The Stripe of Primary Lateral Sclerosis

Focal Primary Motor Cortex Hypometabolism Seen on Fluorodeoxyglucose F18 Positron Emission Tomography

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Background: Primary lateral sclerosis (PLS) is a progressive upper motor neuron neurodegenerative condition. The diagnosis is made using clinical history, objective neurological assessment, and exclusion of other neurodegenerative disorders.

Objective: To evaluate the role of fluorodeoxyglucose F18 positron emission tomography and 3-dimensional stereotactic surface projection in the diagnosis of PLS.

Design: Case series.

Setting: Outpatient neurology clinic.

Patients: Three cases of probable PLS.

Intervention: Fluorodeoxyglucose F18 positron emission tomography in 3 patients with PLS.

Results: Three patients (2 male and 1 female; mean age, 65 years) were identified with a clinical diagnosis of PLS. Fluorodeoxyglucose F18 positron emission tomography demonstrated varying degrees of primary motor cortex hypometabolism.

Conclusion: Fluorodeoxyglucose F18 positron emission tomography and 3-dimensional stereotactic surface projection provide a useful diagnostic method to support a clinical diagnosis of PLS.

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PRIMARY LATERAL SCLEROSIS (PLS) is a progressive upper motor neuron neurodegenerative disorder. Clinical presentation and disease course are characterized by slowly progressive symptoms ranging from bulbar dysfunction, spastic dysthria, dysphagia, and emotional lability to corticospinal tract findings such as limb weakness with spasticity.1 Pure PLS represents a more benign neurodegenerative condition thought to affect only upper motor neurons and is characterized with a better prognosis than amyotrophic lateral sclerosis (ALS).2 For the clinician, PLS is a challenging diagnosis because it can mimic several disorders such as Parkinson disease, multiple system atrophy, corticobasal syndrome,3 neurofilament inclusion body disease,4 and hereditary spastic paraplegia.5

In PLS, functional neuroimaging can highlight selective upper motor neuron degeneration in areas such as the pericentral cortex6 or primary motor cortex.7 However, functional imaging studies such as positron emission tomography (PET) are not always interpreted uniformly.8 In clinical practice, fluorodeoxyglucose F18 (FDG) is used to evaluate regional cerebral glucose metabolism. Research PET ligands such as [11C]flumazenil can identify cortical neuronal dysfunction but are not widely available. We used the clinical tool of 3-dimensional stereotactic surface projection for the interpretation of FDG-PET and compared metabolic changes with a database of age-matched healthy individuals using Cortex ID software (GE Healthcare, Waukesha, Wisconsin). In each case, this technique identified a homogeneous pattern of hypometabolism in the primary motor cortex, which supports the diagnosis of suspected PLS.

METHODS

We retrospectively reviewed the medical records of patients evaluated by one of us (K.A.J.) with FDG-PET imaging and a diagnosis of PLS. The diagnosis of PLS was made first, and FDG-PET was obtained for further clarification. Once patients were identified, further information in the medical record including age, sex, presenting symptoms, neurological findings, laboratory testing results, neurophysiological testing results, and radiological features were reviewed. Each FDG-PET study was processed using Cortex ID software.
RESULTS

We identified 3 cases with a clinical diagnosis of PLS, and FDG-PET was completed in each case. The Table illustrates pertinent details of the clinical evaluation.

PATIENT 1

A 60-year-old, right-handed man presented with a 4- to 5-year history of left upper extremity and bilateral lower extremity weakness and rigidity along with dysarthria. He first noticed difficulty with fine motor control of his left hand. Shortly thereafter, he noticed a tendency to drag his left leg. His symptoms progressed to the right lower extremity over a 6-month period. He developed pronounced gait imbalance and had numerous falls. More recently, he developed mild speech difficulty as well as pseudobulbar affect.

The patient presented with an outside diagnosis of corticobasal syndrome based on mild right upper extremity parkinsonism, spasticity, and magnetic resonance imaging changes suggestive of subtle parietal lobe atrophy. He had numerous normal results on electromyography (EMG) and unremarkable results on electroencephalography. Results from laboratory studies were normal, including ceruloplasmin, antinuclear antibody, Lyme disease serologies, anti-Sjögren syndrome A and anti-Sjögren syndrome B antibodies, vitamin E, calcium, parathyroid hormone, vitamin B12, folate, and erythrocyte sedimentation rate. Physical examination revealed mild dysarthria, pseudobulbar affect, right-greater-than-left upper extremity spasticity, diffusely brisk reflexes, bilateral circumduction of gait, and a positive pull sign.

There was a notable absence of both cortical sensory deficits and myoclonus. Repeat EMG failed to show lower motor neuron disease. Speech pathology consultation confirmed spastic dysarthria. Results on further laboratory studies including thyroid-stimulating hormone, Lyme disease serologies, syphilis serologies, and lactate were normal. Magnetic resonance imaging of the head revealed mild generalized cerebral and cerebellar atrophy with no evidence of parietal asymmetry. Scanning with FDG-PET with Cortex ID software showed prominent hypometabolism over both motor cortices (Figure 1).

PATIENT 2

A 65-year-old, left-handed man presented with a 7-year history of progressive dysarthria and gait spasticity. He first noticed mild slurring of speech along with difficulty clearing his throat. This was shortly followed by left leg spasticity with clonus. His gait continued to deteriorate over time and he was evaluated at an outside facility for marked imbalance and falls. More recently,

Table. Clinical Characteristics

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Symptom Duration, y</th>
<th>CST Pattern of Spasticity</th>
<th>Bulbar Spasticity</th>
<th>Pseudobulbar Affect</th>
<th>EMG and NCS Results</th>
<th>CSF Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/60</td>
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<td>Bilateral lower extremity</td>
<td>Spastic dysarthria</td>
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<td>Bilateral lower extremity</td>
<td>Spastic dysarthria</td>
<td>Yes</td>
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<td>Normal</td>
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<tr>
<td>3/F/69</td>
<td>3</td>
<td>Left upper extremity</td>
<td>Spastic dysarthria</td>
<td>Yes</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; CST, corticospinal tract; EMG, electromyography; NCS, nerve conduction study.

Figure 1. Images from a 60-year-old man with bulbar and upper extremity spasticity. Fluorodeoxyglucose F18 (FDG) positron emission tomography (PET) shows a right-greater-than-left linear hypometabolic stripe along the primary motor cortex (arrows). FLAIR MRI indicates fluid-attenuated inversion recovery magnetic resonance image; 3-D SSP, 3-dimensional stereotactic surface projection.
he developed symptoms of emotional lability. His family history was notable for a brother and sister with spas- tic torticollis as well as a maternal aunt with ALS. Physical examination revealed spastic dysarthria, bilateral lower extremity hyperreflexia, and a spastic gait.

Workup included nerve conduction studies and EMG, which failed to show any lower motor neuron disease. Results from laboratory studies including electrolyte panel, paraneoplastic antibody test, Lyme disease serologies, human T-cell lymphotrophic virus type 1 and type 2 studies, human immunodeficiency virus studies, hexosaminidase level, heavy metal screen for copper, peroxisomal panel, and a cerebrospinal fluid analysis were normal. Genetic testing results for hereditary spastic paraplegia (sequence variants SPG3A, SPG4, NIPA1, and SPG31) and Kennedy disease/spinal bulbar muscular atrophy were negative.

Results from both computed tomography and magnetic resonance imaging of the brain were normal. Results from diffusion tensor imaging of the corticospinal and corticobulbar tracts were unremarkable. Scanning with FDG-PET demonstrated bilateral hypometabolism in the motor strip. Positron emission tomography with 3-dimensional stereotactic surface projection showed additional diminished activity in the motor strip bilaterally (Figure 2).

PATIENT 3

A 69-year-old, right-handed woman presented with a 3-year history of progressive dysarthria, dysphonia, and dyspha-
gia. While her speech was initially affected, over time she noticed difficulty with chewing and swallowing, difficulty moving the left side of her face, drooling, and weakness of her left upper extremity. Also, she recently developed marked emotional lability characterized by inappropriate crying or laughter. Her facial weakness resulted in a loss of facial expression. She presented with an outside diagnosis of progressive supranuclear palsy.

Physical examination results were notable for spastic dysarthria, left upper extremity spasticity with clonus, and brisk reflexes in the left-greater-than-right upper extremity. Speech consultation confirmed spastic dysarthria with evidence of stridor. Results of EMG were normal and failed to show evidence of lower motor neuron involvement. Results of laboratory studies including paraneoplastic antibodies, cobalamin, thyroid-stimulating hormone, antinuclear antibodies, ganglioside antibodies, and Lyme disease antibodies were negative.

Results of magnetic resonance imaging of the head, including diffusion tensor imaging of the corticospinal and corticobulbar tracts, were unremarkable. Positron emission tomography with 3-dimensional stereotactic surface projection showed evidence of hypometabolism over the motor and supplementary motor cortices, right greater than left (Figure 3).

**COMMENT**

Clinically, the distinction between ALS and PLS is not always clear as some patients who present with upper motor neuron dysfunction may eventually progress to ALS, while others can remain with only upper motor neuron dysfunction symptoms. Even so, other disorders can mimic PLS and include hereditary spastic paraplegia and atypical parkinsonism. A clinician must rely on clinical symptoms and examination findings and must take the duration of symptoms into account to secure a diagnosis. For this reason, some have argued for a 3- to 4-year duration of symptoms to be required for a diagnosis of PLS.²,⁶

The primary motor cortex seems to be the main region of vulnerability in PLS. There are few autopsy studies available for PLS. This is likely due to both the rarity of PLS and its relatively good prognosis. However, from the existing pathological data, PLS tends to affect the precentral gyrus or primary motor cortex and may show a decreased number of Betz cells.¹ Comparatively, PLS appears to involve the primary motor cortex more so than pure ALS.¹⁰

Neuroimaging studies have confirmed selective vulnerability of the primary motor cortex. Diffusion tensor imaging suggests that when compared with patients with ALS, those with PLS show more axon and myelin breakdown in the primary motor cortex as well as the corpus callosum.¹¹ Primary motor cortex involvement is confirmed on serial magnetic resonance imaging,¹² magnetic resonance spectroscopy,¹³ [¹¹C]flumazenil (cortical binding compound) PET,⁷ and FDG-PET.⁶ Patients with ALS seem to have more diffuse frontal cortical hypometabolism as evidenced by both [¹¹C]flumazenil PET⁷ and dynamic PET.¹⁴ Therefore, it is reasonable to conjecture that pure PLS should primarily affect the primary motor cortex.

In our 3 cases, all of the patients had symptoms for at least 3 years. All other mimickers of PLS were excluded. The absence of EMG findings showing lower motor neuron disorder was vital to the diagnosis. Studies with FDG-PET demonstrate predominant primary motor strip involvement. This pattern is illustrative of a “stripe” of hypometabolism. Cortex ID software was useful for clear visualization of the region of hypometabolism as it uses a statistical comparison to healthy individuals of a similar age range. In 2 patients, diffusion tensor imaging failed to highlight abnormality, suggesting that FDG-PET is more sensitive than diffusion tensor imaging for identification of underlying motor cortex abnormality. We believe FDG-PET can aid in the diagnosis of PLS.

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**REFERENCES**