Dopaminergic deficit in amyotrophic lateral sclerosis assessed with [I-123] IPT single photon emission computed tomography

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Abstract
Dopamine transporter imaging was performed in 18 patients with sporadic amyotrophic lateral sclerosis (ALS) and 11 age matched controls with [I-123] IPT (N-(3-iodopropen-2-yl)-2β-carbomethoxy-3β-(4-chlorophenyl)-tropane), a new cocaine analogue that selectively binds to the dopamine transporter located on dopaminergic nerve terminals. Image analysis showed that striatal IPT binding was moderately but significantly reduced in the ALS group compared with controls (p<0.01). The reduction of IPT binding was similar for patients with bulbar onset compared with those with limb onset. There was no correlation between values for uptake of striatal IPT and the age of the patients or the duration of the disease. These data indicate that nigrostriatal dopaminergic neurons are subclinically affected in a subset of patients with sporadic ALS.

Keywords: dopamine transporter; basal ganglia; motor neuron disease; single photon emission tomography

Similarities between amyotrophic lateral sclerosis (ALS) and Parkinson’s disease suggest possible common traits in their pathogenesis. The incidence of both disorders increases with age, their onset is gradual, and their course relentlessly progressive. The underlying pathological process is thought in both cases to begin long before the appearance of clinical symptoms, and there are indications of a shared genetic susceptibility. At postmortem examination, the brains of patients with ALS and patients with Parkinson’s disease share several features, including accumulation of neurofilamentous material in damaged neurons. A prominent example of association between these disorders is the ALS-Parkinsonism-dementia complex, once highly prevalent in the western Pacific. Neuropathologically and PET studies have provided evidence for an involvement of the dopaminergic system in ALS. The purpose of this study was to investigate whether patients with ALS show presynaptic nigrostriatal dopaminergic deficits detectable by single photon emission computed tomography (SPECT).

Materials and methods
We investigated 18 patients (age 42–79, mean 62.5 (SD 10.5) years; disease duration 4–107 months, mean 38.7 months) with sporadic ALS, from the motor neuron disease clinic of the Department of Neurology, University of Munich, and 11 age matched controls (age 41–81, mean 61.2 (SD 12.1) years). All patients fulfilled the El Escorial criteria of the World Federation of Neurology for probable or definite ALS. None of the patients showed signs of dementia, parkinsonism, or ophthalmoplegia by clinical examination. The protocol for the SPECT study was approved by the local ethics committee and signed informed consent was obtained from the patients.

N-(3-iodopropen-2-yl)-2β-carbomethoxy-3β-(4-chlorophenyl)tropane (IPT) was labelled with [123I]iodine as described previously. The sodium [123I]iodide was obtained commercially (Cygne BV, Eindhoven, The Netherlands). The radionuclidic purity of the [123I] was >99.9% and the specific activity was calculated to be 2×10⁷ Bq/mol. Data acquisition and processing has been described in detail. Briefly, the patients were injected with 150 to 180 MBq of radioactively labelled IPT in an antecubital vein. Brain SPECT images were acquired from 90 to 120 minutes after injection. Previous studies have shown that this period (corresponding to the washout phase after peak activity has been reached) may be suitable to clearly discriminate between patients with striatal disease and controls. For acquisition a triple headed gamma camera (Picker Prism 3000) equipped with high resolution fan beam collimators was used. The acquisition parameters comprised a rotational radius of ≤13.2 cm, a 20% energy window centred on 159 keV, 120 projection angles over 360°, an acquisition time of 45 seconds per projection, and a 128×128 matrix with a pixel width of 2.11 mm in the projection domain. The projection images were reconstructed by filtered back projection and further processed with a count rate dependent restorative (Wiener) filter. For uniform attenuation correction Chang’s first order
method was used. Images were resliced parallel to the AC-PC line.

To assess specific tracer uptake in the striatum we used the region of interest (ROI) technique. ROIs of the striatum, caudate nucleus, and putamen were defined by templates established from the data set of the control group. Non-specific activity was estimated by drawing a large ROI around the entire supratentorial brain on the slices containing the basal ganglia, which excluded the basal ganglia and the thalamus. Mean specific activity in basal ganglia regions was calculated by subtracting the mean counts per pixel in the background (BG) from the mean counts per pixel in the basal ganglia regions and dividing the results by the mean counts per pixel in the background ((ROI-BG)/BG). The table shows the IPT uptake ratios measured in patients and controls. Statistical significance was assessed with Student’s t test (two tailed).

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>(S-BG)/BG</th>
<th>(C-BG)/BG</th>
<th>(P-BG)/BG</th>
<th>P/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>8</td>
<td>7.1(1.1)</td>
<td>8.3(1.3)</td>
<td>6.4(1.1)</td>
<td>0.78</td>
</tr>
<tr>
<td>ALS patients</td>
<td>18</td>
<td>5.6(1.1)**</td>
<td>6.8(1.4)*</td>
<td>4.8(1.1)**</td>
<td>0.71</td>
</tr>
<tr>
<td>Limb onset</td>
<td>10</td>
<td>5.8(1.2)</td>
<td>6.9(1.8)</td>
<td>4.9(1.3)</td>
<td>0.71</td>
</tr>
<tr>
<td>Bulbar onset</td>
<td>8</td>
<td>5.5(1.0)</td>
<td>6.6(1.2)</td>
<td>4.6(0.9)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

*p<0.01; **p<0.005 vs controls. Data are given as mean (SD)

Figure 1  Striatal IPT uptake ratios of patients and controls. No correlation can be seen between specific striatal IPT binding and disease duration.

Discussion

In ALS, structures distinct from the upper and lower motor neurons, such as the prefrontal cortex, the spinocerebellar and dorsal tracts, show subclinical neuropathological involvement in some but not all patients. Neuropathological damage to the substantia nigra of patients with ALS has been previously documented. However, many of these patients showed atypical clinical features such as parkinsonism, dementia, or ophthalmoplegia. Although the concomitant occurrence of ALS and parkinsonian features in the same patient is reportedly more frequent than expected by chance, this does not seem to be true for ALS and idiopathic Lewy body Parkinson’s disease.

Figure 2  IPT-SPECT of two patients with ALS. The patient on the right exhibits a marked decrease in striatal IPT binding ((S-BG)/BG = 4.4; disease duration 28 months), whereas the patient on the left shows IPT binding in the upper normal range ((S-BG)/BG = 8.3), despite a disease duration of 106 months.
Presynaptic dopaminergic nerve terminals have usually been investigated with fluorodopa-PET, which primarily reflects levodopa metabolism. Dopamine transporter binding might provide a more accurate tool for estimating the number of dopaminergic neurons. This hypothesis is corroborated by recent data from a primate model showing that in vivo quantification of dopamine transporter binding strongly correlates with the number of striatal dopaminergic nerve terminals as assessed by postmortem autoradiography. However, the possibility that down regulation or altered post-translational processing of the dopamine transporter might contribute to the decreased striatal IPT binding cannot be ruled out.

The imaging method and characteristics of IPT have been described in detail previously. The uptake ratio used in our study may serve as a measure of specific IPT binding to striatal structures. With our study design no attempt was made to prove that outcome measures are linearly related to the density of dopamine transporters. As measurements were performed during the washout phase of striatal activity, outcome measures theoretically could have non-linearly overestimated differences between patients and controls.

In a PET study on 16 patients with ALS, Takahashi et al. found a significant negative correlation between 6-fluorodopa uptake and duration of disease. Four patients had an uptake rate <2 SD below the control mean, whereas the mean uptake was not significantly different from the control value. We did not find any correlation with disease duration, despite the inclusion of four patients with a prolonged clinical course. This is in agreement with recent data from patients with familial ALS. However, due to the few patients, we cannot completely exclude the possibility of a correlation between dopaminergic damage and disease duration in ALS. The overlap between patients and controls seen in both our study and the previous one is consistent with the subclinical nature of the involvement of the dopaminergic system in ALS. Interestingly, although transgenic SOD1 mice display midbrain dopaminergic degeneration, patients with familial ALS carrying SOD1 mutations were less likely to show dopaminergic damage as compared to non-SOD1 patients with familial ALS.

Taken together, our data suggest a heterogeneity in the ALS patient population, with a significant subset of patients whose disease subtype is more likely to affect nigrostriatal dopaminergic cells. This hypothesis is consistent with the well known genetic heterogeneity in familial ALS, implying that numerous types of chronic damage to motor neurons can ultimately lead to the common final pathway of the disease. Follow up measurements are currently in progress to corroborate and extend the findings of this pilot study.