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Case Report

Mimicking Mills' syndrome: progressive spastic hemiparesis on upper motor neuron dominant amyotrophic lateral sclerosis

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ABSTRACT

Mills' syndrome is an idiopathic, slowly progressive, spastic hemiparetic variant of primary lateral sclerosis (PLS). Despite this classic definition, this syndrome has recently been suggested to be present on all the variants of motor neuron disease (MND) spectrum (ALS, PLS or UMNdALS). Authors presented a 63 years old male with history of gradually progressive right-side hemiparesis associated with dysarthria and dysphagia. Neurologic examination revealed intact cognition, weak bilateral orofacial muscles, marked right-side spasticity with hyperreflexia and mild sensory deficit, progressing to right-upper extremity atrophy upon follow-up. Relevant blood and CSF examinations were within normal limits. MRI of brain and cervical spine were unremarkable. electromyography (EMG), nerve conduction velocity (NCV), facial motor and blinks studies initially revealed no evidence of lower motor neuron involvement. Based on the revised El escorial criteria, patient was diagnosed as upper motor neuron dominant amyotrophic lateral sclerosis (UMNdALS) mimicking the classic PLS-Mills' hemiparetic variant.

Keywords: Upper motor neuron dominant, ALS, Hemiparesis, Mills syndrome

INTRODUCTION

Motor neuron disease (MND) designates a group of progressive degenerative disorders of motor neurons in the spinal cord, brainstem and motor cortex, which presents clinically as muscular weakness, atrophy, and corticospinal tract signs in varying combinations. This disease group is subdivided into several subtypes on the basis of the grouping of symptoms and signs. The most frequent form is ALS in which amyotrophy and hyperreflexia are combined, though other patterns of clinical evolutions are also present.[1] One pattern of MND in which involvement of arm and leg are affected on the same side, first with spasticity and then with some degree of amyotrophy, has been described and is called Mills' hemiplegic variant or Mills' Syndrome.

Mills' syndrome, initially described by the American neurologist Charles Karsner Mills in the 1900, is an extremely rare syndrome of gradually progressive hemiplegia which may be ascending or descending in pattern. Mills' initially claimed that this disorder was new form of degenerative disease characterized by progressive degeneration of the corticospinal pyramidal pathways, however, it is currently classified as a variant of PLS.[2,3]

A recent study presented by Barua et al suggested the possibility of Mills' hemiparetic syndrome on a patient with evident ALS suggesting that this syndrome could be present in all the variants of MND spectrum (ALS, PLS or UMN-ALS) with a hemiplegic/ asymmetrical pattern of involvement.[6] However, comprehensive review by Jaiser et al cases descriptive of Mills' syndrome clearly excluded non-PLS patients on diagnosis.[4]

CASE REPORT

This is a case of a 63-year-old right-handed male presenting with 15 months history of gradually progressive right-side hemiparesis starting on his right

arm progressing to his right thigh and leg associated with dysphagia and dysarthria. There was no history of involuntary movements or rippling of muscles on any extremity but there were occasional muscle cramps on the right leg. There was no similar history in the family nor any episode of urinary or bowel incontinence.

Clinical examination revealed intact cognition (Mini mental status examination: 29/30) but with severe dysarthria, weak bilateral jaw clench, temporalis muscle atrophy, weak closure of bilateral orbicularis oculi and orbicularis oris and weakness on tongue protrusion and lateral movements. Indirect laryngoscopy revealed right vocal cord paralysis. Spasticity of right upper and lower extremity was pronounced (Ashworth scale 3/4) with mild sensory deficit to light touch and pain modalities (10% sensory loss). Right upper and lower extremities were hyper reflexic with positive Hoffman's sign. No evident atrophy nor fasciculations appreciated. Clinical examination on the left side was essentially normal.

Routine blood examinations were within normal limits. Vitamin B12 determination revealed normal results (784 pg/mL). CSF examination revealed normal pressure (12 cm H_2O), mildly elevated protein (781 mg/L), normal glucose level (0.92 x serum glucose) and normal differential count. CSF RPR test was negative. MRI of the brain was normal. MRI of the cervical spine only revealed multilevel disc bulge with no neural compromise.

Initial nerve conduction study revealed focal mononeuropathy of left median nerve indicative of carpal tunnel syndrome with no definite evidence for myopathy or lower motor neuron involvement. EMG of right genioglossus muscles revealed reduced recruitment (Table 1). Facial nerve conduction study and blink reflex studies were normal. Patient was prescribed with resveratrol Tablet 1 tablet daily.

During follow-up examination after 5 months, neurologic examination revealed the same right-sided spastic hemiparesis now with associated left lower extremity weakness and spasticity (Ashworth scale 2/4) with evident muscle wasting of the right thenar and forearm muscles associated with urinary urgency. Repeat EMG-NCV of all extremities revealed chronic denervation on multiple bilateral muscle groups and persistence of focal mononeuropathy on left median nerve (Table 2). Repeat facial motor and blink studies revealed demyelinating pattern suggestive of bilateral facial and trigeminal nerve neuropathies (Table 3).

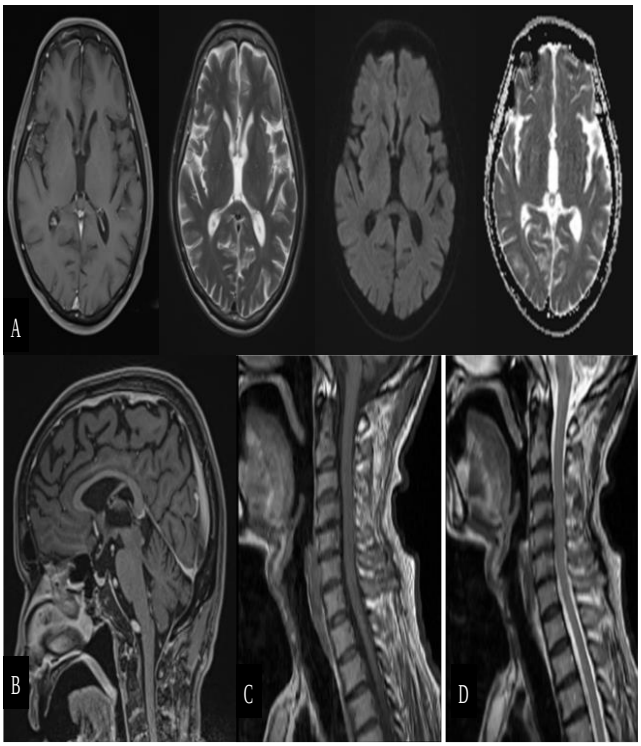

Figure 1 (A-D): Cranial MRI images at the level of internal capsule (T1, T2, DWI and ADC sequences in order) showing normal brain parenchyma. Post-contrast sagittal MRI of the brain, T1 sequence sagittal MRI of cervical spine, T2 sequence sagittal MRI of cervical spine.

Table 1: Initial NCV examination results showing reduced CMAP amplitude and slowed conduction velocity on left median nerve. Needle examination of right genioglossus revealed reduced pattern of recruitment.

Left median nerve			**Right median nerve**		
SAP (index to wrist)	5.19 uV	43.6 m/sec	SAP (index to wrist)	14.92 uV	54.0 m/sec
SAP (palm to wrist)	38.35 uV	40.3 m/sec	SAP (palm to wrist)	44.65 uV	53.7 m/sec
SAP (wrist to elbow)	20.91 uV	58.4 m/sec	SAP (wrist to elbow)	31.69 uV	61.5 m/sec
MCV	53.7 m/sec		MCV	62.5 m/sec	
Distal latency	3.75 ms		Distal latency	3.25 ms	
CMAP (wrist)	8.18 mV		CMAP (wrist)	7.45 mV	
CMAP (elbow)	7.79 mV		CMAP (elbow)	7.04 mV	
F-wave to APB	27.15 ms		F-wave to APB	25.60 ms	
Muscles	**Insertional activity**		**Spontaneous activity**		**Motor unit potentials**
			FIBS	**FASC** / **PSW**	
Right genioglossus	Normal		-	- / -	Reduced recruitment

Table 2: Follow-up nerve EMG-NCV examination after 5 months showing slowed conduction velocity on left median nerve and signs of chronic denervation in almost all the muscles tested.

Left median nerve			Right median nerve		
SAP (Index to wrist)	10.90 uV	48.7 m/sec	SAP (index to wrist)	17.30 uV	53.8 m/sec
SAP (Palm to wrist)	133.9 uV	43 m/sec	SAP (palm to wrist)	89.72 uV	51.3 m/sec
SAP (Wrist to elbow)	46.08 uV	51.8 m/sec	SAP (wrist to elbow)	43.55 uV	53.9 m/sec
MCV	59.2 m/sec		MCV	55.6 m/sec	
Distal latency	3.70 ms		Distal latency	3.65 ms	
CMAP (Wrist)	9.74 mV		CMAP (wrist)	6.55 mV	
CMAP (Elbow)	9.27 mV		CMAP (elbow)	6.07 mV	
F-wave to APB	27.25 ms		F-wave to APB	27.00 ms	

Muscles	**Insertional activity**	**Spontaneous activity**			**Motor unit potentials**
		FIBS	**FASC**	**PSW**	
Right tibialis anterior	Normal	-	-	-	Polyphasic, reduced recruitment
Right medial gastrocnemius	Normal	-	-	-	
Left rectus femoris	Normal	-	-	-	Occasionally polyphasic
Left deltoid	Normal	-	-	-	Mildly reduced recruitment
Left biceps	Normal	-	-	-	Normal
Left first dorsal interosseous	Normal	-	-	-	Reduced recruitment
Left genioglossus	Normal	-	-	-	Reduced recruitment, long duration
Right genioglossus	Normal	-	-	-	Reduced recruitment

Table 3: Facial NCV showing decreased amplitudes on bilateral frontalis muscles and prolonged latencies on bilateral frontalis and orbicularis oris muscles. Blink reflex study shows bilaterally prolonged ipsilateral R1 and R2 with no response to contralateral R2 bilaterally. This is consistent with bilateral facial and trigeminal nerve neuropathies.

Facial muscles NCV	Left		Right	
	Latency	**Amplitude**	**Latency**	**Amplitude**
Frontalis	5.20 ms	0.58 uV	4.50 ms	0.94 uV
Nasalis	4.25 ms	1.59 uV	4.20 ms	1.78 uV
Orbicularis oculi	4.10 ms	1.22 uV	4.45 ms	1.18 uV
Orbicularis oris	3.80 ms	1.01 uV	4.30 ms	1.33 uV
Blink reflex study	**R1 ipsilateral**	**R2 ipsilateral**	**R2 contralateral**	
Left-Supraorbital nerve	17.7	45.7	NR	
Right-Supraorbital nerve	17.1	45.6	NR	

DISCUSSION

Mills' variant of ALS was originally described by the Dr. Charles Karsner Mills as slowly progressive unilateral ascending (less often descending) paralysis on eight cases in the 1900s.[2] This variant was supposedly due to primary degeneration of the corticospinal pyramidal pathways, however, pathological examination was only performed on one case which revealed non-specific results. From that publication, five more cases were published between 1927 and 1951 all of which presents with hemiplegia with ipsilateral pyramidal signs. In those 13 cases, moderate amyotrophy without fasciculations was common (6 of 15 cases). Five of 15 cases involved facial palsy. Mild sensory disturbance (minimal hypesthesias similar to our case) seen on 3 of 15 cases. Manifestations very gradually worsened. Progression was more often ascending (13 of 15) than descending (2 of 15).

Involvement of both sides of the body has been reported in advanced stages (5 of 15). Family history of the syndrome was not noted in any of the cases.[5]

Twenty-six cases of Mills' syndrome have been reported since 1906, mostly as single case reports, but only 16 of these conformed to Mills' original description of an idiopathic, isolated, progressive, spastic hemiparesis. A review Jaiser et al of all these 16 cases together with a case series of 3 more patients diagnosed with Mills' Syndrome led to a proposed refinement of the diagnosis to exclude those with structural, vascular, and inflammatory etiologies as well as those with bulbar/pseudobulbar dysfunctions and rapidly progressive ascending hemiparesis of less than 4 years (Figure 2).[4]

Our patient presented with the same spastic hemiparesis with descending pattern of involvement and progression

of symptoms after follow-ups. Work-ups done excluded possible ALS mimickers. However, contrary to the classic Mills' Variant, the progression of symptoms from onset to complete hemiplegia was more abrupt (<4 years). Progression to initial manifestation of lower motor neuron signs was also more acute compared to the usual 10 to 16 years seen in Mills' Variant[4]. Our patient also presented with evident bulbar symptoms which has never been documented on Mills' Syndrome but is a common manifestation of patients with UMN-ALS.[6]

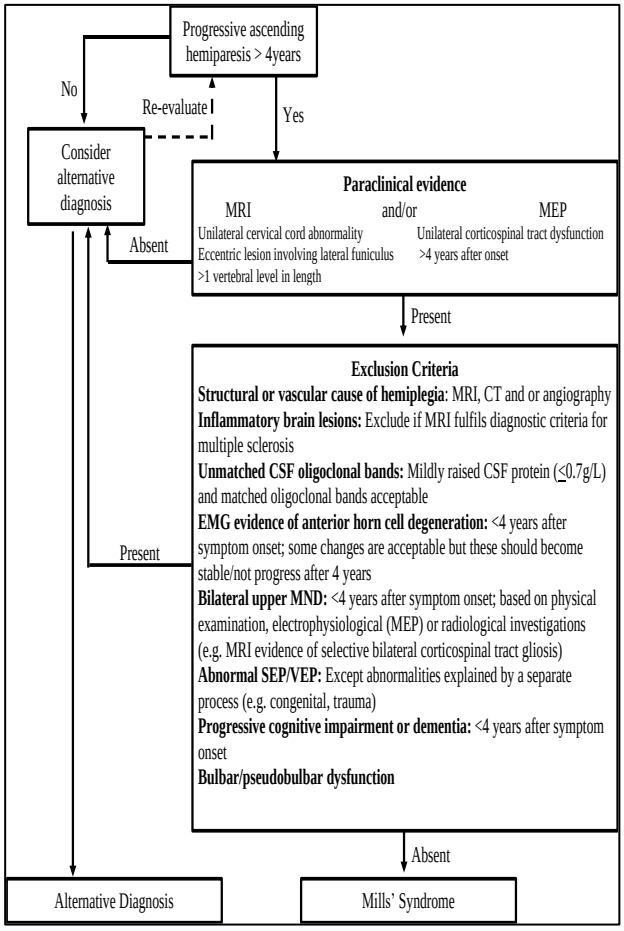

Figure 2: Proposed diagnostic algorithm for Mills' syndrome.[4]

Similar cases of rapidly progressive ALS type of "Mills' syndrome" with prominent bulbar manifestations has been suggested on 2 case reports:

Barua et al last 2020, reported a case of a 47-year-old female with gradually progressive ascending left side hemiparesis with prominent dysarthria presenting with spasticity, hyper-reflexia, positive Hoffmann and Babinski response as well as muscle wasting, fasciculations and chronic denervation potentials in EMG examination (bilateral for the paravertebral muscles) all occurring within the span of 2 years. Vasculitic profile, brain MRI and whole spine MRI were normal. Patient was diagnosed as Mills' variant of ALS.[7]

A similar case was reported by Baumer et al last 2014, a 72-year-old man with 1 year history of progressively worsening speech difficulty and right-side weakness. Patient presented with adequate comprehension but a profound inability to generate speech, spastic right-sided hemiparesis and severe bulbar dysfunction with visible tongue wasting. Patient died within 1 year due to respiratory failure and postmortem examination revealed left hemispheric atrophy involving the primary motor cortex as well as presence of Bunina bodies in the medulla which are eosinophilic neuronal inclusions pathognomonic for ALS. Despite the aggressive nature of the disease, patient was also diagnosed as Mills' phenotype of ALS.[8]

CONCLUSION

Together with the case reports of Barua et al and Baumer et al the presented case clearly shows an ALS/ UMN-ALS counterpart of the classic PLS-Mills' syndrome-a variant where the progression of spastic hemiparesis is more rapid and bulbar manifestations are evident. This disease variation fills in the gap left in the disease continuum of ALS, UMNdALS and PLS for patients presenting with progressive spastic hemiparesis. If this clinical presentation will remain to be classified as Mills' syndrome, a revision of the proposed diagnostic algorithm by Jaiser et al must be done, otherwise this disease process should be considered a separate entity.

This extremely uncommon presentation of MND with uncertain nosology needs further research, more subjects and longer follow-ups in order to be better understood.

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