Clinical Reasoning: A 64 year-old woman with progressive leg weakness and ophthalmoplegia

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**Manuscript Category:** Resident and Fellow Section Clinical Reasoning

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SECTION 1:

A 64-year-old female with type 2 diabetes (HbA1C: 6.6%) experienced pain radiating down her right leg with intermittent numbness and tingling in her feet, followed by right leg weakness and recurrent falls. Two months after onset, she required a walker to ambulate long distances. Over the next five months, she experienced slow and progressive right leg weakness. Her neurologic examination revealed normal cranial nerves, fasciculations in the right leg, and non-pyramidal weakness in right L3-S1 myotomes. She had intact strength elsewhere. Reflexes were pathologically brisk (3+), except for absent right patellar and bilateral Achille’s reflexes. Plantar responses were flexor. There was mild length dependent distal sensory loss in both lower extremities.

Nerve conduction studies (NCS) revealed attenuated motor responses throughout the right leg with relative sparing of conduction velocity. There was no motor conduction block or evidence of demyelination. Sensory responses were absent in both legs. Needle electromyography (EMG) revealed ongoing neurogenic denervation in multiple bilateral lumbosacral and right thoracic myotomes.

1. What is the expected localization of this patient’s deficits?

2. What is the differential diagnosis?
SECTION 2:

Given her asymmetric non-pyramidal weakness, fasciculations, and sensory loss, this process localizes to lumbosacral lower motor neurons (LMN) and peripheral nerves. A right lumbosacral radiculoplexus-neuropathy with superimposed diabetic sensory polyneuropathy was considered. However, neurogenic denervation spreading to thoracic myotomes and her clinically unaffected leg argued against a unilateral radiculoplexopathy. Overall, her presentation suggested more LMN dysfunction, but pathologically brisk reflexes suggested early upper motor neuron (UMN) involvement.

Though her sensory findings and lack of weakness in other limbs was atypical, the presence of both LMN and UMN findings was suspicious for a LMN-predominant motor neuron disease (MND), such as a variant of amyotrophic lateral sclerosis (ALS), with superimposed diabetic polyneuropathy. The differential diagnosis also included motor neuronopathy and motor neuropathy, such as multifocal motor neuropathy and multifocal acquired motor axonopathy, along with diabetic sensory polyneuropathy. She had normal serum B12, ceruloplasmin, protein electrophoresis, TSH, and inflammatory panel. Creatine kinase was mildly elevated as can be seen in axonal neuropathy and MND. Non-enhanced MRI-spine was normal aside from L5/S1 spondylolisthesis and moderate foraminal stenosis.

For the next 4 months she remained stable. However, 11 months after her initial symptoms, she developed five-weeks of progressive upper extremity weakness, falls, diplopia, dyspnea, and dysphagia with twenty-five pounds of weight loss. She noted binocular horizontal diplopia with lateral gaze, which progressed to complete paresis of horizontal gaze. She also noticed new numbness and tingling in her left leg and bilateral
hands that progressed up her left arm to the elbow. There were no accompanying cognitive changes, seizures or fevers.

Her exam revealed normal visual acuity and fields. While convergence and vertical gaze were intact, horizontal eye movements were absent bilaterally. This was not overcome by the vestibulo-ocular reflex (VOR). There was LMN bilateral facial paresis. The palate elevated symmetrically, and her tongue had normal movements without fasciculations. Her speech was dysarthric. She had a brisk jaw-jerk reflex. Her motor exam revealed reduced bulk and fasciculations in the right quadriceps. Mild non-pyramidal weakness was noted in neck flexors, deltoids, and biceps bilaterally. Worsened non-pyramidal weakness was noted in the right leg. Weakness was not appreciated in the left leg. Reflexes remained pathologically brisk in the upper extremities, but absent in the legs. Her left plantar response was flexor, but mute on the right. She had reduced vibration sense distally in the lower extremities.

1. Where do the patient’s ocular findings localize?
2. Does this new presentation revise your previous differential diagnosis?
3. What additional investigations are indicated now?
SECTION 3:

Bilateral horizontal gaze paresis not overcome by VOR; preserved convergence; and bilateral facial paresis, localizes to the pons at the level of the facial colliculus – involving bilateral cranial nerve VI nuclei and the fascicles of cranial nerve VII. MRI demonstrated increased T2-FLAIR signal in the posterior pons (Figure 1).

While ophthalmoplegia can rarely occur in bulbar ALS and impairment in extraocular movements occurs as a late manifestation of ALS in chronically-ventilated patients, ophthalmoplegia is atypical of ALS. One consideration, given her dysphagia and weight loss, was a superimposed Wernicke’s causing ophthalmoplegia. However, the patient continued to worsen despite high dose IV thiamine. Though progressive supra-nuclear palsy (PSP) and multi-system atrophy (MSA) can rarely co-occur with MND, the absence of vertical eye movement abnormalities, parkinsonism, autonomic dysfunction, and ataxia was not consistent with PSP or MSA. Although her examination and EMG revealed predominant LMN dysfunction, the rapidity of her decline, worsened sensory symptoms, ophthalmoplegia and her pontine lesion challenged the diagnosis of ALS and broadened our differential to include inflammatory, paraneoplastic and autoimmune etiologies affecting motor neurons and cranial nerve nuclei.

A CT chest, abdomen, pelvis and transvaginal ultrasound did not reveal evidence of malignancy or lymphadenopathy. CSF analysis revealed a protein of 503 mg/L, but otherwise cytology, cytometry and extensive bacterial and viral studies were unremarkable. Serum anti-GQ1b, anti-GM1 and lyme serology were negative. Repeated NCS revealed new-onset patchy, non-length dependent loss of sensory responses in the left upper extremity. She was started on high dose methylprednisone and IVIG
without clinical improvement. The patient developed progressive respiratory decline, disorientation and lethargy. An EEG did not reveal evidence of seizures and repeated MRI brain remained stable. The patient continued to decline and eventually died from respiratory failure. Her paraneoplastic antibody panel later revealed positive serum and CSF anti-Hu antibodies. The family declined autopsy.

**DISCUSSION**

This clinical reasoning case highlights the challenges of diagnosing atypical motor neuropathies and LMN-predominant ALS. Without a reliable biomarker, upwards of 10% of ALS cases are erroneously diagnosed.\(^1\) Cervical spondylotic myeloradiculopathy, polyradiculopathy, MSA, and multifocal motor neuropathy are conditions erroneously misdiagnosed as ALS.\(^1\) The diagnosis is especially challenging early in the disease when UMN and LMN signs have not disseminated. Initially, the clinical evidence of LMN and mild UMN involvement early in our patient’s disease course, as well as ongoing neurogenic denervation in multiple thoracic and lumbosacral myotomes satisfied the revised El Escorial diagnostic criteria for probable ALS-laboratory supported.\(^1\)

Rarely, paraneoplastic disorders can cause MND and masquerade as ALS, the most common of which is anti-Hu associated MND.\(^2\) Paraneoplastic MND can be pure LMN syndromes in 63% of cases, and both LMN and UMN presentations in 37% of cases.\(^3\) Paraneoplastic MND should be suspected in those under 40 years of age, with known malignancy, rapid progression, subacute onset, extra-motor neuron involvement,
monoclonal gammopathy, lymphadenopathy, or elevated inflammatory markers.²

Indeed, the rapid and profound weakness in the right leg without clinical involvement of the left leg is atypical for ALS. While diabetes could explain the initial length-dependent distal sensory symptoms, the new-onset of patchy sensory loss represented another red-flag for an extra-motor process affecting the dorsal root ganglia, likely secondary to anti-Hu. When she rapidly deteriorated with ophthalmoplegia, it was clear that she did not have ALS.

This is the first reported case of anti-Hu antibody associated ophthalmoplegia and MND. Anti-Hu associated MND was first reported in 1995 in the context of small cell lung cancer (SCLC) with demonstrated loss of anterior horn cells, neurogenic denervation and loss of cerebellar Purkinje cells.⁴ The clinical spectrum of anti-Hu paraneoplastic disorders has since expanded to include limbic and brainstem encephalitis, encephalomyelitis, sensory neuronopathy, Lambert-Eaton syndrome, and opsoclonus myoclonus.⁵ Ophthalmoplegia has been reported recently in a patient with liposarcoma and anti-Hu antibodies, but without MND.⁶ Anti-Hu syndromes are most often associated with SCLC (85% of cases), but have been reported in lymphoma, neuroblastoma, pancreatic neuroendocrine tumors, as well as prostate, intestinal, bladder, and ovarian carcinomas.⁵ In a study of 200 anti-Hu positive cases, no tumor was found in 33 patients.⁵ In another study of 20 patients with paraneoplastic antibodies and without evidence of malignancy, positron emission tomography (PET) had an 83% sensitivity in detecting a cancer.⁷ In this study, 13/20 patients had Anti-Hu antibodies and, 8 of 9 cases who died during the study were Anti-Hu positive.
The importance of rapidly identifying onconeural antibodies with prompt treatment of malignancy in paraneoplastic MND was highlighted by cases of SCLC with chemotherapy responsive anti-Hu MND. Furthermore, in a single case report, a patient with SCLC and Anti-Hu associated limbic encephalitis and MND stabilized with IVIG treatment and survived to receive radiotherapy with remission and neurological improvement. Therefore, cases of atypical motor neuronopathy should have paraneoplastic antibody screening and, if identified, extensive imaging, including PET, should be performed. In those with a paraneoplastic antibody, consensus opinion continues to recommend prompt cancer screening and treatment of the primary cancer as the optimal intervention.

In summary, this case expands on the clinical spectrum of Anti-Hu paraneoplastic disorders. This is the first reported description of a patient with MND and ophthalmoplegia associated with Anti-Hu antibodies. The prevalence of paraneoplastic associated MND is unknown and likely rare, but this etiology should be included in the differential diagnosis for patients presenting with atypical forms of motor neuronopathy or MND. It is especially important to identify ALS mimickers that are potentially treatable as earlier identification and interventions might predict a more favorable prognosis.
## Appendix 1: Authors

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References


**Figure 1:** Axial MRI demonstrating increased T2-FLAIR signal in the posterior pons.

**FIGURE LEGEND**

**Figure 1:** Axial MRI T2-FLAIR demonstrating increased signal hyperintensity in the posterior pons (as indicated by the red arrows). In the caudal pons, depicted in images A and B, T2-FLAIR signal hyperintensities are visualized affecting the region of the bilateral facial colliculi and cranial nerve VI nuclei. T2-FLAIR signal hyperintensities continue into the rostral pons as indicated by the red arrows in images C and D. There was no associated parenchymal, leptomeningeal or cranial nerve enhancement with MRI T1 post-gadolinium imaging. There was no evidence of restricted diffusion on DWI/ADC modalities. The remaining MRI brain and spine were both unremarkable.
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Ryan T. Muir, Agessandro Abrahao, David Fam, et al.
Neurology published online July 17, 2020
DOI 10.1212/WNL.0000000000010363

This information is current as of July 17, 2020