A Positron Emission Tomography Study on the Role of Nigral Lesions in Parkinsonism in Patients With Amyotrophic Lateral Sclerosis

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Background: Patients with amyotrophic lateral sclerosis (ALS) sometimes exhibit parkinsonism, but the lesion responsible for parkinsonism has not been extensively studied.

Objective: To test whether nigrostriatal system dysfunction is responsible for parkinsonism in ALS.

Design: From the 182 ALS patients who were admitted to our neurology ward during the past 10 years, we extracted all the patients who satisfied the criteria of both parkinsonism and ALS.

Setting: The University of Tokyo Hospital.

Methods: We conducted [18F]L-dopa and [11C]N-methylspiperone positron emission tomography and technetium Tc 99m hexamethylpropyleneamine oxime single-photon emission computed tomography studies on 5 patients with ALS manifesting overt parkinsonism.

Results: Two male and 3 female patients (average age, 63.2±5.8 years) had ALS for an average of 28.6±21.5 months and had parkinsonism for an average of 15.2±11.4 months. Features of their parkinsonism were characterized by outstanding bradykinesia without resting tremor or dementia. The results of positron emission tomography studies indicated normal nigrostriatal function, but those of single-photon emission computed tomography demonstrated decreased blood flow in the frontotemporal cortices.

Conclusion: It is likely that parkinsonism in ALS is due to cortical lesions rather than nigrostriatal dysfunction and that both symptoms are the clinical manifestation of frontotemporal dementia with motor neuron diseases, including classic ALS.

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PATIENTS WITH AMYOTROPHIC lateral sclerosis (ALS) or motor neuron disease (MND) rarely exhibit clinically overt parkinsonism.1 Neuropathological studies of ALS report changes in the extramotor systems, including the substantia nigra, but also note rare findings of Lewy bodies in the affected substantia nigra.2 Neuroimaging studies have demonstrated a subclinical reduction of striatoni- gral dopaminergic systems in ALS patients without clinically overt parkinsonism.3 Therefore, it is possible that nigrostriatal system dysfunction occurs in ALS, but is not responsible for parkinsonism. We conducted [18F]L-dopa and [11C]N-methylspiperone positron emission tomography (PET) scans and technetium Tc 99m hexamethylpropyleneamine oxime single-photon emission computed tomography studies on 5 patients who exhibited both parkinsonism and ALS to further clarify the neurophysical effects of these combined conditions.

PATIENTS

Among the 2485 inpatients in the neurology ward of the University of Tokyo Hospital during the past 10 years (1995-2005), 182 patients were diagnosed with probable or definite ALS according to the revised El Escorial criteria.4 Ten of these 182 patients exhibited clinically overt parkinsonism, and 5 of these patients were studied with PET.

POSITRON EMISSION TOMOGRAPHY

Studies using [18F]L-dopa and [11C]N-methylspiperone PET were performed with a HEADTOME IV (Shimadzu, Kyoto, Japan). Fourteen transaxial images were obtained, with a 6.5-mm interval parallel to the orbitomeatal line. Final resolution of the reconstructed image was 7.5 mm in the transaxial direction and 9.5 mm in the axial direction at full width half maximum. Transmission scans to correct photon attenuation were carried out at the begin-
ning of each study with germanium 68/gallium 68 external rotating sources. $[^{11}C]N$-methylspiperone (1110 MBq) was injected intravenously and a static image was obtained over a 10-minute period, starting at 85 minutes after the $[^{11}C]N$-methylspiperone injection. The $[^{18}F]$L-dopa study was performed on a different day. One hundred twenty minutes after an intravenous injection of 370 MBq of $[^{18}F]$L-dopa, a 12-minute static image was taken. As previously described, the tissue radioactivity in each region of interest was corrected by subtracting the nonspecific retention in the cerebellar hemisphere; retention values of the caudate and putamen were expressed as the ratio of radioactivity in each region to that in the cerebellum.

### RESULTS

Demographic data of the patients are presented in Table 1. The 2 male and 3 female patients were 63.2±5.8 years of age (mean ± SD; range, 59-73 years), with a mean ALS duration of 28.6±21.5 months (range, 7-60 months) and mean parkinsonism duration of 15.2±11.4 months (range, 4-30 months). Three patients initially displayed bulbar palsy, 1 had weakness in the lower extremities, and 1 had a gait disturbance (hesitation). Parkinsonism appeared after onset of ALS symptoms in 4 patients and at the same time as ALS symptoms in 1 patient. All patients exhibited predominant upper and lower motor neuron signs, and 4 patients had additional bulbar symptoms. Lower motor neuron involvement was demonstrated by needle electromyogram in all patients. Parkinsonism was characterized by severe bradykinesia and moderate muscle rigidity without resting tremor. Four patients had severe disturbance in postural reflex with marked pulsion, 2 patients had outstanding frozen gait, and all 5 patients had moderate muscle rigidity; however, none of the patients had resting tremors. Three patients were treated with levodopa for 2 to 6 months without any significant beneficial effect on their parkinsonism (Table 2). None of the patients exhibited overt dementia, and all of them scored within normal ranges in the Mini-Mental State Examination and the Wechsler Adult Intelligence Scales–Revised. All patients exhibited normal brain magnetic resonance images. Both $[^{18}F]$L-dopa uptake and $[^{11}C]N$-methylspiperone binding were normal in all areas, including the caudal putamen (Table 3 and Figure). Single-photon emission computed tomography demonstrated a decrease in the cortical blood flow in 4 of 5 patients (Table 3).

### COMMENT

Our PET studies indicate that both preganglionic and postganglionic striatonigral dopaminergic systems were preserved in the patients who exhibited overt parkinsonism, in marked contrast to previous studies reporting that $[^{18}F]$L-dopa uptake was reduced in ALS patients without overt parkinsonism. Clinical and neuropathological studies have presented findings from patients with parkinsonism associated with ALS, including, other than classic type, ALS with dementia, multisystem atrophy, postencephalitic ALS, diffuse Lewy body disease, and familial ALS. Our ALS patients' clinical parkinsonism features were similar to those in the published literature but were atypical when compared with the typical features of Parkinson disease; all of these patients exhibited predominant akinesia, but none of them had exhibited resting tremor or considerable improvement after levodopa treatment. The relatively late age at onset and lack of dementia or autonomic dysfunction were common clinical features. There was a mild to moderate reduction in
Table 3. Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT) Findings of 5 Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>PET Striatum</th>
<th>[¹⁸F]-dopa</th>
<th></th>
<th>NMSP</th>
<th>SPECT</th>
<th></th>
<th>Cortex</th>
<th>Basal Ganglia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Ventral</td>
<td>2.13</td>
<td>2.15</td>
<td>3.73</td>
<td>3.85</td>
<td>Blood flow decreased in areas 4, 6, 8, 10, and in the right cerebellar hemisphere.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>2.18</td>
<td>2.10</td>
<td>3.78</td>
<td>3.94</td>
<td>Blood flow decreased in the right corpus striatum.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dorsal</td>
<td>2.00</td>
<td>1.94</td>
<td>3.40</td>
<td>3.37</td>
<td>Blood flow decreased in the right corpus striatum and in the right thalamus.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ventral</td>
<td>3.03</td>
<td>3.20</td>
<td>4.09</td>
<td>4.53</td>
<td>Blood flow decreased in the frontal lobe (greater decrease in the right frontal lobe) and in the left cerebellar hemisphere.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>3.20</td>
<td>3.00</td>
<td>4.46</td>
<td>4.70</td>
<td>Blood flow decreased in the bilateral corpus striatum and in the right thalamus.</td>
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<tr>
<td></td>
<td>Dorsal</td>
<td>2.96</td>
<td>2.58</td>
<td>3.90</td>
<td>4.09</td>
<td>Normal</td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td>Ventral</td>
<td>2.49</td>
<td>2.69</td>
<td>4.23</td>
<td>4.25</td>
<td>Blood flow decreased in the bilateral frontal lobe (especially area 6) and in the bilateral temporoparietal lobe.</td>
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<tr>
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<td>Intermediate</td>
<td>2.62</td>
<td>2.69</td>
<td>4.23</td>
<td>4.25</td>
<td>Normal</td>
<td></td>
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<tr>
<td></td>
<td>Dorsal</td>
<td>2.40</td>
<td>2.39</td>
<td>3.70</td>
<td>3.86</td>
<td>Blood flow decreased in the left basal ganglia.</td>
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<tr>
<td>4</td>
<td>Ventral</td>
<td>2.15</td>
<td>2.23</td>
<td>4.31</td>
<td>4.18</td>
<td>Normal</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Intermediate</td>
<td>2.46</td>
<td>2.40</td>
<td>4.44</td>
<td>4.60</td>
<td>Blood flow decreased in the right temporal occipital parietal lobe.</td>
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<tr>
<td></td>
<td>Dorsal</td>
<td>2.24</td>
<td>2.31</td>
<td>3.79</td>
<td>4.12</td>
<td>Blood flow decreased in the left basal ganglia.</td>
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<tr>
<td>5</td>
<td>Ventral</td>
<td>2.85</td>
<td>2.90</td>
<td>3.23</td>
<td>3.31</td>
<td>Blood flow decreased in the right temporal occipital parietal lobe.</td>
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<td></td>
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<tr>
<td></td>
<td>Intermediate</td>
<td>3.05</td>
<td>3.10</td>
<td>3.82</td>
<td>3.56</td>
<td>Blood flow decreased in the left basal ganglia.</td>
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<td></td>
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<tr>
<td></td>
<td>Dorsal</td>
<td>2.41</td>
<td>2.56</td>
<td>3.18</td>
<td>3.16</td>
<td>Blood flow decreased in the left basal ganglia.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Figure. Positron emission tomography images of study patients. A, [¹⁸F]-dopa images. B, [¹¹C]N-methylspiperone images. Two adjacent sections including the basal ganglia are shown.
the number of neurons in the substantia nigra; Lewy bodies were rarely reported. These lines of evidence suggest that parkinsonism in ALS is not likely an association of Parkinson disease with ALS, but is likely due to pathological changes in areas other than the substantia nigra.

In this context, it is worth noting that isolated lesions in the supplementary motor area are associated with clinical features very similar to parkinsonism, dominated by severe akinesia and mild rigidity without resting tremor. Regional cerebral blood flow has been reported to be decreased in the frontal cortices, including the supplementary motor area of patients with Parkinson disease; however, flow could be reversed with antiparkinsonian treatment. Thus, clinical manifestations quite similar to parkinsonism can be produced by isolated cortical lesions in the supplementary motor area. Reduction of regional cerebral blood flow in the frontal and/or temporal cortices extending beyond the primary motor area has been demonstrated in both ALS with dementia and classic ALS without dementia. This observation is in accordance with our single-photon emission computed tomography scan results showing 4 patients with a decrease of regional cerebral blood flow in the frontal and/or temporal cortices.

The degree of regional cerebral blood flow reduction in the frontal and anterior temporal lobes has been reported to correlate with severity of dementia in ALS patients with associated dementia; these blood flow characteristics are indistinguishable from those seen in patients with frontotemporal dementia. Indeed, ALS is not infrequently (approximately 15% of cases) associated with frontotemporal dementia, and involvement of lower motor neurons was found in a group of patients with frontotemporal dementia without a prior diagnosis of ALS. A subclass of frontotemporal dementia with tau-negative and ubiquitin-positive inclusions has been classified as frontotemporal lobar degeneration with motor neuron disease (FTLD-MND) and frontotemporal lobar degeneration with motor neuron disease type (FTLD-MND type), respectively, depending on the presence or absence of clinically overt motor neuron signs. These diagnostic subclasses (FTLD-MND and FTLD-MND type) have been reported to comprise 40% of pathologically proven frontotemporal dementia cases. In addition, patients with frontotemporal dementia frequently exhibit parkinsonism, but neuropathological changes in the substantia nigra were more marked in patients with concomitant dementia irrespective of the presence or absence of parkinsonism, as compared with patients without dementia; hence, reduction of nigrostriatal dopaminergic function may not be associated with parkinsonism. Common pathological changes have been demonstrated in FTLD-MND, FTLD-MND type, and classic ALS without dementia, implying that these diseases comprise a clinicopathological spectrum rather than individual entities.

Taken together, parkinsonism associated with ALS or FTLD-MND may not be due to a dysfunction of the nigrostriatal dopaminergic neurons but rather frontal lesions including the supplementary motor area.

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REFERENCES


