SHORT REPORT

Primary lateral sclerosis presenting parkinsonian symptoms without nigrostriatal involvement

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We encountered three patients with primary lateral sclerosis (PLS) showing bradykinesia, frozen gait, and severe postural instability, as well as slowly progressive spinobulbar spasticity. Cranial magnetic resonance (MR) imaging showed precentral gyrus atrophy. Central motor conduction was markedly prolonged or failed to evoke a response. Positron emission tomography (PET) showed significant reduction of [^{18}F]fluoro-2-deoxy-D-glucose uptake in the area of the precentral gyrus extending to the prefrontal, medial frontal, and cingulate areas. No abnormalities were seen in the nigrostriatal system with PET using [^{18}F]fluorodopa or [^{11}C]raclopride or with proton MR spectroscopy. Thus, widespread prefrontal, medial, and cingulate frontal lobe involvement can be associated with the parkinsonian symptoms in PLS.

Primary lateral sclerosis (PLS), a form of motor neurone disease (MND), is a rare non-familial neurodegenerative disorder. PLS is characterised by slowly progressive spinobulbar spasticity reflecting exclusive involvement of upper motor neurones.^{1,2} Spastic dysarthria and paraparesis, emotional lability, and pseudobulbar palsy are major clinical features of PLS.

On rare occasions, MND may give rise to bradykinesia and motor fatigue. These probably arise from generalised spasticity. However, freezing of gait and severe postural instability suggest more widespread system involvement and have not been well described. We present three patients with PLS showing these two parkinsonian-like features in addition to spinobulbar spasticity and bradykinesia. We investigated these symptoms in the patients using positron emission tomography (PET) including [^{18}F]fluoro-2-deoxy-D-glucose (FDG), [^{18}F]fluorodopa (F-dopa), and [^{11}C]raclopride (RACLO), as well as proton magnetic resonance spectroscopy (^1H -MRS).

PATIENTS AND METHODS

Patients

The three patients, all men, fulfilled Pringle's diagnostic criteria for PLS.¹ None had a familial history of PLS, and all showed a slowly progressive course.

Patient 1

Slowness and clumsiness of the right hand became evident at the age of 43 years. Spasticity involved the right leg, and caused spastic dysarthria by age 44. Soon afterward, the spasticity spread to all four limbs. At age 45, he showed a severely frozen gait and occasional falling, especially backward. He also showed severe akinetic posturing and postural instability. He was unable to walk unaided by age 51. Speech gradually became unintelligible because of severe spastic dysarthria, and he was unable to speak aloud at age 53.

Patient 2

Frozen gait with initial hesitation developed at age 62, followed by cramping in both legs during sleep at age 64. He began to experience speech disturbance with spastic dysarthria and bouts of unprovoked laughing and crying. He showed severe postural instability with occasional falling, especially backward, as well as akinesia. He could not stand up or initiate walking smoothly. He also showed facial hypokinesia with reduced blinking. All symptoms showed gradual progression.

Patient 3

Postural instability and gait disturbance were present by age 68. He noted left arm clumsiness, and paucity of movement gradually worsened and progressed to akinesia. He developed spastic dysarthria at age 69. He showed occasional falling, especially backward. All symptoms showed gradual progression.

Methods

PET study

PET studies were performed using a ECAT EXACT HR47 (CTI/Siemens, Knoxville, TN) and HEADTOME-IV (Shimadzu, Kyoto, Japan) for three patients with F-dopa, FDG, and two of the three patients with RACLO in three dimensional acquisition mode, which yielded 47 simultaneous planes, with an axial full width half maximum resolution of 4.8 mm and an inplane resolution of 3.9×3.9 mm. The protocol for F-dopa and FDG injection has been described previously.^{3,4} RACLO was injected at 494 MBq, and scanning consisted of 19 time frames for a total of 64 minutes. Photo data were presented with three dimensional stereotactic surface projection (3D-SSP) as normalised for the whole brain. 3D-SSP was performed as described by Minoshima *et al.*⁵ Data were normalised to global activities. The patients' datasets were compared individually with the normal database by calculating a z score on a pixel-to-pixel basis, and were displayed in a 3D-SSP display for visual inspection.

 ^1H -MRS study

^1H -MRS was performed with a 3.0-T system (Bruker, Germany) using a standard head coil with circular polarisation. The spectroscopic volume of interest was placed in the putamen (1 cm^3). ^1H -MR spectra were acquired using a point-resolved spectroscopy sequence with chemical-shift selective water suppression. The metabolic ratios *N*-acetyl-aspartate (NAA)/creatine (Cr), and choline containing phospholipids (Cho)/Cr were determined as semiquantitative values. Data were compared with those of 18 age matched control subjects. The protocol was as previously described.⁶

Abbreviations: FDG, [^{18}F]fluoro-2-deoxy-D-glucose; F-dopa, [^{18}F]fluorodopa; PET, positron emission tomography; ^1H -MRS, proton magnetic resonance spectroscopy; MND, motor neurone disease; PLS, primary lateral sclerosis; RACLO, [^{11}C]raclopride

Table 1 Characteristics of the three patients with primary lateral sclerosis

	Patient 1	Patient 2	Patient 3
Age at examination, (years)/sex	53/M	66/M	72/M
Duration of illness (years)	10	4	4
Spastic dysarthria	++	++	++
Babinski sign (left/right)	Present/ present	Present/ present	Present/ present
Spasticity in limbs	++	++	++
Bradykinesia	++	++	++
Postural instability	+++	+++	+++
Frozen gait	++	++	+
Decrease of amplitude in finger and foot tapping	++	++	++
Rigidity	-	-	-
Tremor	-	-	-

-, absent; +, mild; ++, moderate; +++, severe.

RESULTS

The clinical features of the three patients are shown in table 1. General physical examinations were normal in all patients. On neurologic examination, all three patients showed spastic dysarthria. Ocular movements were saccadic, but covered a full range. Muscle power was essentially normal (patient 1, all limbs normal; patient 2, Medical Research Council grade 4/5 in the legs and 5/5 in the arms; patient 3, 4/5 in the left biceps and iliopsoas muscles, but otherwise normal). Muscle tone was greatly increased in the limb flexor muscles but not in the extensors, this was appreciated best upon rapid movement. The jaw jerk reflex and deep tendon reflexes in the legs were brisk, and plantar responses were bilaterally extensor in all patients. No wasting, fasciculations, amyotrophy, sensory impairment, or cognitive dysfunction was seen in any patient.

With respect to parkinsonian symptoms, slowness and fatiguing of voluntary movement, poverty of movement, loss of facial expression, and reduction of blinking were observed in all patients. Finger tapping and foot tapping were performed slowly, with gradual reduction in amplitude. All patients showed a shuffling, short stepped gait with backward falling en bloc without corrective steps when equilibrium was momentarily upset. The posture of patient 1 was

stooped. Patient 2 showed some emotional lability. Patients 1 and 2 showed freezing, particularly at initiation of gait, although ability to move otherwise was relatively preserved. Kinésie paradoxale was not observed. Levodopa was not effective in any patient.

Haematological and serum biochemistry tests gave normal results. Tests for human T lymphocytotropic virus 1 and syphilis were negative in all patients. Cerebrospinal fluid test results were normal except in patient 2, who had slightly elevated protein (65 mg/dl). MR images of the cervical spine were normal except for non-specific degenerative changes without spinal cord compression. Cranial MR images showed generally mild cortical atrophy including the precentral gyrus in all patients.^{2 7 8} Nerve conduction studies were normal. Concentric needle electromyography (EMG) showed only focal neurogenic change in the right first dorsal interosseous muscle (patients 1 and 2), left gastrocnemius (patient 2), and right triceps (patient 1) without fulfilling revised El Escorial criteria.⁹ In all patients, motor evoked potentials showed markedly increased central motor conduction time or failed to evoke responses in the lower limbs.^{2 10}

FDG-PET showed significantly decreased glucose uptake in the area of the precentral gyrus (table 2, fig 1). The reduced glucose uptake extended to the medial frontal lobe including the prefrontal area (patients 1 and 2) and the anterior cingulate cortex (patients 2 and 3). In addition, patient 3 showed significantly low glucose uptake in the medial posterior parietal lobe. No significant reduction of glucose utilisation was observed in the basal ganglia in any patient. In addition, F-dopa and RACLO PET showed no significant reduction of uptake in the putamen and caudate nucleus compared with control subjects. NAA/Cr and Cho/Cr values in the putamen were also within the normal range.

DISCUSSION

We studied three patients with PLS who, in addition to the expected bulbospinal spasticity, presented poverty of movement, loss of facial expression with reduced blinking, frozen gait with initial hesitation, gradual reduction in finger and foot tapping rate and amplitude, and severe postural instability that mimicked parkinsonism. They also all showed symmetric spasticity, hyperreflexia, extensor plantar responses, and spastic dysarthria. No fasciculations, muscle

Figure 1 Positron emission tomographic (PET) images are shown for three patients with primary lateral sclerosis (PLS). (A) An FDG-PET image (right medial view) shows significant reduction of FDG uptake from the precentral cortex to the supplementary motor cortex (patient 1); from the precentral cortex to the anterior cingulate cortex (patient 2); and near the precentral gyrus (patient 3). (B) No uptake reductions were observed in the basal ganglia with F-dopa (all patients) or (C) [¹¹C]raclopride (patients 2 and 3).

Table 2 Electrophysiological, MRI, and ¹H-MRS features in the three patients with primary lateral sclerosis

	Patient 1	Patient 2	Patient 3
Nerve conduction	Normal	Normal	Normal
EMG	±	±	–
Central motor conduction time			
UE (normal; <9 ms)	No response evoked	17.6 ms	No response evoked
LE (normal; <15 ms)	No response evoked	No response evoked	No response evoked
MRI			
¹ H-MRS	Precentral gyrus atrophy	Precentral gyrus atrophy	Precentral gyrus atrophy
Putamen	Normal	Normal	Normal
PET			
FDG	Decrease in precentral gyrus and SMA	Decrease in precentral gyrus, AC, and SMA	Decrease in precentral gyrus and AC
F-dopa	Normal	Normal	Normal
RACLO	Not available	Normal	Normal

±, neurogenic change present but not fulfilling revised El Escorial criteria; –, no abnormality.

AC, anterior cingulate cortex; EMG, electromyography; FDG, [¹⁸F]fluoro-2-deoxy-D-glucose; F-dopa, [¹⁸F]fluorodopa; UE, upper extremities; LE, lower extremities; MRI, magnetic resonance imaging; ¹H-MRS, proton magnetic resonance spectroscopy; PET, positron emission tomography; RACLO, [¹¹C]raclopride; SMA, supplementary motor area.

atrophy, or weakness were noted, and the sensory and other systems were uninvolved. No patient fulfilled the diagnostic criteria for amyotrophic lateral sclerosis,⁹ but all fulfilled the criteria for PLS proposed by Pringle *et al.*¹ In the symptomatology of PLS, facial hypokinesia and lack of animation have been reported,¹ but patients presenting not only generalised bradykinesia but also parkinsonian-like frozen gait with initial hesitation and severe postural instability have not been well described.

Several neurodegenerative diseases including multiple system atrophy, frontotemporal dementia,¹¹ and progressive supranuclear palsy show pyramidal tract signs and parkinsonism. These signs have also been reported concomitant with amyotrophic lateral sclerosis and Parkinson's disease.^{12–13} However, the present patients did not show symptoms clearly indicative of these diseases. Furthermore, characteristic signal abnormalities and morphologic changes were not observed on MR images. None of the three patients exhibited nigrostriatal system involvement on PET (FDG, F-dopa, and RACLO) and ¹H-MRS images. In addition, there was no improvement with dopaminergic medication. Considering all observations, the parkinsonian symptoms in our three patients were unlikely to have been caused by nigrostriatal involvement.

Frozen gait and severe postural instability including falling backward en bloc without corrective steps are commonly reported in pathologically proved progressive supranuclear palsy, vascular parkinsonism, and advanced Parkinson's disease.^{14–15} Although the pathophysiological background of such symptoms is unclear, several PET studies have emphasised the causal importance of medial frontal lobe involvement.^{16–18} In addition, pathological examination of patients showing frozen gait suggested that the frontal lobe as well as the basal ganglia would represent essential lesion sites.^{14–15} The most striking observation in the present study was that FDG-PET uptake showed significant reductions extending from the precentral gyrus to the medial frontal cortex in all patients, including the supplementary motor area and anterior cingulate cortex. In contrast, the basal ganglia of all three patients were well preserved according to PET and ¹H-MRS. Considering these observations together, it would seem that not only generalised spasticity but also widespread frontal lobe impairment was responsible for the parkinsonian symptoms in our patients with PLS.^{7–15}

Recent MRI and PET studies have demonstrated widespread involvement of the precentral gyrus as well as ventrolateral, prefrontal, and anterior cingulate cortices in PLS.²⁰ Although spasticity may mask the presence of other

clinical features, precise radiological study is expected to shed further light on the pathophysiology and symptomatology of PLS. We believe that parkinsonian symptoms in PLS without nigrostriatal involvement can result from frontal lobe involvement.

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