

# Pearls and Oy-sters: Myasthenic Crisis in a Patient With Motor Neuron Disease: Hickam's Dictum vs Occam's Razor

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## Pearls

- Extraocular muscles are generally spared in amyotrophic lateral sclerosis (ALS). New-onset ptosis or diplopia in these patients should raise clinical suspicion for an alternative diagnosis or an overlapping condition.
- The determination of the presence of comorbid myasthenia gravis (MG) in the setting of known motor neuron disease should be based on the clinical picture and the response to empirical treatment.

## Oy-sters

- Positive antibodies are neither necessary nor sufficient to make a diagnosis of MG, particularly in the setting of concomitant ALS.
- Repetitive nerve stimulation (RNS) testing may be abnormal in patients with ALS, reducing its specificity and sensitivity in the diagnosis of MG.

## Case Report

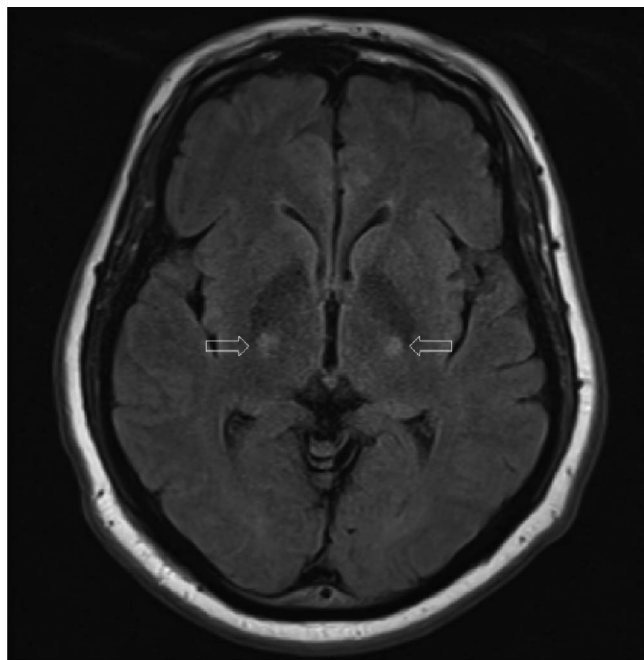
A 46-year-old man diagnosed with ALS came to establish care at our multidisciplinary ALS clinic. He developed progressive, nonfluctuating weakness of the left hand approximately 23 months before presentation, followed by dysphonia and dysarthria 11 months later. His medical history was notable for psoriasis and hypothyroidism. Routine laboratory tests for complete blood count, comprehensive metabolic panel, magnesium, thyroid stimulating hormone, creatine kinase, serum, and urine protein electrophoresis were normal. MRI of the brain revealed T2 signal hyperintensity in the bilateral corticospinal tracts without abnormal uptake of gadolinium contrast (Figure 1). MRI of the cervical spine without gadolinium was unrevealing for inflammatory, infectious, demyelinating, or compressive lesions. Nerve conduction studies and needle EMG revealed active and chronic denervation in the cervical-, thoracic-, and lumbar-innervated myotomes. He was diagnosed with limb-onset ALS, approximately 18 months after symptom onset. His treatments included riluzole for disease modification, dextromethorphan/quinidine for pseudobulbar affect, and baclofen for spasticity.

On presentation to our clinic 6 months after the diagnosis of ALS, he was ambulatory but experienced progression of hand weakness and speech disturbances. Physical examination revealed upper motor neuron (UMN) signs in the cranial, cervical, and lumbar regions, manifesting as a slow dysarthria with brisk jaw jerk, spasticity, upper extremity hyperreflexia, bilateral ankle clonus, and an extensor plantar reflex on the right. There were also lower motor neuron (LMN) signs in the cranial and cervical regions characterized by muscle atrophy and fasciculations in the tongue, weakness with lip closure and tongue protrusion, atrophy in the bilateral thenar eminences and first dorsal interossei, and weakness in finger abduction and extension, worse in the left than right hand. Extraocular muscles and orbicularis oculi were

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**Figure 1** MRI T2 FLAIR



Axial fluid attenuated inversion recovery image demonstrating bilateral signal hyperintensities (white arrows) in the posterior limbs of the internal capsules. These findings have previously been described in ALS and have been proposed to reflect corticospinal tract degeneration.

intact. ALS Functional Rating Scale was 29/48, and forced vital capacity (FVC) was 87% of predicted value. The patient wished to pursue edaravone therapy to modestly slow disease progression. He received his first edaravone infusion at approximately 2 years of symptom onset and tolerated the first cycle of therapy without side effects.

On the antepenultimate and penultimate days of the second infusion cycle at home (days 38 and 39 of the therapy plan), he developed malaise and incurred 2 separate falls with head trauma. He was evaluated twice in an emergency department (ED) and returned home as no acute intracranial pathology was identified. He was referred to ophthalmology for a routine outpatient evaluation of subjective diplopia, the records of which were unavailable for review. Three weeks after the second cycle of edaravone infusion, he was brought by the family to the ED for failure to thrive at which point neurology was consulted.

Evaluation revealed a significant functional decline relative to examination 2 months earlier in ALS clinic. He was not able to ambulate nor take any solids or liquids by mouth. He was tachycardiac, mildly diaphoretic, and significantly dyspneic with the use of accessory respiratory muscles. Furthermore, he was quadriparetic and had weakness of neck extensors and bilateral levator palpebrae superioris muscles. Eyelid closure could be overcome by the examiner, but Bell phenomenon was absent. Pursuit testing showed a near complete paralysis of cranial nerves III, IV, and VI, except for partial abduction of the right eye with

lateral gaze, making fatiguability difficult to assess. Manual maneuvers of the head in vertical and horizontal directions with visual fixation on an object did not improve his gaze palsy. Impairment of both horizontal and vertical saccades were observed.

Owing to the acute change, rapid decompensation, and new ocular findings, a diagnosis of MG was suspected. Serum testing for antibodies against the acetylcholine receptor was positive (binding, 2.84 nmol/L; ref <0.3 nmol/L), and antibodies against muscle-specific tyrosine kinase (MuSK) was negative. Repetitive nerve stimulation of the ulnar-abductor digitorum minimus system was nondiagnostic, limited by the extremely low compound muscle action potential amplitudes at baseline (0.2 mV; reference >6 mV), and evaluation of the peroneal-extensor digitorum brevis system was limited by electrical artifacts in the ICU. Contrast-enhanced CT scan of the chest did not show evidence of a thymoma (Figure 2).

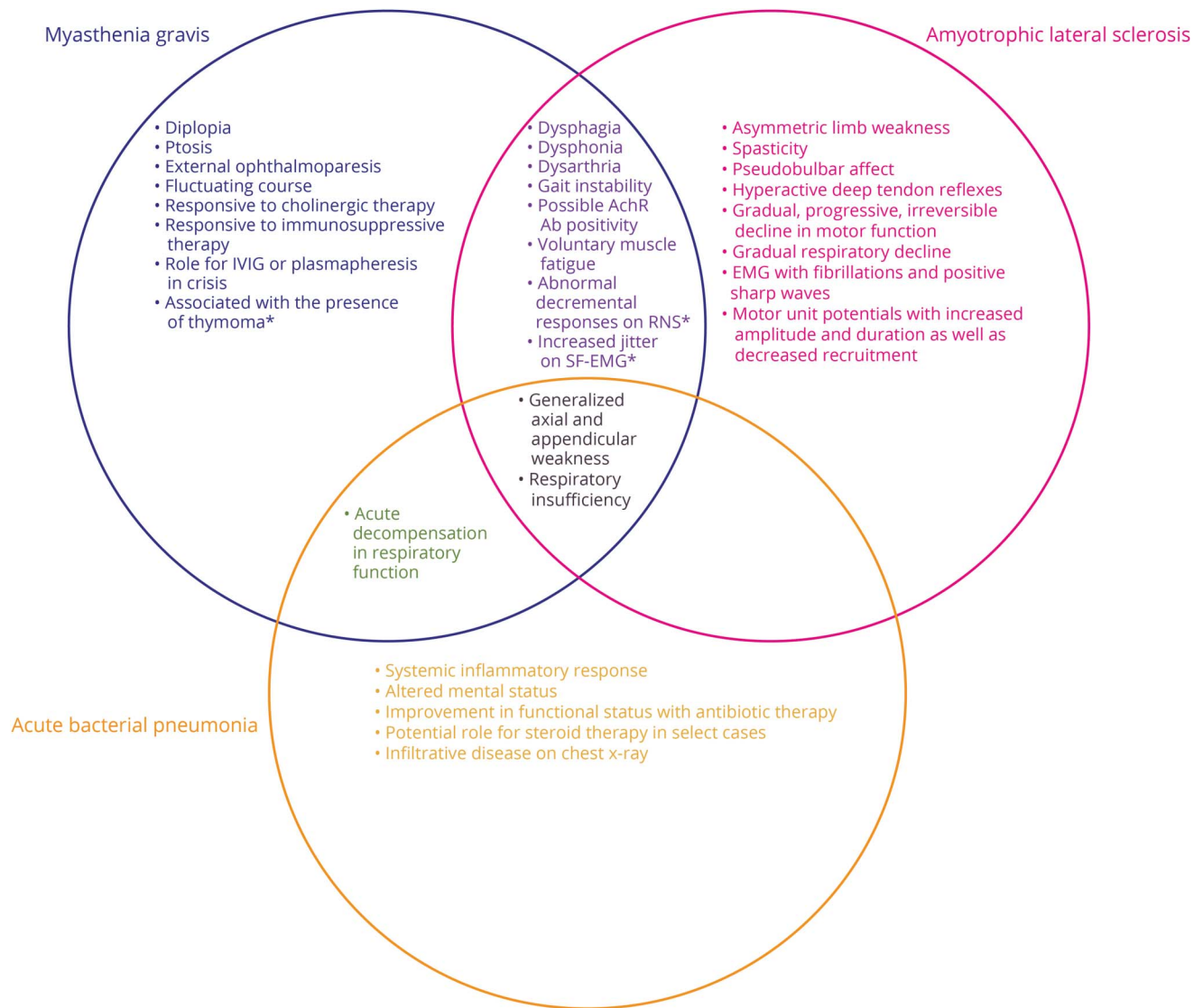
Although the antibody test results were pending, the patient was initially placed on bilevel positive airway pressure (BiPAP) for respiratory support and trialed on pyridostigmine for MG. He required short-term intubation because of respiratory decompensation with methicillin-sensitive *Staphylococcus aureus* pneumonia complicated by bilobar pulmonary collapse. He was treated with antibiotics and glucocorticoids. He received 2g/kg of intravenous immunoglobulin divided over 5 days for myasthenic crisis. Over the subsequent weeks, ptosis and ophthalmoplegia ultimately resolved. Weakness in his proximal legs and left arm also improved. He was able to use an eye-gaze device for communication during the latter portion of hospitalization and on discharge. He returned home after 38 days of hospitalization with gastrostomy, tracheostomy, and the addition of prednisone for MG. Ventilatory support was gradually weaned to nocturnal use only. Pyridostigmine was discontinued because of increased bronchial secretions. Subsequent cycles of edaravone were not administered, given the change of clinical status.

## Discussion

ALS is an adult-onset degenerative disease of the motor nervous system. Patients typically present with focal weakness, followed by a gradually progressive course involving other body parts over months to years. The disease may be dichotomized into limb-onset presentation, as in our case, or bulbar-onset presentation. Our patient exhibited the classic and more commonly encountered limb-onset presentation, and the classic phenotype characterized by prominent and coexisting UMN and LMN signs. The etiopathology of ALS is complex, and the diagnosis remains a clinical one in the absence of diagnostic biomarkers.

In contrast, MG is an autoimmune-mediated disease characterized by dysfunction of the neuromuscular junction. Patients typically present with fluctuating ptosis of eyelid muscles and diplopia, which may progress and cause episodic dysfunction in the bulbar, truncal, appendicular, or respiratory

**Figure 2** Disease-specific Symptoms and Tests



Signs, symptoms, and tests critical for establishing the diagnoses were considered and have been summarized in the accompanying Venn diagram. Asterisks denote observations that were not present in this case but may be helpful in further discerning the underlying pathology.

muscles. Although compromised respiratory function may develop with progression of either ALS or MG, respiratory insufficiency is almost invariably associated with a more gradual course in the former relative to the latter.

MG was suspected in this case because we recognized that ophthalmoparesis is not typically seen in ALS except in advanced stages, when patients are locked-in and dependent on mechanical ventilatory support.<sup>1</sup> This could potentially be explained by the fact that 20% of extraocular muscle fibers conform to an *en grappe* neuromuscular endplate pattern comprised of smaller endplates in grape-like clusters, anatomically and functionally distinct from the singly innervated fibers typical of skeletal muscles, which may confer some resistance to the effects of early neurodegeneration.<sup>2</sup> Furthermore, the rapid decline in respiratory function observed in this case is not consistent with the projected clinical course of

respiratory deterioration in ALS, which typically demonstrates a monthly decline in FVC of 1.6%–3.5%.<sup>3,4</sup>

Although pneumonia could contribute to acute respiratory decompensation and appendicular motor weakness, it could not readily explain the observed infranuclear gaze palsy. Acute inflammatory demyelinating neuropathy was considered but seemed less likely in the setting of preserved hyperreflexia on examination. Posttraumatic diplopia was also initially considered, but the combination of bilateral ocular involvement, subacute progressive decline, and absence of findings on imaging, as well as the clinical improvement in response to immunotherapy, rendered a diagnosis of traumatic cranial neuropathy less plausible.

This case highlights the importance of clinical reasoning and the limitations of diagnostic testing. (1) RNS is not specific for

MG and may be abnormal in patients with ALS.<sup>5</sup> (2) Single-fiber EMG can be confounded by LMN degeneration. (3) Antibody testing may be negative in patients with MG<sup>6</sup> or falsely positive in patients with ALS<sup>7</sup> at rates estimated as high as 5%.<sup>8,9</sup> Reports of patients with overlapping ALS and MG are very rare but occur out of proportion to what would be expected by chance alone<sup>10</sup> and likely reflect shared risk factors<sup>11</sup> or mechanisms of immune dysregulation in these 2 disease processes.<sup>12</sup> Our patient imparts on us the importance of understanding the typical course and progression of different diseases and affirms the need for vigilance in the pursuit of reversible or treatable disorders, particularly when caring for individuals suffering from chronic progressive neurodegenerative conditions. Although Occam's razor, the law of parsimony, represents an essential and invaluable postulate to inform the practice of medicine, Hickam's dictum underlies the ability to reconcile the existence of comorbidities for which a targeted therapy may be clinically indicated.

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## Appendix Authors

Name	Location	Contribution
<b>Adam Seth Greenblatt, MD</b>	Department of Neurology, University of Pennsylvania, Philadelphia	Drafting/revision of the manuscript for content, including medical writing for content, major role in the acquisition of data, and study concept or design

## Appendix (continued)


Name	Location	Contribution
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