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Diffuse Muscle Weakness: The Toxicologist's Approach

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The differential diagnosis is daunting in this case of an elderly woman with new-onset inability to walk. However, results of her lab work and other testing provide important clues that ultimately point to her medication regimen.

Case

An 81-year-old woman presents to the ED with a 5-day history of generalized weakness and dyspnea. She denies sensory symptoms, diplopia, dysarthria, and dysphagia. Her medical history includes hypertension, hyperlipidemia, and atrial fibrillation. Her surgical history is notable for a remote thymectomy. She is currently taking warfarin, digoxin, and simvastatin.

On physical examination, her vital signs are within normal limits. She is awake, alert, and cooperative. Her cardiac, pulmonary, and abdominal exams are all unremarkable. On neurologic examination, her cranial nerves II through XII are intact. She has bilateral upper extremity weakness (4/5) that is slightly worse proximally compared to distally. She has bilateral lower extremity weakness (2/5) that is also slightly more pronounced in the proximal muscle groups. Her neck flexion is weak (3/5), deep tendon reflexes are absent throughout, and she is unable to walk. Perception of light touch is intact throughout. Her proximal muscles are slightly tender to palpation, and their consistency is normal.

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What is a practical toxicologic differential diagnosis for diffuse muscle weakness?

There are numerous etiologies for muscle weakness, including infectious, metabolic, autoimmune, endocrine, and toxicologic causes. One approach to this daunting differential diagnosis considers whether the pathology originates within the peripheral motor neuron, at the neuromuscular junction, or within the muscle itself. This framework subsequently allows the history, physical exam findings, and clinical progression to further narrow the list of likely causes.

The classic clinical findings of neuronal dysfunction leading to paralysis are exemplified in a demyelinating syndrome such as Guillain-Barré syndrome (GBS). This condition typically presents as an ascending motor weakness in the 2 to 4 weeks following a viral illness or *Campylobacter jejuni* infection. Symptoms often begin with paresthesias of the distal extremities, followed by weakness that may progress to involve the trunk, upper extremities, cranial nerves, or diaphragm over a period of days to weeks. Deep tendon reflexes tend to be absent early in the disease course, and objective sensory deficits are rare.[1] Muscle pain or tenderness does not occur.

Toxicologic mimics such as tick paralysis and botulism, resulting from the inhibition of acetylcholine release at the neuromuscular junction, similarly present with diplopia, dysphagia, and other manifestations of cranial nerve dysfunction. This is followed by descending paralysis with consequential involvement of the respiratory musculature.[2] GBS may present as a descending paralytic syndrome as well, and this is

Table. Nontoxicologic Causes of Diffuse Muscle Weakness

Etiology	Mechanism	Clinical Presentation
Lambert-Eaton syndrome[4]	Presynaptic voltage-gated calcium channels blocked by autoantibodies	• Starts with proximal leg weakness • Slowly progressive • Improves with exertion • Possible diaphragm involvement
Myasthenia gravis[4]	Postsynaptic nicotinic ACh receptors blocked by autoantibodies	• Starts with diplopia, cranial neuropathies • Worsens with repeated effort • Possible diaphragm involvement
Primary periodic paralyses (hyperkalemic or hypokalemic)[5]	Alterations in L-type calcium channel or skeletal muscle sodium channel subunits	• Attacks of flaccid paralysis sparing facial muscles • Rare diaphragm involvement • Common after exercise or large carbohydrate meal
Myopathies	Infection (eg, influenza) Autoimmune (eg, lupus) Endocrine (eg, hypothyroidism)	• Muscle pain • Proximal limb weakness • Elevated CPK level

ACh = acetylcholine; CPK = creatine phosphokinase.
Data from Wirtz et al[4] and Venance et al.[5]

known as the Miller Fisher variant.

A variety of toxic-metabolic derangements, such as hypermagnesemia[3] or hypokalemia, can affect transmission at the neuromuscular junction and result in weakness or flaccid paralysis. Both of these electrolyte abnormalities alter neuronal excitability—hypokalemia, by changing the electrochemical potential of excitable cells, thus blocking repolarization; and hypermagnesemia, by blocking presynaptic calcium ion entry. In patients with severe electrolyte abnormalities, alterations in cardiac conduction can also occur. However, muscle pain is not expected.

Finally, myopathies are a group of disease processes that affect the muscle fibers themselves, resulting in symmetrical weakness that tends to involve the more proximal muscle groups. Patients may complain of muscle pain and have muscle tenderness on palpation. Although congenital disorders are a common cause in infancy (Duchenne muscular dystrophy), acquired myopathies in adults are commonly related to use of medications such as corticosteroids, zidovudine, colchicine, and statins. The Table summarizes nontoxicologic etiologies of diffuse muscle weakness.

Case Continuation

The patient's initial laboratory values are notable for the following: creatine phosphokinase (CPK), 3,513 U/L (normal <40 U/L); blood urea nitrogen, 68 mg/dL; and creatinine, 2.3 mg/dL. A lumbar puncture is performed, with cerebrospinal fluid (CSF) showing no red or white blood cells and normal protein and glucose measurements. The patient is admitted to the hospital and undergoes nerve conduction studies (NCS) with unremarkable results and electromyography (EMG) with abnormal findings that are consistent with the diagnosis of myopathy.

How should the potential etiologies of diffuse muscle weakness be approached?

Clinical features of the history and physical examination assist in the differential diagnosis. For example, in this patient, the weakness is localized to her limbs and trunk with no cranial nerve abnormalities—a finding that lowers the likelihood of either botulism or myasthenia gravis.

Also, initial laboratory studies from the ED, including electrolyte, CSF, and CPK measurements, can help differentiate among these causes. In this case, normal serum potassium and magnesium concentrations essentially rule out hypermagnesemia or hypokalemia as causes of weakness. Lumbar puncture was performed to identify GBS by looking for "cytoalbumin dissociation." This classic CSF finding of an elevated protein level and a normal white blood cell count suggests GBS

but is not always present in the first few days of the disease process. Still, a normal CSF protein level and cell count, which are seen in this case, make GBS an unlikely etiology. Additionally, this patient's elevated serum CPK level of 3,513 U/L, reflecting muscle breakdown and release of myocyte contents into the systemic circulation, suggests myopathy as an etiology. Elevations in serum CPK sometimes occur in conjunction with a reddish discoloration of urine and a urine dipstick result that is positive for blood in the setting of a urinalysis that is negative for red blood cells—pointing to the presence of urinary myoglobin.

Lastly, a number of studies can be performed during hospitalization to further narrow the differential diagnosis. For example, this patient underwent NCS, which may be helpful to diagnose diseases of neuronal transmission, such as GBS. In this test, a peripheral nerve is electrically stimulated, and the time it takes the impulse to travel to the motor end plate is measured. As was the case with this patient, NCS may be ordered with EMG. EMG evaluates the electrical activity of muscle cells by generating electrical impulses at the muscles and measuring the resulting action potentials. In a myopathy, for instance, one would expect to see a decrease in the duration of the action potential of the muscle cells. In this patient, the normal NCS results together with the abnormal EMG results also pointed toward myopathy.

Many patients in the ED take statins for management of hyperlipidemia. Are particular statins more likely to cause a myopathy?

Statins are the most widely prescribed lipid-lowering drugs, largely due to their outstanding efficacy and favorable safety profile.[6] They work by inhibiting HMG-CoA reductase, the rate-limiting enzyme in the chemical synthesis of mevalonic acid and subsequently endogenous cholesterol. Though generally safe when taken at low doses, statins can cause elevated liver enzyme levels and muscle breakdown in susceptible individuals. One possible mechanism for these unintended effects is that inhibition of HMG-CoA reductase also leads to decreased levels of ubiquinone, also known as coenzyme Q (CoQ). This chemical is a key player in the electron transport chain and intracellular signaling as well as an intracellular antioxidant.[6] As a result, CoQ supplementation has been studied as a treatment for statin-associated myalgias (with sporadic success).[7,8]

Statins undergo glucuronidation, and coadministration of other drugs that undergo glucuronidation, such as gemfibrozil, may increase blood statin concentrations.[9] Additionally, most statins are metabolized by the CYP3A4 enzyme system. Concurrent administration of drugs that are also metabolized by this enzyme, such as macrolide antibiotics, nondihydropyridine calcium channel blockers, and protease inhibitors, may increase blood statin concentrations.[9]

While decreased levels of CoQ and elevated statin concentrations due to drug interactions are biologically plausible mechanisms for statin toxicity, the exact mechanism has not yet been fully elucidated. Some suggest that multiple minor metabolic abnormalities place patients at risk for muscle complications during statin therapy.[10] In such patients, any lipid-lowering drug that results in decreased delivery of fat substrate to muscles might exacerbate their underlying disorder. This theory would explain why some patients develop muscle symptoms while taking lipid-lowering medications with different mechanisms, and why others develop rhabdomyolysis following lipid apheresis (a sort of "fat dialysis" during which no drugs are given).[10]

While the severe myopathy and rhabdomyolysis observed in this case are relatively rare occurrences among the large number of patients who take statins, statin-related complications occur on a spectrum and should be considered in all patients taking statins who present to the ED with weakness or muscle pain. Some patients have only muscle pain without an observable rise in their CPK level, while others have mild CPK elevations at baseline or following vigorous exercise. Other patients may have clinically important muscle weakness with little or no elevation of their CPK.[6] Little consensus exists on how to screen for this complication beyond clinical monitoring.

Recent data suggest that while all statins may cause myopathy, high-dose simvastatin (80 mg) is associated with particularly high rates of statin-induced myopathy. Following an extensive review of the safety and efficacy data, the FDA recently required changes in safety labeling for simvastatin.[11,12] In these changes, they specified

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that the 80-mg dose of simvastatin should be used only by persons who have taken the medication for more than 12 months without complications. The revised label also includes new absolute and relative contraindications regarding the use of simvastatin with drugs that are metabolized by the CYP3A4 system.[11]

Case Conclusion

Given that the patient's medications included high-dose simvastatin (80 mg daily), simvastatin was presumed to be the cause of the myopathy and the medication was discontinued. The patient was managed supportively, her CPK level trended downward, and she was ultimately discharged to a rehabilitation facility. **EM**

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