PET studies of the presynaptic and postsynaptic dopaminergic system in Tourette’s syndrome

N Turjanski, G V Sawle, E D Playford, R Weeks, A A Lammerstma, A J Lees, D J Brooks

Abstract

Dysfunction of the dopaminergic pathway has been postulated to underlie the symptomatology of Tourette’s syndrome. Presynaptic functional integrity of dopaminergic terminals was assessed with 18F-dopa PET in 10 patients with Tourette’s syndrome, three of whom were drug free and seven of whom were on neuroleptic treatment. Dopamine D2 receptor site density was measured with 11C-raclopride PET in a further group of five drug free patients with Tourette’s syndrome. Mean caudate and putamen 18F-dopa influx constants were similar in patients with Tourette’s syndrome and controls, and there was no difference in striatal 18F-dopa uptake between the treated and untreated Tourette’s syndrome groups. Mean caudate and putamen 11C-raclopride binding potentials in patients with Tourette’s syndrome were also similar to control values. The findings suggest that striatal metabolism of exogenous levodopa and the density of striatal D2 receptors are both normal in patients with Tourette’s syndrome and that Tourette’s syndrome does not arise from a primary dysfunction of dopaminergic terminals.

(J Neural Neurosurg Psychiatry 1994;57:688–692)

Patients and methods

Patients

Fifteen patients with Tourette’s syndrome were recruited for this study from the movement disorder clinics at the National Hospital of Neurology and Neurosurgery, Queen Square and Charing Cross Hospital, London. Fourteen patients with Tourette’s syndrome satisfied DSM-III-R criteria for Tourette’s syndrome and the other had multiple tic disease. Eight had not been given neuroleptic drugs, or had been off medication at least three months before PET. Preliminary data for six of these patients have been previously reported.

Patients studied with 18F-dopa PET

Ten patients were studied with 18F-dopa PET. Their mean age at the time of PET was 30 (range 18–48) years, and at disease onset it was 6 (2–13) years. Seven patients (five men, two women), were taking neuroleptic drugs at the time of PET. Three male patients had not been treated with drugs; two had Tourette’s
Table 1  Details of patients with Tourette's syndrome studied with ¹⁸F-dopa PET

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Onset (y)</th>
<th>Simple tics</th>
<th>Complex tics</th>
<th>Obsessions/</th>
<th>Current drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Motor</td>
<td>Vocal</td>
<td>Motor</td>
<td>Vocal</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>48</td>
<td>4</td>
<td>Generalised</td>
<td>Throat clearing, barking, shouting</td>
<td>Jumping</td>
<td>Coprolalia, echolalia</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>24</td>
<td>9</td>
<td>Generalised</td>
<td>Sniffing, grunting, barking, shouting</td>
<td>Self injury, stamping</td>
<td>Echolalia</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>19</td>
<td>3</td>
<td>Generalised</td>
<td>Sniffing, barking, throat clearing</td>
<td>Bending legs</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>18</td>
<td>13</td>
<td>Generalised</td>
<td>Throat clearing, clicking</td>
<td>Facial gestures, touching self</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>29</td>
<td>2</td>
<td>Generalised</td>
<td>Sniffing, grunting</td>
<td>Turning, touching self</td>
<td>Palilalia</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>29</td>
<td>5</td>
<td>Head</td>
<td>Barking, grunting</td>
<td>Jumping, knee bends</td>
<td>Echolalia, coprolalia</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>46</td>
<td>7</td>
<td>Head</td>
<td>Shouting</td>
<td>Stamping</td>
<td>Coprolalia</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>24</td>
<td>7</td>
<td>Generalised</td>
<td>Screaming, barking, grunting</td>
<td>Turning, self injury</td>
<td>Coprolalia</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>26</td>
<td>5</td>
<td>Head</td>
<td>Coughing, sniffing</td>
<td>None</td>
<td>Echolalia, coprolalia</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>44</td>
<td>10</td>
<td>Head</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Methods

PET procedure

The PET was performed on a CTI 931/08/12 scanner at the MRC Cyclotron Unit, Hammersmith Hospital, London, UK. The reconstructed spatial resolution of this scanner, for 15 simultaneously acquired slices, is 7.0 x 8.5 x 8.5 mm (full width half maximum). ¹⁴

A thermoplastic head mould was made for each subject to gently immobilise the head while in the scanner. Patients were aligned with the orbitomeatal line parallel to the detector rings. A 10 minute transmission scan was collected with an external ⁶⁸Ga/⁶⁸Ge retractable ring source to correct for tissue attenuation of emitted radiation.

All medication was withdrawn for at least 12 hours before the PET. On the morning of the study, patients ate a light breakfast. One hour before ¹⁸F-dopa PET, they received an oral dose of 100 mg carbidopa, a peripheral dopa decarboxylase blocker.

¹⁸F-dopa—A mean dose of 123 (SD 41) MBq of ¹⁸F-dopa in 5 ml of normal saline (mean specific activity 6.0 MBq/µmol) was given by intravenous infusion over two minutes. Scanning began at the start of tracer infusion with collection of 25 serial time frames, increasing in duration from one to five minutes over a study period of 94 minutes.

¹⁴C-raclopride—A mean dose of 329(SD 61)

Table 2  Details of patients with Tourette's syndrome studied with ¹⁴C-raclopride PET

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Onset (y)</th>
<th>Simple tics</th>
<th>Complex tics</th>
<th>Obsessions/</th>
<th>Drugs*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Motor</td>
<td>Vocal</td>
<td>Motor</td>
<td>Vocal</td>
</tr>
<tr>
<td>1†</td>
<td>M</td>
<td>26</td>
<td>5</td>
<td>Head</td>
<td>Coughing, sniffing</td>
<td>None</td>
<td>Coprolalia, echolalia</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>46</td>
<td>10</td>
<td>Face</td>
<td>Sniffing, grunting, coughing</td>
<td>Touching self</td>
<td>Coprolalia</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>18</td>
<td>8</td>
<td>Head</td>
<td>Sniffing, whistling</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>37</td>
<td>5</td>
<td>Generalised</td>
<td>Throat clearing, grunting, barking</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>39</td>
<td>12</td>
<td>Generalised</td>
<td>Coughing, grunting</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

*At the time of the scan.
†Patient previously studied with ¹⁸F-dopa PET (number 9).
MBq of tracer in 5 ml of normal saline (mean specific activity: 19 072 MBq/µmol) was injected as a bolus. Scanning began after a 30 second background frame, with collection of 22 serial time frames, increasing from five seconds to 10 minutes duration over a 60 minute study period.

**DATA ANALYSIS**

Image analysis was performed with Analyze software (version 5.0-1, BRU, Mayo Foundation, Rochester, MN, USA), on SUN Sparc2 computer workstations. Regions of interest were defined by inspection of an image of integrated tracer activity. This image contained the activity collected from 30–94 minutes for 18F-dopa scans and from 20–60 minutes for 11C-raclopride scans. Regions of interest were placed with a standard template arrangement as previously reported. Regional time activity plots were then obtained for each region by projecting these regions of interest on the dynamic time frames.

**18F-dopa**—The data were analysed with a modified multiple time graphical analysis approach, with the occipital lobe as a non-specific tissue reference input function. This method generates influx constants (K, values), for both caudate and putamen. The K, value is an influx constant that reflects the uptake and subsequent metabolism of 18F-dopa by the nigrostriatal terminals, and therefore reflects the functional integrity of the dopaminergic projections.

**11C-raclopride**—Regional time activity curves were analysed with a reference tissue model with cerebellar input as described elsewhere. This method provides estimates of the binding potential of caudate and putamen, a measure of the number of available D2 receptors. Mean striatal 18F-dopa K, values and 11C-raclopride binding potentials for each group were compared by Student's unpaired t statistics, with a Bonferroni correction for multiple comparisons (n = 10).

**Results**

Some patients exhibited tics during PET, but this did not lead to any significant degradation of the images.

**18F-dopa PET**

The mean values for caudate and putamen 18F-dopa influx constants were similar in patients with Tourette's syndrome and controls. All individual patient caudate and putamen K, values were within two SDs of the normal mean (fig 1). The Tourette's syndrome K, values were also similar to the subgroup of age matched normal controls (mean normal caudate: 0.0098 (0.0011), putamen: 0.0093 (0.0009) min-1). There were no differences in striatal 18F-dopa K, values between treated and untreated Tourette's syndrome.

**11C-raclopride PET**

The mean caudate and putamen binding potentials in Tourette's syndrome were similar to control values. Figure 2 shows individual caudate and putamen binding potentials for Tourette's syndrome and control subjects. All except one lay within two SDs of the normal means. When the patients with Tourette's syndrome were compared with a smaller subgroup of five age matched normal controls, mean binding potentials of both groups remained similar (mean normal caudate: 2.36 (0.19) and putamen: 2.45 (0.07)).

**Discussion**

Our nine patients with Tourette's syndrome and one patient with multiple tic disease studied with 18F-dopa PET all had normal uptake and storage of this tracer in their nigrostriatal dopaminergic terminals. A further group of five patients with Tourette's syndrome studied with 11C-raclopride exhibited normal postsynaptic striatal D2 receptor binding potentials.

![Figure 1](http://jnnp.bmj.com/)

**Figure 1** Scatter diagram showing individual caudate and putamen 18F-dopa influx constants for patients with Tourette's syndrome (TS) and controls. All patients K, values were within two SDs of the control mean. No significant difference was found between mean striatal K, values for treated and untreated Tourette's syndrome groups; MT = multiple tic disease.

![Figure 2](http://jnnp.bmj.com/)

**Figure 2** Scatter diagram showing individual caudate and putamen 11C-raclopride binding potentials for patients with Tourette's syndrome and controls. Binding potential values for four out of five patients were within two SDs of the normal mean.
As seven of the ten patients scanned with \(^{18}\text{F}-\text{dopa}\) were receiving chronic neuroleptic treatment at the time of PET it is necessary to consider the effects of these drugs on the activity of aromatic amino acid decarboxylase, the enzyme in the dopaminergic terminals responsible for decarboxylating exogenous \(^{18}\text{F}-\text{dopa}\). These neuroleptics, in selective areas of the brain. A preliminary \(^{18}\text{F}-2\)-fluoro-\(^2\)deoxyglucose (\(^{18}\text{FDG}\)) PET study in drug free patients with Tourette’s syndrome found a 16% increase in glucose utilisation in the basal ganglia of patients with Tourette’s syndrome compared with controls and relative hypermetabolism in frontal and temporal areas bilaterally.\(^1\) Later, the same group reported regional hypermetabolism in superior frontal and sensorimotor cortices and suggested that the normal relation between the function of motor cortex and other brain regions was disturbed.\(^2\) A confounding problem, however, is that these patients may have had tics during the \(^{18}\text{FDG}\) PET. It remains unclear, therefore, how much of the increased activity represented tic generation, and how much simply reflected increased motor activity. Sawle et al\(^3\) recently reported a PET study of regional cerebral oxygen metabolism before and after cingulotomy in a patient with Tourette’s syndrome. Interestingly, preoperatively there was caudate and thalamus hypermetabolism, but after cingulotomy the metabolic rate decreased considerably in the caudate, in association with improvement of both tics and obsessive-compulsive syndrome.

In conclusion, using \(^{18}\text{F}-\text{dopa}\) and \(^{12}\text{C}\)-raclopride PET, we have been unable to find any abnormality of dopamine metabolism and storage in the nigrostriatal dopaminergic terminals, or in the density of striatal postsynaptic \(^{12}\text{D}\) receptors in patients with Tourette’s syndrome. Our findings, however, do not exclude a dysfunction of endogenous dopamine production, or altered proportions of \(^{12}\text{D}\) receptors in high and low agonist affinity conformations in this condition.

We thank colleagues of the Chemistry and PET methods sections at the NRC Cyclotron Unit for their expert assistance, and also Mrs A Williams, Ms CIV Taylor, and Mr GC Lewington for their help with scanning.

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10 Goetz CG, Tanner CM. Gilles de la Tourette’s syndrome.
François Magendie (1783–1855)

François Magendie, born in Bordeaux in 1783, was appointed Professor of Medicine at the College de France in Paris in 1831. He made important discoveries in neurophysiology and nutrition and is regarded by some as the father of experimental pharmacology. He is best remembered for his work on the cerebrospinal fluid and the canal in the brain that bears his name. One of his most important contributions was proof (in a litter of puppies) that the anterior roots of the spinal nerve were motor and the posterior sensory. A bitter dispute over the priority for the discovery ensued with the distinguished physiologist Charles Bell.

Magendie was also the first to produce decerebrate rigidity, the effects of excision or section of the cerebellum and of “circus movement” resulting from a lesion of the optic thalamus.

His investigations in pharmacology introduced bromine, quinine, emetine, and morphine into medical practice and he showed the effect of strychnine on the paralysed spinal cord. His Formulaire was published in 1821.

In 1815, post-revolutionary France was short of food. Magendie was appointed Chairman of a Commission to investigate the nutritional value of various food extracts. He showed the need for adequate amounts of the right sort of protein in a diet, laying the foundations for the science of nutrition. In 1842 he published an influential book that helped to reform clinical medicine along physiological lines.

He died on his birthday in 1855 and was honoured in 1985 in the Heroes of Medicine series issued by the Republic of Transkei. (Stanley Gibbons 178).
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J Neurol Neurosurg Psychiatry 1994 57: 688-692
doi: 10.1136/jnnp.57.6.688

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