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CASE REPORT

Mills' syndrome is a unique entity of upper motor neuron disease with N-shaped progression: Three case reports

Zhi-Yun Zhang, Zhi-Yuan Ouyang, Guo-Hua Zhao, Jia-Jia Fang

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Abstract

BACKGROUND

Mills' syndrome is an extremely rare degenerative motor neuron disorder first described by Mills in 1900, but its nosological status is still not clear. We aimed to analyze the clinical features of Mills' syndrome.

CASE SUMMARY

Herein, we present 3 cases with similar features as those described in Mills' original paper and review the related literature. Our patients showed middle- and older-age onset, with only upper motor neuron symptoms evident throughout the course of the disease. Spastic hemiplegia began in the lower extremity with a unique progressive pattern.

CONCLUSION

We consider that Mills' syndrome is a unique entity of motor neuron disorder with an N-shaped progression. Clinicians should maintain a high index of suspicion for the diagnosis of Mills' syndrome when the onset involves lower extremity paralysis without evidence of lower motor neuron or sensory involvement.

Key Words: Mills' syndrome; Motor neuron disease; Primary lateral sclerosis; Amyotrophic lateral sclerosis; N-shaped progression; Case report

Core Tip: Mills' syndrome is an extremely rare degenerative motor neuron disorder, whose nosological status is currently uncertain. We report 3 cases with similar features as those described in Mills' original paper. All patients had initial symptoms in one lower extremity that spread up to the homolateral upper limb, followed by the contralateral lower limb, and finally the contralateral upper limb. It is necessary to clarify the clinical features to receive more attention from clinicians.

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INTRODUCTION

In 1900, Mills[1] described 8 cases of progressive hemiplegia that began in the extremity of the lower limb and ascended to the ipsilateral upper extremity without significant sensory impairment. Mills claimed that this disorder was a new form of degenerative disease characterized by a gradually progressive, unilateral ascending clinical syndrome of upper motor neuron-predominant hemiparesis. His description was based on clinical examination only, and different disorders such as multiple sclerosis, syphilis, parkinsonism, and amyotrophic lateral sclerosis were not excluded. Analysis of the post-mortem findings of a patient from one of his original case series who had been symptomatic for 8 years showed unilateral degeneration of the crossed and uncrossed pyramidal tracts at the level of the spinal cord and brainstem but no Betz cell degeneration in the motor cortex and no attrition of anterior horn cells[2]. The advances in the diagnostic laboratory, electromyography (EMG), and neuroimaging tests confirmed the picture of progressive unilateral ascending weakness associated with pyramidal tract impairment of Mills' syndrome.

In the recent 2 decades, only about 50 additional cases have been reported in the literature[3,4] and mostly as single case reports. Owing to the lack of pathological examination, most of the cases did not allow reliable differential diagnosis; A patient progressed to frontotemporal dementia[5] and developed an extrapyramidal syndrome[6]. Although the syndrome currently has an uncertain nosological status, some authors consider it as a lateralized variant of primary lateral sclerosis (PLS)[4,7], while others refer to it purely as a clinical term including different disorders[8,9]. The progression of the disease and the natural course of the reported cases suggest a different pathophysiologic basis for neuronal death. Here, we report 3 cases that have similar features as those described in Mills' original paper to shed light on the clinical characteristics of Mills' syndrome.

CASE PRESENTATION

Chief complaints

Case 1: A 68-year-old woman was admitted to our outpatient clinic with chief complaints of stiffness in her left lower extremity for about 3 years.

Case 2: A 72-year-old woman presented with a half year history of slow progressive right-sided hemiparesis.

Case 3: A 55-year-old man was admitted to the hospital with complaints of weakness in his left lower extremity for 7 mo.

History of present illness

Case 1: The symptoms developed slowly and remained unnoticed to the patient until 1 year ago when she felt weakness in her left leg that affected her walking. She did not notice any muscle twitching. Furthermore, altered cognitive function, language and swallowing problems, sensory disturbance, and sphincter dysfunction were noted.

Case 2: The onset was described as "heaviness" in her right leg when running and progressively difficult walking with tripping and stumbling. She experienced weakness that ascended to her right upper limb 2 mo before presentation. She also noticed that her handwriting worsened, and she was unable to raise her right arm above her head. She denied any abnormal sensation or altered perception, any language problem, bulbar symptom, or bowel or bladder incontinence. Madopar was prescribed because the diagnosis of the outpatient doctor was Parkinson's disease.

Case 3: Evaluations included multiple brain, spine, and lower limb magnetic resonance imaging (MRI), abdominal computed tomography, cerebrospinal fluid examination, EMG, and visual, auditory, and somatosensory evoked potentials; all tests showed negative results. The patient was discharged without treatment but continued to be followed up. Sixteen months after he noticed weakness in his left lower extremity, he experienced weakness in his left arm. The paresis became increasingly evident, and the symptoms progressed from difficulty in walking to dependence on a wheeled walker.

History of past illness

Case 1: Her personal and social history were unremarkable.

Case 2: Her personal and social history were unremarkable.

Case 3: His personal history was unremarkable, except for paroxysmal atrial fibrillation.

Personal and family history

Family history of genetic disease was negative in the 3 cases.

Physical examination

Case 1: Physical examination revealed left hemiparesis with spastic hypertonia and hyperreflexia, particularly in the left lower limb. Muscle power in the left lower limb was graded 3/5 based on the Medical Research Council scale. Babinski sign was negative. Superficial and proprioceptive sensations were normal, and cranial nerve functions were unimpaired.

Case 2: Neurological examination revealed mild weakness in the right-sided limbs (Medical Research Council grade 4) with hypermyotonia; tendon reflexes were pathologically brisk in all limbs, particularly on the right side. Right foot clonus was noted, and right Babinski's and Hoffmann's signs were positive. Sensory examination including pain sensation, position sensation, and vibration sensation was unremarkable. Cranial nerve functions were unimpaired, and coordination and vision were normal.

Case 3: Neurological examination revealed left-side hemiparesis with hyperreflexia, hypertonia, and ankle clonus. Muscle power was graded 4/5 in the left upper limb and 1/5 in the left lower limb. Babinski's and Hoffmann's signs were negative, and amyotrophy was not detected. The right limbs, cranial nerves, superficial and proprioceptive sensation, and cerebellar functions were normal.

Laboratory examinations

Case 1: The results of routine laboratory tests including blood routine examination, biochemical and immunoserologic indices, tumor markers, thyroid function test, vitamin B_{12} level, serological tests for syphilis and HIV, and cerebrospinal fluid examination were negative.

Case 2: Blood tests for paraneoplastic autoantibodies, serum B_{12}, copper, HIV, and syphilis showed negative results. Nerve conduction study was normal, and somatosensory evoked potentials were unremarkable.

Case 3: Routine blood, creatine kinase, autoantibodies, and HIV and syphilis screening were normal. Cerebrospinal fluid test with isoimmune electrofocusing was negative.

Imaging examinations

Case 1: Brain MRI showed isolated atrophy of the right occipital lobe. No remarkable findings were observed with the cervical and thoracic vertebrae on either MRI or EMG.

Case 2: No decrement was noted in repetitive nerve stimulation. Brain MRI showed mild periventricular ischemic changes, but cervical spine MRI was normal. Positron-emission tomography scan was essentially normal.

Case 3: Brain MRI was normal, and cervical spinal MRI showed mild noncompressive degeneration of the C5/6 and C6/7 disks. EMG was performed again; the results showed minor chronic denervation in the left dorsal interosseous, left sternocleidomastoid muscle, and thoracic paraspinal muscles. No evidence of lower motor neuron involvement or polyneuropathic impairment was found. We performed MR diffusion tensor imaging to study the brain white matter connections, but the findings were normal.

FINAL DIAGNOSIS

The final diagnosis was motor neuron disorder (MND) in the 3 patients.

TREATMENT

Case 1: No special treatment of the patient.

Case 2: By consensus, baclofen and riluzole were prescribed upon discharge.

Case 3: The patient was discharged without treatment but continued to be followed up.

OUTCOME AND FOLLOW-UP

Case 1

The patient underwent 28 mo of follow-up, and she developed slow progressive spastic hemiplegia without sensory disturbance. The stiffness gradually spread to the left upper extremity and mildly affected her housework activities. She progressed to using a cane outside the home 4.5 years after the first symptom manifested. She felt slight stiffness in her right lower limb, but no bulbar symptoms were observed at the last follow-up visit.

Case 2

Over the subsequent months, the stiffness and weakness in her right limb gradually aggravated. She noted stiffness in her left leg 6 mo later, and she became wheelchair-bound. Sixteen months into her disease course, she noted her left hand became clumsy, and her daily living abilities were limited. Eighteen months into her course, she developed mild pseudobulbar symptoms and occasional choking when eating. She died from respiratory failure 32 mo after the initial onset of symptoms.

Case 3

The patient's symptoms progressed sharply during the course of the follow-up. The right lower limb was affected within 19 mo of his disease onset, and the right upper limb was affected 24 mo after onset. After 28 mo of the first symptoms onset, the patient developed severe bulbar dysfunction including dysarthria and dysphagia. He died from respiratory failure 44 mo after the onset of symptoms. Throughout his course, he had no marked fasciculations or muscle atrophy.

DISCUSSION

The clinical picture presented by our 3 patients (details shown in Table 1) showed several primary distinctive features: (1) Onset at middle- and old-age; (2) Only upper motor neuron findings were evident throughout the course of their disease; (3) Could affect bilateral limbs in advanced stages but strictly began in one lower extremity and spread to the homolateral upper limb, followed by the contralateral lower limb, and finally the contralateral upper limb, which we refer to as N-shaped progression; and (4) Extremely asymmetric, and the lower extremity is much more severely affected than the upper limb, even in the late stages of the disease. Features supporting its classification fall within the spectrum of MND, and evolution to both amyotrophic lateral sclerosis (ALS) and PLS has been described[4]. We propose that Mills' syndrome can be considered a unique entity of MND because there is some heterogeneity in the progression, including its N-shaped progressive manner. It should be emphasized that few published cases that did not have onset in the lower limb or did not show descending progressive hemiplegia[9,10] did not strictly meet the criteria of Mills' syndrome.

In light of the present situation, these cases were differentially diagnosed from ALS. The clinical hallmarks of ALS are clear; there are definitive electrophysiological criteria called EI Escorial Criteria that requires evidence of both upper and lower MND. The symptoms usually spread and progress within a segment and from one segment to the other (cranial, cervical, thoracic, and lumbosacral)[11]. Obviously, our patients did not meet these diagnostic criteria for ALS, given the absence of lower motor neuron signs in the clinical and electrophysiological examination.

Some authors have illustrated the associated clinical and radiologic asymmetry and absence of lower motor neuron involvement, supporting a hemiparetic variant of PLS[12]. PLS is a progressive upper MND without the clinical signs of lower motor neuron involvement, wherein the patterns of progression most commonly spread from side to side and from region to region that commonly start symmetrically in the lower extremities and evolve to spastic tetraparesis, ultimately with bulbar involvement[13]. Zhai *et al*[14] conducted a study to identify the subsets of PLS patients with common clinical, physiological, and anatomical features; they termed PLS as ascending, multifocal, or sporadic paraparesis owing to its pattern of symptom progression. Ascending progression was noted in patients with one limb onset and progression from one side to the other occurring first, followed by ascending progression[15]. Therefore, we speculate that the pattern of symptom progression is one of the key features to distinguish Mills' syndrome from PLS.

Table 1 Patient clinical characteristics

Characteristics	Case 1	Case 2	Case 3
Sex	F	F	M
Age at onset, yr	65	71	54
Duration of disease from onset, mo	36	6	7
Site of disease onset	LLL	RLL	LLL
Evolution of symptoms	LLL-LUL-RLL	RLL-RUL-LLL-LUL-bulbar symptoms	LLL-LUL-RLL-RUL-bulbar symptoms
Bulbar symptoms	None	Yes	Yes
Sensory symptoms	None	None	None
Tone	Hypertonia in left side	Hypertonia in right side	Hypertonia in left side
Power (MRC grade)	Left side (grade 3/5)	Right side (grade 4/5)	LLL (grade 1/5); LUL (grade 4/5)
Reflexes	Hyperreflexia in left side	Hyperreflexia in all limbs right ankle clonus	Hyperreflexia in left side, left ankle clonus
Babinski's sign	Negative	Positive in right side	Negative
Laboratory test	Normal	Normal	Normal
EMG	Increased polyphonic motor unit potentials	Unremarkable	Minor chronic denervation
Follow-up	Mobility with the help of a cane	Died from respiratory failure 32 mo after the onset of symptoms	Died from respiratory failure 44 mo after the onset of symptoms

F: Female; M: Male; RUL: Right upper limb; RLL: Right lower limb; LUL: Left upper limb; LLL: Left lower limb; EMG: Electromyography; MRC: Medical Research Council.

Maragakis *et al*[7] reported 5 cases that have features consistent with the original clinical description by Mills. The researchers claimed that these cases should be classified as hemiparetic PLS rather than a distinct clinical entity. However, 2 patients described in this paper had onset in the upper extremity, without the tell-tale N-shaped progression pattern. The different sequences of clinical manifestations presumably reflect the different nosology with PLS. Moreover, through Pringle's diagnostic criteria, PLS shows benign clinical prognosis, slow rate of progression, and average symptom duration ranging from 7.2-14.5 years[16]. Distinct from that, the duration from the onset of symptoms to death was < 4 years in patient 3, whereas the bulbar symptoms evolved rapidly in patient 2. The prognosis of our cases was not so benign (Table 2). A recent 18F-fluorodeoxyglucose positron-emission tomography study[17] found significant hypometabolism in motor and premotor areas contralateral to the limb weakness in Mills' syndrome patients, which is more limited than that of ALS and PLS patients. Taken together, Mills' syndrome should be considered a unique nosological entity of the MND spectrum rather than a variant of PLS.

Another dominant view about Mills' syndrome is that it is purely a clinical description that can have secondary etiologies. The cases reported in the literature related to Mills' syndrome included different disorders such as multiple sclerosis, syphilis, and unilateral cerebral atrophy[8]. Mirian *et al*[3] described a 63-year-old woman diagnosed with Mills' syndrome progressing to corticobasal syndrome. Turner *et al*[13] used 11C-(R)-PK11195 positron-emission tomography scanning *in vivo* to explore the cortical lesion in cases of upper MND. In this study, 2 patients had clinical features similar to Mills' syndrome: A patient demonstrated a marked focal increase in the binding of (11)C-(R)-PK11195 in the superior frontal region contralateral to the affected limbs; and by contrast, the other patient showed no focal areas of increased binding in the cerebral cortex. The second patient however had a high cervical cord lesion and was presumed to have extra cerebral inflammatory disease. The authors summarized that Mills' syndrome is a purely clinical description that should be reserved for patients with a progressive spastic hemiparesis for which no other explanation can be found. The lack of evidence of secondary etiology in our 3 patients enables us to propose that the degeneration may be idiopathic. However, given that neither pathological examination nor autopsy was conducted, we failed to conclude whether Mills' syndrome is a clinical diagnosis that includes complex disorders.

In our first case, MRI of the brain showed atrophy of the right occipital lobe, while the spinal cord was normal. No other alternative etiologies seemed plausible after serological tests and cerebrospinal fluid screening. Previous imaging studies demonstrated that cerebral atrophy is widespread in ALS, involving the grey matter, white matter, and motor and extra-motor regions[18]. Recently, a study using deformation-based morphometry analysis showed significant bilateral atrophy in the motor cortex and corticospinal tract and ventricular enlargement, along with significant longitudinal atrophy in the

Table 2 Differential diagnosis of Mills' syndrome from amyotrophic lateral sclerosis and primary lateral sclerosis

	Mills' syndrome	ALS	PLS
Upper motor neuron signs	Positive	Positive	Positive
Lower motor neuron signs	Negative	Positive	Negative
Initial site of disease onset	Unilateral lower limb	Commonly bilateral	Commonly bilateral
Progression manner	One side lower limb - the same side upper limb - contralateral lower limb - contralateral upper limb	From one segment to the others (cranial, cervical, thoracic, and lumbosacral)	Usually ascending
Bulbar involvement	Late stage	Middle or late stage	Late stage
Symmetry of the symptom	Significant asymmetry	Could be symmetric or asymmetric	Commonly symmetric
Electrophysiological examination	Non-special	Positive	Non-special
Prognosis	Uncertain, probably rapid progression	Rapid progression, poor prognosis	Relatively benign

ALS: Amyotrophic lateral sclerosis; PLS: Primary lateral sclerosis.

precentral gyrus, frontal, and parietal white matter[19]. To our knowledge, no previous morphometric study of MND has mentioned occipital lobe atrophy, and we believe that this change is not related to this syndrome.

Phosphorylated transactive response DNA-binding protein 43 kDa (pTDP-43) aggregates in the cytoplasm of motor neurons and neuroglia in the brain are one of the pathological hallmarks of ALS [20]. Correlation analysis showed that the severity of pTDP-43 pathology in the white matter was linearly associated to that in the overlying grey matter. In addition, the severity of pTDP-43 pathology and neuronal loss correlated closely with grey and white matter oligodendrocyte involvement.

Sainouchi *et al*[21] reported the clinicopathological features of 2 autopsy cases of hemiplegic-type ALS and discussed the possible pathomechanism. Their results revealed that in the upper motor neuron system there was heavier pTDP-43 accumulation in the motor areas controlling the clinically predominant limb. Bäumer *et al*[22] reported a 72-year-old patient with co-occurrence of aphasia and progressive right hemiparesis. Postmortem examination revealed striking left hemisphere atrophy within the primary motor cortex, accompanied by neuronal loss, gliosis, and TDP-43-positive neuronal and glial cytoplasmic inclusions. However, with respect to axonal propagation, pTDP-43 oligomers would have primarily spread along the unilateral corticospinal tract[23]. The N-shaped progression pattern in Mills' syndrome is considered an orderly and sequential process in the upper motor neuron system, and such contiguous lesion spread in Mills' syndrome may further support the above-mentioned TDP-43 propagation hypothesis. Additional studies are needed to further understand the commonalities and differences from other neurodegenerative diseases and elucidate its underlying physiopathology.

A proper diagnosis can hardly be provided at the early stage of disease for cases when weakness emerges unilaterally in one limb. In the second patient of our report, Parkinson's disease was initially considered. Thus, understanding the N-shaped progression pattern of Mills' syndrome is particularly important to improve the clinician's ability to identify these patients early in their disease course and to provide patients with adequate counselling.

CONCLUSION

Mills' syndrome should be conceptualized as a unique nosological entity of upper MND spectrum, with typical onset in one lower extremity that eventually spreads with an N-shaped progression pattern. Clinicians should maintain a high index of suspicion for the diagnosis of Mills' syndrome when the onset is restricted to one lower extremity paralysis without evidence of lower motor neuron involvement or sensory impairment. However, whether Mills' syndrome is a clinical diagnosis that includes complex disorders remains unclear. Further studies should extensively look into this matter to gain a better understanding of the natural history and underlying pathogenic mechanisms.

FOOTNOTES

Author contributions: Zhang ZY and Ouyang ZY both wrote and revised the text; Zhao GH and Fang JJ revised the manuscript for intellectual content; All authors read and approved the final manuscript.

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