A 41 year old man with parkinsonism and pyramidal signs is described. He was non-responsive to levodopa and dopamine receptor agonists but dramatically responded to trihexyphenidyl. In this patient, brain MRI showed bilateral hyperintensities along the corticospinal tracts on T2 weighted images. PET studies showed a decrease in $^{18}$F-6-fluorodopa (FD) uptake in the putamen contralateral to the more affected limbs and normal D$_2$ receptor binding in the putamen. The PET and MRI findings and responsiveness to antiparkinsonian agents suggested degeneration of nigrostriatal dopaminergic neurons, striatal output pathways, and corticospinal tracts.

**CASE REPORT**

A 41 year old man with no remarkable personal or familial medical history was admitted to our clinic with complaints of clumsiness in the left upper limb and gait disturbance. He was well until 36 years of age, when he developed postural tremor and clumsiness in his left hand. At the age of 38, he was diagnosed as having idiopathic Parkinson’s disease and was started on carbidopa/levodopa (20/200 to 90/900 mg/day) and bromocriptine (2.5 to 15 mg/day) after 6 months of treatment. However, his condition progressively deteriorated. The dose of levodopa and bromocriptine was increased, but still non-responsive to dopaminergic medications and the adverse events, these agents were discontinued. On neurological examination, he had bilateral cogwheel rigidity, which was worse on the left than the right, and mild bradykinesia. Although resting tremor was absent, postural tremor was present in his hands. Deep tendon reflexes were moderately exaggerated, and muscle tone of the lower limbs was spastic, but plantar responses were bilaterally flexor. His gait was spastic as well as slow and unstable with festination on initiation of walking. Postural reflexes were impaired with retropulsion. The remaining neurological findings were normal, including those for autonomic function and cerebellar function. Laboratory investigations were normal, including serum chemistry, thyroid function, serum copper, and serum ceruloplasmin.

Concentration of homovanillic acid in CSF was 13.5 ng/ml (normal: 33.1 (SD 11.2) ng/ml). The concentration of plasma levodopa was 2.2 ng/ml before oral carbidopa/levodopa (10/100 mg) administration; it increased to 854.0 ng/ml at 15 minutes after administration, and then fell to 521.0 ng/ml at 30 minutes, 376.5 ng/ml at 60 minutes, and 82.0 ng/ml at 120 minutes. Brain MRI showed no atrophy in the cerebellum and brain stem but demonstrated bilateral hyperintensities along the corticospinal tracts from the internal capsules to the cerebral peduncles on T2 weighted images (fig 1). Due to the patient’s failure to respond to levodopa and dopamine receptor agonists, a trial of trihexyphenidyl (2 mg twice daily for 2 weeks followed by 2 mg three times daily), started. A few days after the beginning of the trial, the patient reported improvement. Objectively, there was a noticeable improvement in his walking, rigidity, and bradykinesia, but spasticity of the lower limbs remained unchanged. Four weeks after the administration of trihexyphenidyl, his unified Parkinson’s disease rating scale (UPDRS) motor score decreased from 33 to 18.

**Positron emission tomography**

Studies using FD and $^{11}$C-N-methylspiperone (NMSP) PET were performed with a HEADTOME-IV (Shimadzu, Kyoto, Japan) 1 month after the dopaminergic medications had been stopped. Fourteen transaxial images with a 6.5 mm interval parallel to the orbitomental line were obtained. The final reconstructed image resolution was 7.5 mm in the transaxial direction and 9.5 mm in the axial direction at full width half maximum. Transmission scan to correct the photon attenuation was carried out at the beginning of each study with $^{68}$Ga external rotating sources. NMSP ($1110$ MBq) was injected intravenously and a static image was obtained from 85 to 95 minutes postinjection. The FD study was performed on a different day. After an intravenous injection of 370 MBq FD, a 12 minute static image at 120 minutes postinjection was acquired. As previously described, the tissue radioactivity was corrected by the non-specific retention in the cerebellar hemisphere and the ratios of caudate and putamen to the cerebellum at 90 minutes with NMSP and at 120 minutes with FD were evaluated.

The NMSP uptake ratio to cerebellum was 5.06/4.92 (right/left) in the caudate nucleus, 4.99/5.13 in the anterior putamen. The putamen and caudate were relatively symmetrical, with the caudate slightly more symmetrical than the putamen.

**Abbreviations:** FD, $^{18}$F-6-fluorodopa; UPDRS, unified Parkinson’s disease rating scale; NMSP, $^{11}$C-N-methylspiperone
putamen, and 4.76/4.96 in the posterior putamen which showed no significant abnormality compared with normal control subjects (n=4; 4.61 (0.41)/4.89 (0.40) (mean (SD)) in caudate nucleus, 5.07 (0.26)/4.98 (0.28) in the anterior putamen, and 4.64 (0.37)/4.80 (0.32) in the posterior putamen). The FD uptake ratio was decreased in both sides of the caudate (1.95/2.08; right/left), anterior putamen (1.76/1.97), and posterior putamen (1.48/1.74) compared with normal control subjects (n=9; 2.56 (0.24)/2.56 (0.19) in the caudate, 2.73 (0.21)/2.74 (0.26) in the anterior putamen, and 2.62 (0.21)/2.61 (0.17) in the posterior putamen) (fig 2). The decrease in FD uptake was more prominent in the right than the left side and more prominent on the posterior putamen than the anterior putamen or caudate nucleus.

DISCUSSION

Our patient presented with early onset parkinsonism with pyramidal signs. The parkinsonian symptoms began asymmetrically on the left side and progressed slowly. These clinical features are very similar to those of Parkinson’s disease. Studies with PET showed a marked decrease in FD in the striatum, particularly in the posterior putamen, contralateral

Figure 1  [A] T2 weighted MRI of the patient shows bilateral high signal intensities in posterior limbs of the internal capsule. [B] T2 weighted MRI (coronal section) of the patient shows bilateral high signal intensities along the corticospinal tracts from the internal capsules to the cerebral peduncles.

Figure 2  PET images with FD and NMSP. The patient’s FD uptake in the striatum is decreased, particularly in the posterior part of putamen, compared with a normal subject (upper figures). On the contrary, the patient has normal striatal NMSP uptake (lower figures).
to the more affected limbs and normal binding of NMSP in the putamen. These findings are consistent with those of Parkinson's disease and suggest a dysfunction of the nigrostriatal pathway that would presumably respond to treatment with levodopa or dopamine receptor agonists. Because of no response to dopaminergic medications in spite of normal D2 receptor binding in the striatum, we think that our patients had not only presynaptic dysfunction but dysfunction of striatal output pathways. Furthermore, spasticity of the lower limbs and the abnormal hyperintensities along the pyramidal tracts on T2 weighted images showed possible degeneration of pyramidal tracts.

The remarkable characteristic of our patient is the beneficial effect of trihexyphenidyl but not of levodopa and dopamine receptor agonists. The extrapyramidal signs improved with the low dose of trihexyphenidyl (4 mg/day) but not with the moderate dose of carbidopa/levodopa (90/900 mg/day) and bromocriptine (15 mg/day). Trihexyphenidyl, an anticholinergic agent, is often used as an antiparkinsonian agent that ameliorates symptoms of Parkinson's disease by inhibiting the relative acetylcholine excess as a result of the deficient nigrostriatal dopaminergic activity and potentiates the synaptic actions of dopamine in the striatum by inhibiting dopamine uptake into synaptosomes. These known pharmacological functions fail to explain the effect of trihexyphenidyl in our patient.

Mitsui et al reported on two siblings, with consanguinity in their parents, who exhibited parkinsonism with pyramidal signs and cerebellar ataxia. Anticholinergic drugs, but not levodopa, had a beneficial effect. They concluded that there was a dysfunction of an "indirect pathway" involving the globus pallidus, the subthalamic nucleus, and the nigrostriatal system because anticholinergic drugs have an antagonistic action to N-methyl-D-aspartate. Both our patients and their parents were responsive to trihexyphenidyl but not levodopa, and showed the presence of pyramidal signs. However, their patients had cerebellar signs and consanguinity in the parents and ours had neither.

From the point of view of parkinsonism with pyramidal signs, pallidopiramidal disease must be considered as a differential diagnosis. Pallidopiramidal disease, a rare disease manifested by a parkinsonian syndrome with pyramidal signs, was first described by Davison.

Similar patients have been described whose parkinsonian features adequately respond to levodopa therapy, unlike our patient's failure to respond. The age of onset was much younger in Davison's patients than in ours. Although we also considered if the patient had parkinson mutations, the existence was not studied because we could not obtain his consent. However, the clinical features of our patient were different from those of patients with autosomal recessive juvenile parkinsonism, who showed a striking response to levodopa, sleep benefit, and foot dystonia. The peculiar responsiveness to antiparkinsonian agents and the MRI and PET findings in our patient suggest a previously undescribed condition. Trihexyphenidyl is an agent worth trying for parkinsonian patients resistant to levodopa and dopamine receptor agonists.

**REFERENCES**


