

Acute Limb-Girdle Weakness with myasthenic features

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ABSTRACT

Myasthenia gravis is a disorder characterized by autoantibodies targeting different proteins across the neuromuscular junction. The typical presentation of myasthenia gravis involves oculobulbar weakness, classically ptosis that may or may not be symmetric. Patients may also present with a more dramatic presentation of generalized weakness or in myasthenic crisis requiring respiratory support for oxygenation. While these are the common presentations, atypical presentations sparing the eyes have been described. Here we present the case of a 63-year-old male who presented with proximal arm and leg weakness that rapidly progressed with a negative workup for central structural or inflammatory etiologies and was best explained by a likely limb girdle presentation of myasthenia based on electrophysiologic features and response to therapy. While long term follow-up was limited due to a co-morbid malignancy, the case highlights the utility of advanced electrodiagnostics in the workup of rapidly progressive weakness and the importance of considering a wide differential to identify potentially reversible etiologies.

Introduction

Myasthenia gravis (MG) is a disorder characterized by autoantibodies targeting different proteins on the neuromuscular junction. The incidence of MG ranges from 5 to 30 per million person-years with a prevalence of 10 to 20 cases per 100,000.¹⁻³ The most common of these autoantibodies are ones that directly target the acetylcholine receptor (AChR), which can be seen in 85% of patients with generalized MG and 50% of patients with

ocular MG. Up to 40-70% of patients that are seronegative for AChR antibodies may have MuSK antibodies.⁴ While autoantibodies remain the most specific diagnostic test available, single fiber electromyography is the most sensitive, being abnormal in 94% with generalized and 80% with ocular myasthenia gravis.^{5,6}

The typical presentation of MG involves oculobulbar weakness, classically ptosis, that may or may not be symmetric. Patients may also present with a more dramatic presentation of generalized weakness or even in myasthenic crisis requiring non-invasive or invasive respiratory support for oxygenation. Some of the factors that may worsen or precipitate MG include surgery, pregnancy, stress, antibiotics (most notably fluoroquinolones, tetracyclines, and aminoglycosides), anesthetics, neuromuscular blocking agents, and cardiovascular medications including beta-blockers, calcium channel blockers, quinine, and quinidine.⁷

Case Report

A 63-year-old right-handed male was hospitalized for bilateral upper extremity weakness. His past medical history included benign prostatic hyperplasia, gastroesophageal reflux disease, and a recently diagnosed lung mass concerning for malignancy. The patient had a bronchoscopy 5 days prior for tissue diagnosis of the mass and described muscle pain and ‘pins and needles’ after the procedure, which slowly improved over 24 to 36 hours. Following resolution of the ‘pins and needles’ sensation in a rostral to caudal fashion, the patient started to feel weak, noting he was unable to stand or walk even short distances without some support. Over the next 24 hours, he noted improvement in the strength of his legs, but declining strength of his upper extremities, especially proximally as he found he was unable to lift his arms above his head. The patient denied any changes in bowel or bladder function and denied any muscle pain on initial evaluation. Review of systems was negative for any fevers, chills, nuchal rigidity, headache, changes in vision, weakness of his face, trouble swallowing, neck weakness, trauma, changes in his voice, or shortness of breath. He denied family history of neurologic conditions or autoimmune conditions. He reported drinking one glass of wine nightly but had never smoked himself (did have second-hand smoke from his mother as a child).

Initial exam revealed intact cognition, mental status, repetition, naming, memory, and attention. His cranial nerve exam was without any evidence of diplopia, fatigable changes in extra-ocular movements, ptosis, asymmetry of facial musculature, alterations in sensation or hearing, and intact strength of his sternocleidomastoid and trapezius bilaterally. The patient’s motor exam demonstrated normal tone and bulk without any drift or fix, but significant symmetric weakness in proximal muscles, worse in his upper extremities than lower extremities, and worse in upper extremity extensors and lower extremity flexors. The most significant weakness was found in his deltoids which were

2/5 bilaterally. The patient's reflexes were intact and normal in biceps, triceps, brachioradialis, patellar, and Achilles; his plantars were down-going bilaterally. Complex motor including finger-tapping, finger-to-nose, heel-to-shin, and rapid alternating movements were intact bilaterally without any evidence for tremor. Sensation was grossly intact to pin prick and temperature with vibratory sensation diminished to 3 seconds in distal right lower extremity and 4 seconds in distal left lower extremity with normal findings at the knees bilaterally. There was no sensory level. Gait was physiologic with retained ability to walk tandem, walk on his heels, and walk on his toes.

Laboratory studies at the time of evaluation were normal with thyroid stimulating hormone of 1.930 and no evidence of infection or metabolic derangements, but a slightly elevated creatinine kinase (CK) of 390. The lung biopsy at time of initial evaluation had not been finalized.

MRI Brain and C-Spine, obtained given the possible upper motor neuron pattern of weakness, demonstrated no evidence of metastatic disease or acute diffusion restriction in the brain with mild to moderate nonspecific hyperintense white matter foci attributed to chronic microvascular changes. The MRI C-spine demonstrated no evidence of intraspinal or extradural mass and no cervical cord compression.

The patient's exam remained relatively unchanged per documentation on hospital day (HD) 2 with the exception that reflexes were unobtainable in his bilateral upper extremities by multiple physicians. As a result, clinical concern for possible Guillain-Barre Syndrome (GBS) or a variant was considered versus less likely Lambert-Eaton Myasthenic Syndrome (LEMS) due to his underlying lung mass and possibly fluctuating reflexes. Therefore, the decision was made to schedule an electromyography/nerve conduction study (EMG/NCS) to better differentiate.

EMG/NCS was completed on HD 3 at which time his exam remained unchanged but reflexes continued to have variable documentation. NCS of the right upper and lower extremity demonstrated a prolonged distal latency (6.6 ms) and normal amplitude (6.1 mV) of the right median motor study (consistent with right median neuropathy at the wrist) but otherwise normal distal latencies, amplitudes, and conduction velocities of the right ulnar and radial motor studies. Right peroneal motor study recording over extensor digitorum brevis demonstrated a normal distal latency but reduced amplitude (0.1mV) in all nerve segments. The tibial motor study demonstrated normal distal latency, amplitude, and conduction velocity. F waves were completed and normal in the right ulnar and tibial nerves, but mildly prolonged in the right median nerve (34.8 ms; normal <31 ms).

Sensory studies demonstrated normal peak latencies and amplitudes of the right superficial radial and ulnar-digit V sensory nerves with a prolonged peak latency (5.2 ms) and reduced amplitude (4 μ V) of the right median-digit

II sensory study. The right superficial peroneal sensory response was absent.

Given lack of diffuse demyelinating features and the only findings of a right median neuropathy at the wrist and a lower extremity sensorimotor axonal polyneuropathy, neither of which explained the patient's clinical presentation, repetitive nerve stimulation (RNS) was performed in the upper extremity (Table 1). 2Hz repetitive stimulation of the right ulnar nerve at baseline, immediately after 1 minute isometric exercise, 1 minute post exercise, and 2 minutes post exercise showed a maximal decrement of 23%, 17%, 18%, and 21% respectively. The right radial motor nerve demonstrated a maximal decrement with 2Hz RNS of 60% at baseline which improved slightly to a maximal decrement of 44% after 10 seconds of isometric exercise. The right median nerve also demonstrated a maximal decrement of 22% at baseline with 2 Hz RNS, however, no additional studies were done given the supportive findings in the radial and ulnar RNS studies. Given the above findings, normal compound motor action potential (CMAP) amplitudes (with exception of the right peroneal motor study presumed secondary to neuropathy), and lack of CMAP facilitation with 10 seconds of exercise, the repetitive nerve studies were felt to be most consistent with a postsynaptic neuromuscular junction disorder.

Needle EMG was completed on the right extensor digitorum communis and triceps brachii demonstrated reduced recruitment with very unstable MUPs with near complete exhaustion and absent MUAPs within 10-12 seconds of activation which further supported the diagnostic concern for a disorder of neuromuscular transmission.

Following completion of the EMG/NCS and initial laboratory/imaging studies, the patient's clinical presentation was felt to be inconsistent with a disorder of the upper motor neurons given reassuring brain and spinal imaging. Additionally, while the patient had a mildly elevated CPK, his lack of myopathic motor units on his EMG along with his fluctuating exam made an acute myopathy lower on the differential. While the patient did have a known pulmonary mass concerning for malignancy, his lack of autonomic features, upper greater than lower extremity weakness, normal CMAP amplitudes with lack of facilitation on his EMG, and a pattern on RNS most consistent with a post synaptic neuromuscular junction transmission disorder made the clinical picture less consistent with LEMS.

Review of the patient's chart demonstrated that the bronchoscopy completed 5 days prior to admission was prolonged (approximately 3 hours), during which the patient received 3 doses of succinylcholine for vocal cord spasms in addition to propofol, ketamine, and phenylephrine for sedation. Additionally, it was found that he had another bronchoscopy 15 days prior to admission during which he was diagnosed with pseudomonas pneumonia prompting a 10-day course of levofloxacin (no clear documentation

or prior fluoroquinolone exposure prior to this). While diagnostic uncertainty remained, given his NCS/EMG findings and exposure to two medications (succinylcholine and levofloxacin) associated with potential myasthenia gravis exacerbation prior to his presentation, he was treated empirically for presumed limb-girdle onset myasthenia gravis with a course of plasmapheresis (PLEX) including 5 exchanges over 10 days. He was started on 60mg daily of prednisone following his third exchange. Serology for myasthenia gravis was pending at the time of treatment initiation. By the time the patient completed his third exchange, he had significant recovery of his strength and reflexes. Acetylcholine receptor binding, blocking, and modulating autoantibodies and muscle specific kinase autoantibodies (MuSK) returned negative. A voltage-gated calcium channel antibody was not sent.

Following discharge from the hospital, the patient was maintained on 60mg daily of prednisone with plans for outpatient follow-up and taper. At follow up appointments 1- and 2-months post hospital discharge, it was noted he had returned to his prior activity levels and was walking up to 2-3 miles daily. He did not have any residual weakness documented and he had begun a gradual taper of his prednisone by 10mg monthly which he was tolerating up until 1 month prior to his death (at 40mg daily at that time). Unfortunately, as part of the patient's lung mass evaluation, he was ultimately diagnosed with a metastatic malignancy of unknown primary (assumed pulmonary versus prostate based on biopsy results) and passed away 3 months after his hospital admission due to his burden of metastatic disease.

Discussion

The above case highlights the importance of broadening a differential for acute onset weakness unexplained by initial structural imaging, especially in the setting of a rapidly changing neurological exam. In the above case, given the change in reflexes noted on examination as well as initial laboratory screening demonstrating a mildly elevated CK, the patient was referred for electrodiagnostic studies to evaluate for potential GBS variants and/or muscle and neuromuscular disease.

At the time of the patient's death, the leading proposed etiology for his presentation was an acute atypical limb girdle myasthenic syndrome. While MG typically presents with oculobulbar weakness, a study completed in Italy over 27 years followed a total of 508 patients with newly diagnosed MG. Of the 508 patients that were evaluated, 21 patients had a presentation that was incongruent with a typical presentation of MG including asymmetric distal upper limbs weakness, foot drop, isolated triceps brachii weakness and foot drop, post exertional axial weakness with dropped head, acute facial diplegia, limb-girdle MG, and MG with sudden lower limbs weakness and recurrent falls. The limb-girdle type presentation, like our patient, was

present in 9 patients total (1.8% of the study population). These patients had a high rate (56%) of being seronegative for both AChR (22%) and MuSK (22%) autoantibodies, as was also the case in our patient.⁸

The patient's pattern on RNS was most consistent with a post-synaptic neuromuscular junction disorder, especially given the lack of significant CMAP amplitude facilitation greater than 60% with 10 seconds of isometric exercise. The finding of post-exercise facilitation of CMAP amplitude greater than 60% has been shown to have a high sensitivity of 84-96% for the diagnosis of LEMS.^{9,10} While we cannot definitively rule out the possibility of LEMS based on the short term follow up available after hospitalization, the fact that the patient had such a robust response to immunotherapy despite progression of his cancer and maintenance with only prednisone would be atypical for paraneoplastic LEMS. Severe weakness in the setting of LEMS has been shown to be responsive to PLEX in the short term, however, the effect is only typically present for 6 weeks and maintenance therapy with prednisone (as in our patient) is typically only associated with mild to moderate improvement in symptoms, not the robust improvement we saw in our patient.⁹

Additional etiologies for the patient's electrodiagnostic findings on RNS could include centronuclear myopathies (BIN1, DNMT2, MTM1 mutations), congenital myopathies associated with RYR1 mutations, or even myotonic dystrophy type I and myotonia congenita; all of which have been shown to be associated with co-morbid dysfunction of the neuromuscular junction demonstrable on RNS studies.¹¹ While the patient did have a slightly elevated CK, none of the listed conditions would be expected to respond robustly to immunotherapy and the patient did not have any prior history or stigmata to suggest a long standing neuromuscular disorder at the time of presentation.

While at the time of the patient's death the best explanation for his presentation was an atypical limb-girdle presentation of myasthenia gravis, potentially provoked by recent fluoroquinolone and succinylcholine exposure. We do not believe the syndrome was representative of a paraneoplastic myasthenic syndrome as this tends to present with a distinct non-limb MG presentation characterized by prominent oculobulbar and respiratory symptoms.¹² While long term clinical follow-up and response to tapering of immunotherapy would have helped provide a more definitive diagnosis in this case, we believe the atypical presentation and clinical course highlights the importance of considering disorders of neuromuscular transmission, even when a presentation may not appear to be consistent with typical clinical heuristics for the hallmark disorders.

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