Occp: uptake in striate/uptake in occipital index.
results would have to be sought in the fact that the application of the consensus on clinical criteria for the diagnosis of LBD, established in 1995, gives a Sp range between 29 and 100% and a Se between 22 and 90%, with AD being the most common cause of errors in the diagnosis. A phase III multicentre study published recently concluded a high correlation between an abnormal FP-CIT study and a clinical diagnosis of probable LBD, with high diagnostic accuracy for considering it, from a clinical point of view, useful for distinguishing between LBD and AD. As a result of this paper, the LBD study group carried out a review of the international consensus criteria, recommending that a pathological study with FP-CIT be considered as a criterion for diagnosis.

ROC curve analysis of the semi-quantitative evaluation of the images offered an optimal cut-off point of 1.44 and a Se and Sp of 83 and 82% respectively, somewhat lower than those extracted using visual assessment (Se: 95%-Sp: 90%). In our opinion, semi-quantitative analysis by determination of the specific/non-specific activity index may be an objective tool for supporting the subjective impression after visual analysis of the examination. Furthermore, visual assessment has greater application for a clinical diagnosis, since it provides more information about the uptake patterns which are characteristic of each pathology.

This study has limitations which are evidently linked to the complexity of the group of diseases analysed itself. The lack of a reference gold standard, which can be applied in in vivo studies, and therefore the lack of a definitive diagnosis, makes it necessary to establish the clinical follow-up, more or less prolonged, as a reference parameter, with the imperfections which this may entail, linked to our judgement and basically to the subjectivity of the clinician. Moreover, the Se and Sp values of a certain diagnostic test in normal practice are constituted depending on two strictly established situations, i.e. the existence or absence of disease. This very clear distinction is not always possible in this group of pathologies, especially due to the possible coexistence of different conditions which will behave otherwise in the FP-CIT study (PD and VP, PD and ET, etc.)

The possible interaction of the anti-Parkinsonian medication with the degree of uptake of FP-CIT was not a datum which was tackled directly in our paper.

We consider a brief analysis of this aspect interesting as a factor to take into account as regards a possible limitation of the study, since it has only been considered slightly in it. The first publications in this respect based their results on small series, with little uniformity as regards conclusions and drugs analysed. More recently, Nikolaus et al. evaluated the blockage of dopaminergic receptors (DAT) in experimental animals treated with methylphenidate, concluding a mean reduction of 78% in the uptake of FP-CIT. A similar effect was shown with bupropion, with 20.84% occupation of DAT receptors in patients treated with this drug, in this case using TRODAT-Tc-99m. On the contrary, in a group of drugs most used in these patients, such as selective serotonin reuptake inhibitors, an increase of approximately 10% in the specific uptake index of FP-CIT in patients treated with paroxetine was shown with respect to the placebo group.

In conclusion, the FP-CIT tomographic study allows the involvement of the nigrostriatal dopaminergic pathway to be shown with high diagnostic safety, and therefore the existence of degenerative Parkinsonism in patients with movement disorder, without the diagnostic accuracy of the technique in this group of patients being modified significantly in elderly subjects.
BIBLIOGRAPHY


