

Hemiparetic Primary Lateral Sclerosis: Revisiting Mills Syndrome

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Key Words

Prognosis · Primary lateral sclerosis · Mills syndrome · Asymmetry

Abstract

A slowly progressive hemiparesis beginning in a single limb with evolution to the ipsilateral limb was originally described in 8 patients in 1906 by Mills. We present 5 cases of progressive hemiparetic corticospinal tract degeneration, identified by the clinical presentation and the exclusion of other etiologies using serological, imaging, and electrodiagnostic studies.

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Introduction

A slowly progressive hemiparesis beginning in a single limb with evolution to the ipsilateral limb was originally described in 8 patients in 1906 by Mills [1]. However, the identification of this syndrome as pure degeneration of the corticospinal tract may have been unreliable in the last century because of the lack of availability of imaging studies and other investigations that are available today. Here, we describe 5 cases of progressive hemiparetic corticospinal tract degeneration, identified by the clinical presentation and the exclusion of other etiologies using serological, imaging, and electrodiagnostic studies.

Case Report

Case 1

A 45-year-old right-handed man presented with a 1-year history of slowly progressive loss of dexterity in his right hand manifested by difficulty writing. His lower limbs were unaffected. He did not have any sensory complaints, bulbar symptoms, or bowel or bladder incontinence. His neurological examination showed only mild facial asymmetry and asymmetric spasticity as well as hyperreflexia affecting the right upper limb. He then developed a severe right flexion contracture of the right hand with progressive right lower limb spasticity and a spastic gait. Three years into his course, he developed mild spastic dysarthria and dysphagia as well as some limitations to left upper limb dexterity. Four years into his course, he noted more difficulty with gait and, although asymmetric, bilateral lower limb involvement. The laboratory investigations are detailed in [table 1](#).

Case 2

A 55-year-old man presented with a 13-year history of left hand 'heaviness' when running, difficulty with handwriting and typing, and progressive difficulty raising his arm above his head to wash his hair in the shower. Five years before presentation, he had noticed that his left leg had become clumsy, with tripping and stumbling, and he was given an ankle foot orthosis. He had no symptoms on the right side. He did not have any sensory symptoms, bulbar symptoms, or bowel or bladder incontinence. A neurological examination revealed mild left hand and distal leg weakness with foot drop, asymmetric hyperreflexia, and an extensor plantar response. He had mildly increased tone in the left lower extremity. The sensory examination was normal. He had reduced movements to opening and closing his left hand. His gait was notable for a very mild reduction of the left arm swing and a left steppage gait. The laboratory investigations are detailed in [table 1](#).

Case 3

A 88-year-old woman presented with a 2-year history of a gait disorder. Initially, she noted difficulty with strength and coordination on her right side. She also developed some speech and swallowing difficulties. On examination, she had a spastic dysarthria with facial asymmetry. She had mild right-sided pyramidal distribution weakness. She had diffuse hyperreflexia, which was exaggerated in the right upper and lower limbs with a right extensor plantar response. Muscle atrophy and fasciculations were absent. Tone was increased bilaterally, particularly on the right side. Right finger and toe tapping were very slow and awkward. Sensory findings were normal. She had a cautious gait with reduced right arm swing. The laboratory investigations are detailed in [table 1](#). She ultimately developed progressive pseudobulbar palsy and died 3 years later from aspiration pneumonia.

Case 4

A 45-year-old left-handed man presented with a 4-year history of dragging his right leg when walking. His symptoms had progressed slowly and then involved the right arm, with reduced dexterity when typing on a computer keyboard. There were no sensory complaints or bowel or bladder symptoms. On neurological examination, the right upper limb weakness was noted to be worse distally in the arm, with both proximal and distal pyramidal weakness in the right leg. There was normal strength in the left arm and leg. There was hyperreflexia in the right arm and leg with a Hoffmann sign present on the right. There was an extensor plantar response and a crossed adduction at the right knee. Spasticity was present in the right arm but normal in the left arm. There was mildly increased tone in the right lower

extremity, but the left lower extremity tone was normal. The sensory examination was normal. A gait examination showed decreased right arm swing with a slightly flexed posture of the right arm and abduction of the right leg with minimal right foot drop. The laboratory investigations are detailed in table 1.

Case 5

A 72-year-old woman presented with a 3-year history of left foot drop, with subsequent evolution to involve weakness of the entire left lower limb. There was some associated numbness and paresthesia of the feet, which developed later in the course of her disease and was associated with documented glucose intolerance. Her symptoms eventually progressed to involve left arm weakness. The right side was asymptomatic. On neurological examination, a left hemiparesis was noted with symmetric reflexes in the upper extremities, reduced reflexes at the right knee and ankle, and hyperreflexia at the left knee and ankle. The left plantar response was equivocal, and the right plantar showed a flexor response. Atrophy and fasciculations were absent. The sensory examination was normal. Over the following several years, her symptoms progressed modestly, with worsening left-sided spasticity and more apparent hyperreflexia. These symptoms then plateaued. The laboratory investigations are detailed in table 1.

Discussion

All of our patients met the proposed criteria for primary lateral sclerosis (PLS) based on a disease duration greater than 3 years, insidious adult onset, absence of a family history, and clinical findings limited to corticospinal tract dysfunction [2]. However, their pattern of weakness, unlike in typical PLS, was notably asymmetric. The duration of disease may be relevant, since it is well recognized that many patients who develop the features of ALS initially presented with primarily corticospinal tract dysfunction [3]. While the evaluation of our patients varied, all had electrodiagnostic studies and magnetic resonance imaging, as detailed in table 1.

Only less than 5% of motor neuron disease patients fulfill the criteria for PLS [4]. We have described 5 PLS patients with symptoms and signs of slowly progressive hemiparetic corticospinal tract dysfunction, each of whom has undergone an extensive diagnostic evaluation to exclude other etiologies. While the asymmetry and slow evolution is striking, 2 of these patients (cases 1 and 3) did ultimately develop signs of bilateral corticospinal dysfunction during their disease course. It should be noted that this spread to involve bilateral corticospinal tracts was also noted in Mills' original description.

While there are few documented cases of Mills syndrome in the literature [1, 5–8], it is probably underreported because of difficulties with the nomenclature. For example, Zhai et al. [9] retrospectively studied 25 patients who fulfilled the criteria for PLS in 2003. Of these, 10 were identified as having had a markedly asymmetric or patchy pattern of symptom spread. In a follow-up prospective study, 4 patients with asymmetric PLS presented with features typical of Mills syndrome [10]. However, they also noted an additional 9 patients who had 'multifocal' PLS with asymmetry but evolution of bulbar dysfunction, or with bulbar dysfunction as a presenting symptom but asymmetric limb involvement. Interestingly, they did not see significant differences between the classic ascending symmetric PLS and multifocal PLS with regard to survival, age of onset, or disease duration.

Conclusion

Obviously, Mills was not able to evaluate his patients using electrodiagnostic testing or imaging studies. Taken together, the cases we report have many features consistent with the original clinical description by Mills but, because of our ability to exclude other etiologies via serological, electrophysiological, and imaging technologies, are likely more specific to pure corticospinal tract dysfunction. Therefore, these cases are better classified as hemiparetic PLS rather than a distinct clinical entity.

Statement of Ethics

The study protocol for review of the patient records for research has been approved by the Johns Hopkins Institutional Review Board.

References

- 1 Mills CK: Unilateral ascending paralysis and unilateral descending paralysis. *JAMA* 1906;47:1638–1645.
- 2 Pringle CE, Hudson AJ, Munoz DG, Kiernan JA, Brown WF, Ebers GC: Primary lateral sclerosis. Clinical features, neuropathology and diagnostic criteria. *Brain* 1992;115:495–520.
- 3 Mitsumoto H, Chad D, Pioro EP: Amyotrophic Lateral Sclerosis. Philadelphia, FA Davis, 1998.
- 4 Norris F, Shepherd R, Denys E, Ú KS, Mukai E, Elias L, Holden D, Norris H: Onset, natural history and outcome in idiopathic adult motor neuron disease. *J Neurol Sci* 1993;118:48–55.
- 5 Gastaut JL, Bartolomei F: Mills' syndrome: ascending (or descending) progressive hemiplegia: a hemiplegic form of primary lateral sclerosis? *J Neurol Neurosurg Psychiatry* 1994;57:1280–1281.
- 6 Doran M, Enevoldson TP, Ghadiali EJ, Larner AJ: Mills syndrome with dementia: broadening the phenotype of FTD/MND. *J Neurol* 2005;252:846–847.
- 7 Turner MR, Gerhard A, Al-Chalabi A, Shaw CE, Hughes RA, Banati RB, Brooks DJ, Leigh PN: Mills' and other isolated upper motor neurone syndromes: in vivo study with ¹¹C-(R)-PK11195 PET. *J Neurol Neurosurg Psychiatry* 2005;76:871–874.
- 8 Lachaud S, Soriani MH, Delmont E, Budai M, Desnuelle C, Lebrun C: Mills' syndrome: a rare clinical entity. *Rev Neurol (Paris)* 2007;163:335–340.
- 9 Zhai P, Pagan F, Statland J, Butman JA, Floeter MK: Primary lateral sclerosis: a heterogeneous disorder composed of different subtypes? *Neurology* 2003;60:1258–1265.
- 10 Floeter MK, Mills R: Progression in primary lateral sclerosis: a prospective analysis. *Amyotroph Lateral Scler* 2009;10:339–346.

Table 1. Clinical characteristics and diagnostic studies

Sex	Age at onset, years	Duration of disease from onset, years	Initial symptoms	Evolution of symptoms	Examination findings	EMG findings	Imaging studies	CSF	Other studies
<i>Case 1</i>									
M	44	6	Right hand clumsiness	Initially right hand, then right leg weakness	Initially right hand, then right leg spasticity	Normal twice at the time of diagnosis and 3 years after onset	MRI of brain and cervical spine: normal	CSF with increased protein to 55 mg/dl; absent oligoclonal bands; VDRL test negative	
<i>Case 2</i>									
M	41	14	Left hand clumsiness	Left arm, then left leg weakness	Mild LUE and LLE hyperreflexia, left toe extensor, mild spasticity in LUE; reduced left arm swing and mild UMN left foot drop	Normal 13 years after onset	MRI of brain: mild cortical atrophy	CSF : normal; VDRL test negative	Lyme antibodies absent
<i>Case 3</i>									
F	86	5	Gait disorder with falls	Dysarthria; dysphagia	Legs: right worse than left, with increased tone and asymmetric hyperreflexia; right toe extensor; reduced right arm swing; dysphagia; spastic dysarthria	Normal 2 years after onset	MRI of brain: mild atrophy and periventricular ischemic changes	None	MGUS
<i>Case 4</i>									
M	41	12	Right leg dragging	Initially right leg, then right arm weakness	Hyperreflexia, spasticity, weakness of RUE and RLE; reduced right nasolabial fold; LUE and LLE normal	Normal 4 years after onset	MRI of brain: minimal small vessel ischemic changes 8 years following diagnosis; MRI of cervical, thoracic, and lumbosacral spine: without lesions	None	Lyme antibodies absent; SOD1 gene testing normal; HSP gene testing normal
<i>Case 5</i>									
F	70	9.5	Left leg weakness and foot drop	Burning feet	Left UMN facial weakness; left hemiparesis, leg > arm; LLE hyperreflexia; left toe extensor	Normal 1 year after onset; fibrillations in left gastrocnemius 3 years after onset	MRI of brain: small vessel ischemic changes; MRI of cervical and thoracic spine: without stenosis; MRI of lumbosacral spine: L5–S1 bilateral recess stenosis	None	Lyme antibodies absent; VLCFA normal; RPR negative

CSF = Cerebrospinal fluid; EMG = electromyography; HSP = hereditary spastic paraparesis; LE = lower extremity; MGUS = monoclonal gammopathy of unknown significance; MRI = magnetic resonance imaging; RPR = rapid plasma reagin; SOD1 = superoxide dismutase 1; UE = upper extremity; UMN = upper motor neuron; VDRL = Venereal Disease Research Laboratory; VLCFA = very-long-chained fatty acids.