

Mills' syndrome: case report

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Introduction

The syndrome of progressive, ascending or descending hemiplegia, with no significant sensory impairment was first described by Mills in 1900,¹ which several cases were reported later. However, after diagnostic tests and image improvements, the number of reports has shortened.² A possible explanation for this shortage is the identification of other diseases that could mimic the clinical picture. Currently, the syndrome has an uncertain nosological status, since it was described based on clinical examination only. We can find this clinical presentation (Mills syndrome) in cases of amyotrophic lateral sclerosis (ALS), predominant upper motor neuron amyotrophic lateral sclerosis (UMN-ALS) and primary lateral sclerosis (PLS), besides its symptomatic (secondary) forms. We describe a case (initial presentation and one year follow-up) of progressive ascending hemiplegia with clinical isolated upper neuron signs and normal sensory examination, discussing its nosological status, electromyographic findings, differential diagnosis and prognosis.

Case Report

A man, 55-year-old engineer, was evaluated in the neurology unit presenting a 2-years history of progressive weakness initially on left lower limb, ascending after 6 months to the left upper limb. He had difficulties to walk and constantly fell down. He described occasional feeling of muscle twitches and frequent cramps in the left leg. He denied any abnormal sensation or altered perception. He didn't have abnormal bladder and bowel function or difficulties to swallow.

Neurological examination showed left hemiparesis³ with hyperreflexia, spastic hypertonia⁴ and Babinski sign. Although, on the right side, just the patellar jerk was increased, it was less

intensely than the left one, with no signs of fasciculations.

Screen for HIV, HTLV I-II, VDRL, FTA-ABS were negative, as well as serum rheumatologic tests including antiphospholipid antibody, PTH, calcium and protein electrophoresis. Analysis of spinal fluid showed no abnormalities.

Needle electroneuromyography showed evidence of chronic denervation in the left first dorsal interosseous and left and right gastrocnemius muscles. Nerve conduction studies were normal. Complementary investigation with brain MRI showed subtle hypersignal lesion in the right corona radiata, without contrast enhancement, that is unspecific and could not explain the neurologic syndrome, a mild dilatation of the left lateral ventricle and diffuse bilateral hyperintensities along the pyramidal tract extending from corona radiata to brainstem (Figure A and B). Tractography did not show abnormalities in the pyramidal fibers. MRI of the cervical, thoracic and lumbar spinal MRI was normal. The patient was already using riluzole 100 mg per day and lithium carbonate 600 mg per day (introduced before our evaluation by other medical service). We discussed the possibility of a motor neuron disease with the patient and by consensus; we resolved to keep on the medications despite the lack of certitude about the diagnosis and the efficacy of lithium therapy.⁵

At the follow-up visit, one year after initial evaluation, neurologic examination showed the same pattern of hemiparesis with a slight worst in the pelvic girdle muscles on the right side and in spasticity. He did not have any sign of atrophy or fasciculation, yet he still complained sensation of muscles twitches. He was still able to walk with help of a calf, and denied any bulbar or cognitive symptom. Needle electroneuromyography showed normal sensory and motor nerve conduction velocities and signs of active denervation in distal muscles of the four extremities at needle electromyography. These signs of denervation were represented for positive sharp waves 1 or 2+/4+ or fibrillation potentials 1 or 2+/4+ and rare fasciculation potentials with reduced recruitment of large-amplitude long-duration motor unit action potentials in the affected muscles; these muscles were the right and left first dorsal interosseous of the hands and right and left first dorsal interosseous of the foot. This EMG finding was suggesting active denervation but did not fulfill the EMG parameters of El Escorial Criteria, which are the needed evidences of lower motor neuron degeneration in two muscles supplied by different nerve roots or nerves in a limb.

We discussed the diagnosis with the patient and offered the possibility to remain with riluzol and lithium for possible ALS with atypical presentation. The patient remained under fol-

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low-up in our outpatients' clinic at regular intervals. Another EMG study should be performed later in this patient to pursue more evidence of denervation.

Discussion

This patient presented a progressive ascending motor neuron disease, with a clear asymmetric involvement, with slow paresis progression. Although his symptoms were compatible with fasciculations (muscle twitches sensation), only upper motor neuron findings were evident on clinical examination. MRI was nondiagnostic. Needle electroneuromyography showed mild signs of denervation on muscles of cervical segment on left and right side and lumbosacral segment in both lowers limbs. Other possible causes such as metabolic, infectious, immunologic, and hereditary were excluded by history and complementary studies. A PET scan was considered but unfortunately, the exam was not available in our service. What should then be the diagnosis of this patient?

According to the current proposed diagnostic criteria, this patient has neither ALS nor PLS.^{6,8}

ALS is a neurodegenerative motor neuron disease, in which the current criterion requires evidence of both upper motor neuron and lower motor neuron (LMN) degeneration. This should be demonstrated by clinical, electrophysiological, or neuropathological examinations. According to the disease's pattern, the symptoms ought necessarily to spread and progress within a segment and from one segment throughout others (cranial, cervical, thoracic and lumbosacral) in order to attend ALS criteria.⁶ The El Escorial electrophysiological criterion calls for signs of ongoing/acute denervation (fibrillation potentials and positive sharp waves) and chronic denervation/reinnervation (large motor units, reduced interfer-

ence patters with firing rates higher than 10Hz, and unstable motor units), in at least one muscle innervated by cranial, and thoracic segments. Association of at least two muscles innervated by different peripheral nerves and roots are also required in the cervical and lumbosacral segments.^{6,9,10}

Primary lateral sclerosis is an idiopathic neurodegenerative disorder of UMN, with slowly progressive spastic paresis, usually beginning in the lower limbs and evolving to a spastic tetraparesis, with marked pyramidal signs, and bulbar involvement.¹¹ The two proposed criteria^{7,8} for PLS require the absence of LMN signs on clinical, and electrophysiological examination during the first three years of disease. Other authors prefer four years for a better diagnostic specificity.¹² Moreover, some authors doubt the existence of isolated UMN syndrome, arguing that it is one end of a continuous spectrum of motor neuron diseases.¹³ Regardless this discussion, proposed diagnostic criterion for PLS excludes any lower motor neuron involvement on EMG, even with asymptomatic.

Predominant upper motor neuron ALS¹² is evidenced by degeneration mainly in UMN, with clinical signs and disability due to corticospinal or corticobulbar damage. However, only minor clinical and EMG involvement of LMN, which are not severe enough to meet ALS diagnostic criteria, may be present. UMN-ALS is different from classical ALS in the progression rate and time of survival, which enables a better long-term prognosis.

In 1900, Mills¹⁴ described eight cases of a very slow progressive form of hemiplegia beginning usually in the extremity of a lower limb, then ascending to the homolateral upper limb and believed it was a new motor neuron disease. Some cases were reported later, but fewer of them after advances in diagnostic methods.¹⁵⁻¹⁸ In those cases pyramidal signs were always seen on the side of hemiplegia and often bilaterally, and a moderate amyotrophy without fasciculations can be commonly seen. The symptoms are gradually progressive, and the progression is frequently more ascending than descending, and the palsy can also involve the facial muscles. Sensory disturbances are generally absent. There was no family history of the syndrome in any of the cases. Gastaut *et al.*¹⁴ published in 1994 two further cases, similar to the ones described by Mills. The postmortem findings in one of Mills' original cases even described lesions at the level of the brainstem and spinal cord, sparing the motor cortex.¹⁹ The clinical picture presented by our patient is very similar to that described previously.

A study conducted by Turner *et al.*²⁰ used an 11C-(R)-PK11195 positron emission tomography (PET) to explore and delineate in vivo the cortical lesion in clinically isolated cases of

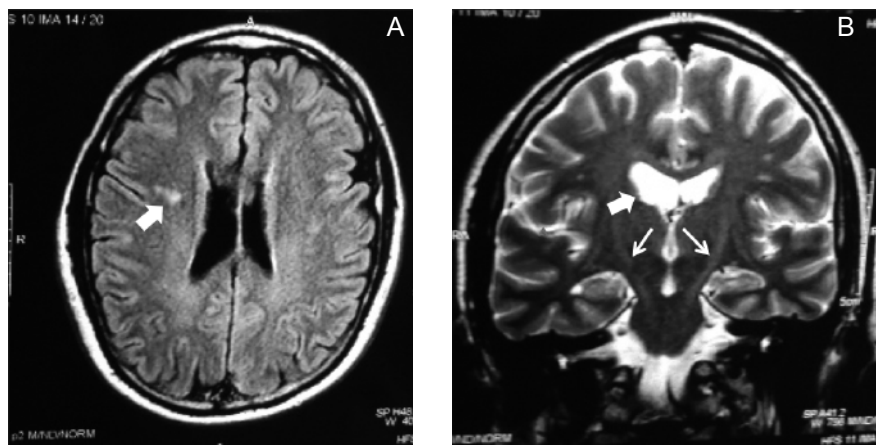


Figure 1. (A) Axial FLAIR MRI: mild rounded foci of high sign intensity in right corona radiata (arrow). (B) Coronal T2 weight MRI: mild dilatation of the right lateral ventricle (large arrow) and diffuse bilateral hyperintensities along the pyramidal tract extending from corona radiata to brainstem (thin arrows).

upper motor neuron syndrome. Two patients had clinical features similar to the cases described by Mills, and demonstrated marked increases in binding in the superior frontal region (supplementary motor region) contralateral to the affected limbs.

What is called Mills' syndrome could be all the variant of motor neuron diseases spectrum (ALS, PLS or UMN-ALS) in a hemiplegic, or asymmetrical pattern of involvement. A syndrome is a collective of symptoms and signs that could have many etiologies. Therefore, Mills syndrome should be conceptualized as a motor neuron syndrome with a hemiplegic or markedly asymmetrical pattern of involvement, not like a different disease. This vision is reinforced by recent reports²⁰⁻²³ that several diseases could cause this patters, including Waldenström macroglobulinemia, antiphospholipid syndrome, progressive multiple sclerosis, myelitis of unknown origin and multiple infarctions. Moreover, the paucity of neuropathological data from autopsies, and the lack of distinction between these motor neuron diseases call in to question the concept of Mills syndrome as a new nosological entity.

With this study, we propose that the clinical syndrome of progressive ascending or descending hemiplegia, or even those with bilateral but marked asymmetry, without significant sensory impairment, should be called Mills' syndrome, considering that there are several diseases that may cause it.

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