123I-FP-CIT SPET striatal uptake in parkinsonian patients with the α-synuclein (G209A) mutation

Abstract

Autosomal dominant familial Parkinson’s disease (PD) due to the α-synuclein (G209A) mutation shares similar clinical characteristics with sporadic PD. Pathological studies however indicate more widespread neuronal degeneration in the familial form. We performed 123I-FP-CIT SPET (DaTSCAN) study in nine patients with familial PD carrying the α-synuclein (G209A) mutation and fifteen matched patients with sporadic disease. Both groups had equal radioligand reduction uptake in the striatum but the α-synuclein patients showed less asymmetry and increased putamen to caudate ratio. Our findings indicate that there are minor differences in DAT SPET parameters between α-synuclein and sporadic PD patients insufficient to provide differential diagnosis.

Introduction

Autosomal dominant familial Parkinson’s disease (PD) due to the α-synuclein G209A mutation (Ala53Thr) is a rare form of parkinsonism presenting with a clinical phenotype almost indistinguishable from sporadic PD [1-3]. However some differences in clinical manifestations have been reported. These include younger age at onset, less prominent or absent rest tremor, more cognitive decline, central hypoventilation and myoclonus [2-4]. Pathological features of the α-synuclein (G209A) mutation were typical for sporadic PD with more widespread neuronal degeneration [4]. Postmortem data from patients with sporadic PD have shown that dopamine transporter (DAT), a marker of dopaminergic nerve terminal integrity, is reduced in the striatum with greater abnormality appearing in the putamen compared to caudate [5]. In living subjects imaging of DAT binding by means of single photon emission tomography (SPET) provides an objective marker of nigrostriatal neuronal loss in PD [6, 7]. We performed with 123I-Ioflupane [123I-N-α-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (123I-FP-CIT)] SPET study of patients with the α-synuclein (G209A) mutation and compared them to sporadic PD in an attempt to assess the discriminative utility of 123I-FP-CIT SPET in differentiating between the two groups.

Patients and methods

Patients’ selection

Nine patients with familial PD due to the G209A (Ala53Thr) α-synuclein gene mutation (α-syn PD group) and fifteen matched patients with sporadic PD were studied (control PD group). All patients were clinically assessed by means of the Unified Parkinson’s Disease Rating Scale [8]. Their clinical characteristics are summarized in Table 1. Selection criteria for patients with sporadic PD were similar age and disease duration to the familial PD cases. One α-syn PD patient and two control PD patients were treated with pramipexole only, while all the others were under levodopa treatment plus pramipexole or ropinirole. All subjects gave informed consent before entering the study.

SPET study

We investigated the dopamine transporter with 123I-FP-CIT. All patients received 185MBq 123I-FP-CIT (DATSCAN™, GE Amersham International PLC) intravenously as a single bolus injection. One hour before injection of the 123I-FP-CIT blockade of the thyroid gland was performed by oral administration of 1gr potassium perchlorate. Three to four hours post-injection, the SPET study was performed using a single headed ADAC γ-camera, connected to a PEGASUS processing unit, filled with a low-energy high resolution collimator (LEHR) and
calibrated using the 159 keV (±10%) photopake energy window. The radius of rotation was set as small as possible (about 15 cm). One hundred twenty eight projections each one with a duration of 20 sec were acquired using a matrix size of 64x64x16 and a detector of 25.4 cm, producing a zoom factor of 1.85. Reconstruction of the data was made using the backprojection algorithm at a cut-off frequency of 0.30 and an order of five. Pixel size was 5.2 mm. The re-oriented images were displayed on horizontal long, vertical long and coronal sections. Normal images were characterized by two symmetrical crescent-shaped areas of equal intensity. Abnormal images were either asymmetric or symmetric with unequal intensity and/or loss or crescent. Irregular regions of interest (ROIs) were drawn on areas corresponding to the left and right striatum, caudate nucleus and putamen, representing the specific binding of the radioligand, and on the visual cortex representing the non-specific binding. The ratio of specific to non-specific binding of the radioligand, and on the visual cortex representing the non-specific binding. The ratio of specific to non-specific radioligand binding was calculated using the equation

\[
\text{ROI–OCC} \div \text{OCC}
\]

in which ROI represented the mean radioactivity (expressed in counts per pixel) in the region of interest (striatum, putamen or caudate nucleus) and OCC depicted the mean radioactivity in the occipital cortex. Laboratory normal values from matched for age controls were: striatum = 2.20±0.30, caudate: 2.50±0.30, putamen: 2.20±0.50. Relative asymmetry between left and right side uptake of the radioligand in the striatum, caudate and putamen was estimated by calculation of an asymmetry index as described by Seibyl et al (1995) [9].

SPET measurements of the side contralateral to disease onset were grouped as contralateral data, while measurements of the other side were grouped as ipsilateral data.

**Statistical analysis**

Statistical analysis was performed by means of the Student’s t test after logarithmic transformation for normalization of SPET data. The Mann-Whitney U test was employed for comparisons of percentage reduction of radioligand uptake in both groups. Analysis was performed by means of the SPSS 12 package for statistical analysis.

**Results**

There was a reduction in $^{123}$I-FP-CIT uptake in the striatum in both groups of patients. Mean percentage reduction in right striatum was 37.7%±25.2% in α-syn PD patients and

**Table 1. Clinical data of the two study groups.**

<table>
<thead>
<tr>
<th></th>
<th>α-syn PD group</th>
<th>Sporadic PD group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)*</td>
<td>47.1±7.5</td>
<td>48.4±5.3</td>
</tr>
<tr>
<td>Duration (yrs)*</td>
<td>7.4±2.1</td>
<td>6.0±2.5</td>
</tr>
<tr>
<td>Stage (Hoehn &amp; Yahr)*</td>
<td>3.0±0.9</td>
<td>2.3±0.6</td>
</tr>
<tr>
<td>UPDRS (Part III)*</td>
<td>36.2±14.1</td>
<td>28.0±11.8</td>
</tr>
</tbody>
</table>
* : not significant difference

**Table 2. $^{123}$I-FP-CIT SPET measures in the two study groups**

<table>
<thead>
<tr>
<th></th>
<th>α-syn PD group</th>
<th>Sporadic PD group</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Striatum asymmetry index</td>
<td>9.22±7.94</td>
<td>15.58±15.19</td>
<td>-1.1*</td>
</tr>
<tr>
<td>Caudate asymmetry index</td>
<td>12.49±9.76</td>
<td>16.06±11.7</td>
<td>-7.4*</td>
</tr>
<tr>
<td>Putamen asymmetry index</td>
<td>9.16±6.77</td>
<td>7.15±15.23</td>
<td>-1.38*</td>
</tr>
<tr>
<td>Contralateral putamen/</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral putamen/</td>
<td>0.85±0.17</td>
<td>0.62±0.18</td>
<td>2.78**</td>
</tr>
<tr>
<td>Contralateral striatum</td>
<td>1.24±0.26</td>
<td>1.36±0.45</td>
<td>-0.691*</td>
</tr>
<tr>
<td>Ipsilateral striatum</td>
<td>1.42±0.38</td>
<td>1.54±0.52</td>
<td>-0.571*</td>
</tr>
<tr>
<td>Contralateral caudate</td>
<td>1.64±0.38</td>
<td>1.65±0.57</td>
<td>-0.034*</td>
</tr>
<tr>
<td>Ipsilateral caudate</td>
<td>1.85±0.49</td>
<td>1.85±0.70</td>
<td>0.007*</td>
</tr>
<tr>
<td>Contralateral putamen</td>
<td>1.01±0.26</td>
<td>1.20±0.35</td>
<td>-1.34*</td>
</tr>
<tr>
<td>Ipsilateral putamen</td>
<td>1.15±0.36</td>
<td>1.29±0.41</td>
<td>0.573</td>
</tr>
</tbody>
</table>

**Discussion**

Imaging of presynaptic dopaminergic function by DAT SPET has provided a useful diagnostic probe in the evaluation of PD having a sensitivity of 0.92-0.97 and a specificity of 0.83-1.00 [10, 11]. Pertinent characteristics of idiopathic PD are asymmetrical decrease of radioligand binding in the contralateral versus ipsilateral striatum with the putamen being more affected than the caudate [9, 12, 13].

We assessed DAT function by means of the $^{123}$I-FP-CIT SPET in parkinsonian patients with the G209A α-synuclein gene mutation and a matched for disease duration and clinical severity group of sporadic PD patients. Radioligand uptake was reduced in the striatum in both groups. Comparisons of subregional basal ganglia $^{123}$I-FP-CIT binding in the two groups did not reach statistical significance. However there were differences between groups in the following aspects. In the α-syn...
group there was not marked asymmetry in the radioligand uptake between the contralateral and ipsilateral striatum, while in the sporadic group a significant decrease was observed in the striatum contralateral to the predominant symptoms. Ipsilateral and contralateral putamen to caudate ratios were increased in the α-syn group only. This may be indicative of a difference between the two groups in terms of a relative greater reduction of radioligand uptake in the caudate of the α-syn PD patients, although comparisons of absolute mean values did not reach significance probably due to the small number of cases.

Various positron emission tomography (PET) and SPECT studies addressing dopaminergic dysfunction in familial parkinsonism, including α-syn patients, have been reported. An 18F-dopa PET study of four α-syn PD patients yielded a reduction pattern concerning caudate and putamen similar to idiopathic PD while asymmetry was less pronounced [14]. In two patients with α-synuclein gene duplication, 123I-F-CIT SPECT showed decreased striatal uptake, more marked in the putamen, in one patient and virtually no uptake in the second patient [15]. Another 18F-dopa PET study in parkinsonian patients carrying mutations in the parkin gene (PARK2) yielded a similar to sporadic PD decrease of radioligand uptake in the striatum with additional reductions in the caudate [16]. Furthermore, 18F-dopa PET in parkinsonian patients with mutations in the PTEN-induced kinase 1 gene (PINK1; PARK6) showed reduction in posterior dorsal putamen uptake, but greater involvement of the head of caudate and anterior putamen compared to sporadic PD [17]. A more recent study with TRODAT Scan in patients with PINK1 mutation reported a relatively even and symmetrical uptake reduction in the putamen and caudate nucleus [18]. Parkinsonian patients with mutations in the Leucine-rich repeat kinase 2 gene (LRRK2; PARK8) had impaired presynaptic dopaminergic function, studied by 18F-dopa and 11C-MP, affecting the putamen more than the caudate [19]. In patients with Spinocerebellar Ataxia Type 2 (SCA2) DAT SPECT imaging showed an identical magnitude of striatal DAT loss compared with sporadic PD [20]. Finally DAT SPECT in patients with Machado-Joseph disease showed symmetrical impairment of bilateral striatal radioligand uptake with putamen more severely affected than caudate [21].

DAT SPECT has not been reported in patients with the α-syn (G209A) mutation to compare our findings with. Pathological data from the few autopsies reported so far revealed a severe cell loss and gliosis in the substantia nigra and locus coeruleus in patients with the α-synuclein mutation [4, 22]. Since DAT distribution in basal ganglia coincides with dopaminergic neuron terminals loss, the absence of significant asymmetry in the radioligand uptake in the striatum and the increased putamen to caudate ratios may implicate a more widespread cell loss in the substantia nigra of the patients with the α-synuclein mutation. However we cannot exclude the possibility of other causes of DAT downregulation or direct effect of the mutant α-synuclein.

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Bibliography