Correlation between visual interpretation and quantification of $^{123}$I-ioflupane SPECT imaging

A Nafati, John R Buscombe*
Department of Nuclear Medicine, Royal Free Hospital, London

Abstract

Aims $^{123}$I-ioflupane (DaTSCAN™) is used for the differentiation of Parkinson’s Syndrome (PS) from parkinsonism without nigrostriatal degeneration in patients with symptoms suggestive of PS. However, there remains some controversy as to the best method to report the resulting images and therefore the aim of this study was to retrospectively compare the visual assessment of $^{123}$I-ioflupane with Specific Binding Indices (SBIs) as calculated using quantitative analysis to see if there was a good correlation between what was reported visually and the objective measurements of uptake measured by SBIs.

Methods The study reviewed the images thirty-one patients with parkinsonism (19 males, mean age 55.3±15 years). Three nuclear medicine consultants visually rated the images, grade 0 for normal to grade 3 for severe abnormality, according to the classification reported by Catafau et al. SBIs were calculated for the striatum and striatal subregions (head of caudate and putamen) quantitatively from two summed consecutive transaxial slices with the most intense striatal binding.

Results 11 patients (35%) were reported as normal. Of the abnormal scans 3 (15%) were reported as grade 1, 14 (70%) as grade 2 and 3 (15%) as grade 3. The mean nigrostriatal SBI was 3.20±0.91 in the visually assessed normal scans, and reduced to 1.97±0.79 in grade 1, 1.47±0.51 in grade 2 and 0.51±0.27 in grade 3 scans with a similar decrease in all nigrostriatal subregions. The visual assessment grades showed a highly significant negative correlation with SBIs from both the striatum and subregions (mean Spearman’s correlation coefficient -0.815, P<0.0001).

Conclusion There is a highly significant correlation between semi-quantitative $^{123}$I-ioflupane image analysis and visual assessment of the severity of PS.

Key words: Parkinson syndrome, I-123 Ioflupane, SPECT quantification

Introduction

Parkinson syndrome (PS) is characterised by degeneration of dopaminergic neurons in the substantia nigra. It comprises Parkinson’s disease (PD), multiple system atrophy (MSA), and progressive supranuclear palsy (PSP).

Imaging of the basal ganglia with $^{123}$I-ioflupane (DaTSCAN™) SPECT is used to study the presynaptic receptors hence demonstrating the decline of striatal dopamine transporter binding in Parkinson syndrome [1, 2]. It is of most value in differentiating Parkinson syndrome (PS) from other causes of parkinsonism and tremor with no nigrostriatal degeneration [3-5].
$^{123}$I-ioflupane SPECT has also been shown to be of use in the early stages of disease when signs and symptoms are not sufficient to fulfil the accepted diagnostic criteria for Parkinson syndrome [3].

Visual assessment of $^{123}$I-ioflupane SPECT images has been shown to have a high diagnostic accuracy in differentiating patients with PS from patients with essential tremor [3]. However, quantification is regarded as advantageous, adding objective information that could be used to assist the visual qualitative interpretation of images [6-10]. In addition, as it is less observer-dependent and more reproducible, it may be useful in follow-up studies [11]. The type of quantification normally used is a measurement of the basal ganglia uptake called the specific binding index (SBI) which can be used for diagnosis and monitoring disease [12,13].

There does however, remain significant debate about the role of these methods of quantification and how they relate to more subjective visual readings of the scans, especially when using a grading system which determines the severity of the disease. This study was set up to determine if there is a correlation between the visual reporting of images as reported using a grading system for severity and the objective measurement provided by the SBIs.

**Methods and materials**

**Study population**

The imaging of thirty-one patients was retrospectively studied after reviewing their case notes to determine if they did indeed have suspected Parkinsonian syndrome. These included 19 males and 12 females, aged between 19 to 84 years (mean age 55.3 ±15 years). The mean age for the onset of symptoms in this group was 52.9 ± 13.44 years. The mean duration of disease from the first onset of symptoms to the $^{123}$I-ioflupane SPECT imaging was 3.5 ± 2.3 years. All patients presented with signs and symptoms suggestive of PS and referred by Specialist Neurologists to the Nuclear Medicine Department, Royal Free Hospital between 1/6/2002 and 18/6/2005 to establish or confirm the diagnosis of Parkinson Syndrome.

We excluded patients who have no CT or MRI imaging after the onset of Parkinsonian symptoms or signs and those who had an abnormal CT or MRI imaging results such as any evidence of cerebrovascular disease and patients with neurological evidence of impairment such as gait ataxia.

The left side was more affected in 10 patients, the right side in 14 patients, both sides were equally affected in six patients and in one patient, there was no data in the patient’s notes as to the site of symptoms recorded (Table 1).

Tremor was the most common symptom reported in all but four patients. In majority of the cases, the tremor as determined by the referring neurologist was asymmetrical (Table 2). Where tremor was present, just under half had rest tremor or postural tremor with a small number having a mixed picture.

Rigidity was the second most common symptom in all but eight patients and most commonly, this was unilateral. Bradykinesia was present in all but 10 patients being unilateral in 55%. Postural instability was rare with six patients having a mild problem and two having sufficient instability that they suffered frequent falls.

Anti-Parkinson’s drugs had been given to 23 patients of these 17 patients had an improvement in signs and symptoms specific to a Parkinson syndrome.

**Imaging**

All patients underwent thyroid blocking on the day of the injection and for 2 subsequent days with 50-60mg potassium iodide bds. 185 MBq of $^{123}$I-ioflupane (GE Healthcare, Amersham, UK), was administered intravenously. SPECT imaging was conducted 3 hours postinjection using the three-headed IRIX gamma camera.
Table 1  Lateralisation of symptoms

<table>
<thead>
<tr>
<th>Side affected</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>10</td>
<td>33</td>
</tr>
<tr>
<td>Right</td>
<td>14</td>
<td>45</td>
</tr>
<tr>
<td>Both</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
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<td>3</td>
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</table>

Table 2  Tremors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Tremor Absent</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Asymmetrical</td>
<td>24</td>
<td>77</td>
</tr>
<tr>
<td>Symmetrical</td>
<td>2</td>
<td>7</td>
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<tr>
<td>Data missing</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 3  Tremor types

<table>
<thead>
<tr>
<th>Type</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Rest</td>
<td>12</td>
<td>39</td>
</tr>
<tr>
<td>Postural</td>
<td>11</td>
<td>36</td>
</tr>
<tr>
<td>Mixed</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Data missing</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 4  Results by severity of abnormal scans using system of Catafou et al. (5)

<table>
<thead>
<tr>
<th>Grade</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>11</td>
<td>35</td>
</tr>
<tr>
<td>Abnormal Grade 1</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Abnormal Grade 2</td>
<td>14</td>
<td>45</td>
</tr>
<tr>
<td>Abnormal Grade 3</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

(Marcomi-Phillips, Cinnicinatti, Ohio. USA) equipped with low-energy general all-purpose (LEGAP) parallel hole collimators and interfaced with Odyssey computer (Picker-Phillips, Cincinatti, Ohio, USA).

With no attenuation correction applied, the raw data of the entire brain was reconstructed using iterative reconstruction at one pixel slice thickness (2.3mm). Four iterations were performed using Ordered Subset Maximum Likelihood Expectation Maximization (OS ML-EM-all) algorithm. Low pass 3-dimentional post filter was applied using the order of 9.0 and the cut-off of 0.25.

Transaxial slices were reformatted into three orthogonal planes with summing of each two consecutive slices together to get slices of 4.6 mm thickness. Transverse sections were generated parallel to Anterior Commissure – Posterior Commissure (AC-PC) line.

Data Analysis-Visual Assessment

Qualitative analysis was performed independently by three highly experienced nuclear medicine physicians, who were blind to patient’s clinical data. An agreement between two of them was taken as a consensus decision. The images were classified according to the classification reported by Catafau et al. [5] as follows:

Normal: symmetric intense tracer uptake in the striatum, both caudate nuclei and putamen

Abnormal grade 1: asymmetrical uptake with reduced putamen activity in one hemisphere

Abnormal grade 2: clear symmetrical reduction of putamen uptake in both hemispheres

Abnormal grade 3: virtual absence of uptake in both putamen and caudate nuclei on each side of the brain, resulting in a significant reduction in contrast and the visualization of background activity throughout the rest of the image.

Any conflict between the readers was resolved by taking the two-third majority answer by the readers.

Quantitative analysis

The specific binding index (SBI) relates the specific uptake of an organ such as the putamen to that of a reference region such as
the putamen to that of a reference region such as the occipital cortex ROI [14]. The occipital cortex was chosen for drawing the background regions of interest as it does not contain dopamine transporter-binding sites but has the same amount of blood perfusion [3]

A transaxial slice (composed of two consecutive slices as mentioned before) representing the most intense striatal binding was chosen. A template of regions of interest was generated including regions for the right ganglia, the left ganglia, the right caudate, the left caudate, the right putamen, the left putamen and occipital region as a background region. Only movement of regions was allowed for different patients (Figure 1). The SBIs were calculated using the formula [15,16]:

\[
\text{Specific Binding Index (SBI)} = \frac{\text{mean ROI counts - mean occipital counts}}{\text{mean occipital counts}}
\]

**Statistical analyses**

Spearman’s correlation coefficients were used to calculate the correlation between visual assessment grades and the SBIs using a standard computer statistical package (SSPS, Chicago Illinois, USA) A probability level of <0.05 was taken as significant.

### Table 5  Correlations between visual assessment scores and SBIs

<table>
<thead>
<tr>
<th>Nuclei</th>
<th>Spearman's correlation co-efficient (r)</th>
<th>95% confidence interval</th>
<th>Significance (p value-2 tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right striatum</td>
<td>-0.84</td>
<td>-0.68 to -0.92</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Left striatum</td>
<td>-0.80</td>
<td>-0.61 to -0.90</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Right caudate</td>
<td>-0.82</td>
<td>-0.66 to -0.91</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Left caudate</td>
<td>-0.74</td>
<td>-0.51 to -0.87</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Right putamen</td>
<td>-0.88</td>
<td>-0.76 to -0.94</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Left putamen</td>
<td>-0.80</td>
<td>-0.62 to -0.90</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Figure 1** (A) Regions of interest on basal ganglia and (B) caudate, putamen and occipital regions of interest
Results

Visual Assessment

Nearly one-thirds of the patients were graded as normal (grade 0) and 20 cases were graded as abnormal with the majority reported with a grade 2 abnormality (Table 3).

The visual assessment grades showed highly significant negative correlation with the SBIs calculated from images with no attenuation correction performed (p<0.01, Table 4). This was true for the both basal ganglia and both nuclei taken together and for individual ganglia and nuclei. The mean correlation coefficient for all regions was -0.815.

The mean SBIs decreases gradually with the severity of PS, as assessed with the three image readers, in a negative linear relationship, emphasizing the negative correlation calculated with the Spearman’s method (Figure 2).

In normal subjects, the SBI values were highest for caudate nuclei, with higher values in the left caudate compared with the right. The putamen nuclei showed equal binding tendency on both sides, although the SBIs were lower than those for caudate nuclei.
Patients with PS demonstrated decreasing SBI values with progression of visual assessment grade. Putamen nuclei showed lesser binding tendency in all the abnormal groups (Figures 3-7).

It was found that in all the patients with abnormal scans, the putamen-to-caudate ratios were reduced. The ratios were seen to decrease as the severity of disease increased. There was also a tendency for the asymmetry to increase proportionate with the degree of abnormality documented by visual grading of the 123I-ioflupane scan (Figure 7).

**Discussion**

This study clearly shows that there is a strong correlation between the qualitative reporting by trained nuclear medicine physicians and the more objective data provided by the SBIs, showing that, as the uptake in the caudate nucleus and putamen decreased (e.g. falling SBI), there was a worsening of the scan appearance. The study also shows that lateralisation of symptoms and signs mirror asymmetrical changes in both the scan appearance and the SBIs.

The clinical diagnosis of PS depends mostly on the identification of motor symptoms and signs such as bradykinesia, rigidity, tremor and postural instability. These symptoms and signs could also be found in other motor movement disorders such as essential tremor (ET) leading to difficulty in diagnosis [17].

One of the major indications for 123I-ioflupane imaging is differentiation between PS and ET. Both diseases present with tremor. PS is associated with nigrostriatal degeneration, which can be imaged with 123I-ioflupane; on the contrary, 123I-ioflupane should be normal in patients with ET. According to The (British) Parkinson’s Disease Society, up to 25% of patients with suspected parkinsonism may not have clinically obvious signs and would require 123I-ioflupane imaging [18]. Costa et al. audited the 123I-ioflupane results of 116 patients with movement disorders and concluded that it is an important tool in the clinical management of these patients. 123I-ioflupane changed the diagnosis in 31% and patient management in 47% [19]. Clinical diagnosis is more difficult in patients with “clinically uncertain Parkinsonian syndromes” (CUPS) presenting with mild or atypical signs. Imaging with 123I-ioflupane in this group increased confidence in diagnosis and lead to change in clinical management in 72% of patients [5].

Quantification of 123I-ioflupane SPECT is often expressed as a ratio of the mean concentration of radioactivity in a striatal or substratal region to the non-specific binding
cortex [20]. $^{123}$I-ioflupane binding indices are age dependent because of the progressive age-related shrinkage in corpus striatum in normal population [21]. So a comparison of binding indices with reference values of age-matched healthy volunteers may be needed to reach an accurate diagnosis [8]. Van Dyck et al. demonstrated that there is an age-dependent decline on striatal specific binding indices of approximately 6.6% per decade for people between 18 and 88 years of age. Rates of decline were similar for the caudate nucleus (6.8%) and putamen (6.5%) [21]. However, our group of patients was too small to identify any specific age related change in either visual reading or the SBIs. Semiquatification methods may still, to some degree, be observer-dependent procedures, because positioning of ROIs is performed manually on one or more transaxial slices of the SPECT study [22].

Benamer et al. demonstrated in a multi-centre study, which included 158 patients with a clinical diagnosis of parkinsonism, 27 ET cases and 35 healthy volunteers, that visual assessment of DaTSCAN SPECT is easy to perform and could be used to differentiate PD from ET with a sensitivity of 95% and specificity 93% for the consensus blinded read. Quantitative analysis of SBIs, especially for caudate and putamen nuclei, were consistent with the results of visual inspection [3]. Dickson et al. studied and compared four methods of quantifying DaTSCAN uptake (UCL, Southampton, Copenhagen, BRASS-Nuclear Diagnostics, Stockholm, Sweden) with visual assessment, and found that there is good agreement between visual inspection and each method of quantification. They suggested that the failure to distinguish between different quantification methods was related to the limitations of visual interpretation, particularly in the caudate [23]. However, as quantification methods still depend on the correct placement of ROIs over the image, the visual interpretation can still be reliable as seen in our results.

Catafau et al. performed a prospective multicenter study of 118 patients of Clinically Uncertain Parkinsonian Syndromes (CUPS) using visual assessment of $^{123}$I-Ioflupane SPECT. The grading system was the same as the one used in this study. They found that 44 (37.3%) patients were normal, 14 (11.9%) abnormal Type 1, 44 (37.3%) abnormal Type 2, 15 (12.7%) Type 3 and 1 (0.8%) with an uninterpretable image [5]. Their results are not much different from those in our series where 11 (35.48%) patients were in the normal group and the distribution of abnormal studies being similar with 70% being read as clearly abnormal (grade 2).

Asymmetry is very common, especially in early stages of idiopathic Parkinson’s disease [24]. There is significant deterioration in the function of the putamen contralateral to the affected body side [25]. It was shown long ago that there is asymmetry of F-dopa uptake by the putamen but not by the caudate. This asymmetry correlated well with the asymmetry in parkinsonian clinical motor signs [26]. Other researchers found same asymmetry using $^{123}$I-ß-CIT [27, 28] and $^{123}$I-FP-CIT [29]. Van Dyck et al. concluded that idiopathic Parkinson’s disease involved a much more marked decrease of SBIs in the putamen and greater hemispheric asymmetry contralateral to the symptomatic side [21]. Benamer et al. studied forty-one patients with Parkinson’s disease (PD), nine with unilateral and 32 with bilateral clinical features. Patients with PD who had unilateral symptoms showed a significant difference between the ipsilateral and contralateral SBIs in both the caudate and putamen, but there was a considerable overlap between the two sides. This result was repeated in patients with bilateral symptoms and there was overlap of SBIs between the two groups [29].

In our study, when calculating the SBIs for the striatum, caudate and putamen contralateral and ipsilateral to the mostly affected side, it is clear that the values are decreasing with an increasing severity of disease. Generally, there is more deterioration of SBIs in the contralateral stratum and nuclei than in the ipsilateral. This is most obvious in the putamen when the percentage of difference is 102.19% in the normal subjects (as visually
assessed) increasing to 300 % in the abnormal grade 3.

**Conclusions**

DaTSCAN SPECT is very useful in the early stages of disease when signs and symptoms are not sufficient to fulfill the diagnostic criteria. This is very important because both conditions have very different prognoses and treatment approaches.

Visual assessment of DaTSCAN SPECT images is the most common method used for interpretation of the scans and for reporting the scan results. However, quantitative analysis provides more objective, observer non-dependent and reproducible results. Visual assessment grading correlated well with the quantification results. SBIs may be produced to help in the interpretation of disease severity and response to treatment. These indices are also needed for the development of a normal range to differentiate between Parkinson syndrome caused by degeneration of basal ganglia and other causes of parkinsonism, which are non-degenerative in nature.

**References**


