



July 1998 EMG Case-of-the-Month

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HISTORY

The patient is a 57-year-old gentleman with a recent history of acute hepatic and renal insufficiency now being referred for evaluation of severe, acute, diffuse weakness of less than 2 weeks duration accompanied by numbness and tingling in his feet that preceded the development of the weakness by several months. He had been admitted to the hospital for recurrent atrial flutter/fibrillation and had been placed on amiodarone for ventricular rate control. During day #3 of hospitalization he was noted to be jaundiced and his liver enzymes were found to be about 20 times normal. Over the next few days his liver function significantly worsened and he developed acute renal failure. These acute problems were assumed to be due to amiodarone toxicity and the drug was stopped. Over the next week, liver function tests showed a gradual improvement and renal function also improved with hydration. While his acute hepatic and renal problems were so severe, he developed difficulty getting up from a chair or holding his arms above his head. He was also complaining of numbness and tingling in his feet. These symptoms were initially overlooked, but a CPK ordered later shows a value of 1103.

- **Prior to continuing, please develop a differential diagnosis, and list each diagnosis in order of likelihood.**
- **Is there any additional information from the clinical history that might be helpful in clarifying your differential list or changing its order of priority?**

COMMENTARY I

The presence of generalized weakness with complaint of sensory alteration in the feet raises a number of possible diagnostic entities. Generalized weakness can occur with primary muscle as well as primary nerve pathology. It can also occur with diseases affecting the function of the neuromuscular junction although this type of weakness can show a fluctuating clinical variation depending on the level of previous activity. Isolated problems affecting the muscle or neuromuscular junction typically are not associated with sensory complaints. The presence of proximal muscle weakness clinically favors a diagnosis of myopathy but the complaint of numbness in the feet suggests peripheral neuropathy involving sensory afferents.

Given the fact that the patient has been immobilized and recently ill, another possible explanation for the progressive muscular weakness could be muscular disuse atrophy. This tends to occur in patients who are at bedrest because of a severe illness. The question to be considered at this point is, "How much bedrest does one have to have before muscle disuse atrophy manifests as symptomatic weakness?" Mueller did studies many years ago to ascertain the answer to this question. He studied persons at strict bedrest and looked at the



amount of loss of muscle strength as a function of time. He found, in his study, a loss of 1.0 to 1.5% of muscle strength is sustained per day when a person remains at strict bedrest. He also found, with prolonged bedrest, that the total loss of muscle strength tends to plateau at about 25%. Greenleaf also did a similar study which showed 0.7% loss of strength per day. Your patient has been at bedrest for eleven days. On the basis of disuse effects he might be expected to have lost 17% of his original muscle strength. A person with a 17% muscle strength loss may not be symptomatic. A longer period of immobilization would likely be necessary to produce the extent of weakness being described. The elevated CPK also suggests a more acute process producing direct damage to the muscle.

HISTORY, continued

The patient states that prior to admission, he was moderately active and able to walk several blocks before becoming "winded." He was completely independent in ambulation without assistive devices. He states he did not notice any weakness until a few days ago when he had improved medically to the point where he was allowed out of bed. He then noted he had some trouble transferring to a chair from bed and standing up from the chair. He states that this activity does not make him "winded", he just feels weak and his upper and lower limbs feel heavy. He notes that the numbness and tingling he has had in his feet has become significantly worse over the past few weeks. He denies a history of diabetes or thyroid disorders. He also denies any past risk factors for HIV, any recent gastrointestinal disturbances, and any past history of muscular weakness. There is no family history of muscular weakness or neuromuscular disorders. He does admit to a history of gout and has been taking colchicine for the last several years.

- **If necessary, revise your differential diagnosis based on the additional clinical history.**
- **On what details of the physical examination do you think you should focus at this point?**

COMMENTARY II

With the further history it seems that the patient has a rapidly acquired, severe weakness. He is clearly more weak than he should be for the amount of bedrest he has had. Thus other pathologies now come into the differential including different acquired myopathies such as toxic myopathies, hypothyroid-induced myopathy or thyrotoxic myopathy.

1. Toxic myopathies - Toxic myopathies can occur either in a focal or generalized pattern and can be either painful or painless. The drugs which can cause a toxic myopathy in this patient are amiodarone or colchicine. Amiodarone induced myopathy tends to be a generalized, painless myopathy. Mild neurologic disorders are common in amiodarone treatment (20 - 40%) and usually consist of fatigue, tremor, abnormal movements or gait abnormalities, ataxia and/or paresthesias. Amiodarone is generally known to be associated with a form of slowly-progressive peripheral neuropathy but has also been recognized as a possible cause of an acute vacuolar myopathy with cases of amiodarone-associated acute necrotizing proximal myopathy having been reported.
2. Hypothyroidism induced myopathy - The primary manifestations of myopathy in hypothyroidism are proximal weakness, fatigue, slowed movements and reflexes,



stiffness, myalgia and leg and muscle cramps and enlargements. Elevated CPK is a common finding in hypothyroid patients (sometimes up to ten times normal).

3. Hyperthyroidism induced myopathy - The incidence of weakness in patients with thyrotoxicosis is high (up to 82%). Patients with thyrotoxicosis tend to have proximal muscle weakness and fatigue as prominent complaints. Serum enzyme levels including CPK and AST tend to be normal.

Although this patient also has complaints of dysesthesiae in the feet, these appear to have preceded the appearance of the weakness and had been slowly progressive until recently. This suggests the possibility of an unrelated peripheral neuropathy producing abnormal sensory afferent activation.

PHYSICAL EXAMINATION

Physical examination reveals a middle aged man with obvious jaundice but no noticeable muscle atrophy or decrease in muscle tone. He is alert and oriented, and his cranial nerves are intact. Manual muscle testing demonstrates a limited ability to resist in proximal muscles especially. The resistance that he manages to generate is felt continuously as his strength is challenged. His strength measurement is shown below.

| UE | Shoulder | | | | Elbow | | Wrist | | Grip |
|----|----------|-----|------|-----|-------|-----|-------|------|------|
| | Abd | Add | Flex | Ext | Flex | Ext | Flex | Ext | |
| R | 3/5 | 3/5 | 3/5 | 3/5 | 4/5 | 4/5 | 4+/5 | 4+/5 | 5/5 |
| L | 3/5 | 3/5 | 3/5 | 3/5 | 4/5 | 4/5 | 4+/5 | 4+/5 | 5/5 |

| LE | Hip | | Knee | | Ankle | | EHL |
|----|------|-----|------|-----|-------|-----|------|
| | Flex | Ext | Flex | Ext | Flex | Ext | |
| R | 2/5 | 2/5 | 3/5 | 4/5 | 4/5 | 4/5 | 4-/5 |
| L | 2/5 | 2/5 | 3/5 | 4/5 | 4/5 | 4/5 | 4-/5 |

- At this point, review your differential diagnosis, and revise as appropriate.
- Are there additional observations on physical examination that might be helpful in narrowing your differential list?

COMMENTARY III

Given the above information documenting a primarily proximal weakness and the acuteness of the event developing shortly after the administration of amiodarone, the most likely diagnosis is an amiodarone-induced toxic myopathy. However, colchicine-induced toxic myopathy is also in the differential since both drugs can produce a similar pattern of generalized myopathy. Both drugs are associated with the histologic appearance of a vacuolar myopathy although by different etiologic mechanisms.



PHYSICAL EXAMINATION, continued

The sensory exam shows a distal loss of pinprick sensation primarily in the feet with a stocking distribution. Stretch reflexes are absent at the Achilles tendons and difficult to elicit at the patellar tendons bilaterally.

- *If necessary, revise your differential diagnosis based on the additional physical findings.*
- *Design your approach to the electrophysiologic examination based on the existing data.*

COMMENTARY IV

The presence of a myopathy alone should not be associated with sensory complaints or clinical sensory loss. Therefore, the possibility of a concomitant peripheral neuropathy must be considered. Myopathy produces a reduction in reflexes but, unless the weakness is severe, the reflexes should still be present. In this patient, the reflexes are absent in the more distal aspect of the lower limb where the weakness is not as severe. Clinically, this suggests the presence of an afferent impairment in the distal lower limb. However, the history suggests that the sensory complaints pre-dated the start of the treatment with amiodarone, although they have become worse since. This suggests that the neuropathy is related to another cause, most likely the long-term administration of colchicine. An EMG with NCS will need to be performed to dissect these clinical problems and to obtain objective evidence of either myopathy, neuropathy or both.

ELECTROPHYSIOLOGIC DATA

| ELECTROMYOGRAPHY | | | | | | | | | | |
|--|------------------------|-----------|--------|---------|-------|-----------|------|------|------|--------|
| N = normal incr = increased decr = decreased 0 = absent 1+ = minimal 4+ = maximal crd = complex repetitive discharge fasc = fasciculation potential myk = myokymic discharge myt = myotonic discharge nmt = neuromyotonic discharge p wave = positive sharp waves fib = fibrillation potentials recr = recruitment amp = amplitude dur = duration poly = polyphasic potential | | | | | | | | | | |
| R/L | MUSCLE | INSERTION | | SPONTAN | | VOLUNTARY | | | | |
| | | activ | p wave | fib | other | recr | amp | dur | poly | effort |
| R | deltoid | myt | 1+ | 2+ | 0 | incr | decr | decr | incr | max |
| R | biceps brachii | myt | 1+ | 3+ | 0 | incr | decr | decr | incr | max |
| R | first dorsal interossi | myt | 1+ | 2+ | 0 | N | N | N | N | max |
| R | tibialis anterior | myt | 1+ | 3+ | 0 | incr | decr | decr | incr | max |
| R | vastus medialis | myt | 1+ | 3+ | 0 | incr | decr | decr | incr | max |
| R | ext hallucis longus | myt | 1+ | 1+ | 0 | N | incr | incr | N | max |



| SENSORY NERVE CONDUCTION | | | | | | | | | |
|---------------------------------|----------------|----|------|----------------|---|------|------------------|---|------|
| nr = no response | | | | | | | | | |
| NERVE | LATENCY (ms) | | | AMPLITUDE (µV) | | | CONDUC VEL (m/s) | | |
| | R | L | Norm | R | L | Norm | R | L | Norm |
| median | - | | | - | | | - | | |
| mid-palm | 1.6 | - | - | 16 | - | - | 44 | - | - |
| wrist | 3.3 | - | - | 8 | - | - | 42 | - | - |
| elbow | 8.6 | - | - | 6 | - | - | 52 | - | - |
| ulnar | - | | | - | | | - | | |
| mid-palm | 1.5 | - | - | 15 | - | - | 45 | - | - |
| wrist | 2.9 | - | - | 14 | - | - | 50 | - | - |
| elbow | 8.3 | - | - | 12 | - | - | 47 | - | - |
| medial dorsal cutaneous | nr | nr | - | - | | | - | | |
| sural | nr | nr | - | - | | | - | | |

| MOTOR NERVE CONDUCTION | | | | | | | | | |
|-------------------------------|--------------|---|------|----------------|---|------|-----------------|---|------|
| nr = no response | | | | | | | | | |
| NERVE | LATENCY (ms) | | | AMPLITUDE (mV) | | | CONDUC VEL(m/s) | | |
| | R | L | Norm | R | L | Norm | R | L | Norm |
| median | - | | | - | | | - | | |
| wrist | 4.2 | - | - | 8.4 | - | - | - | - | - |
| elbow | 9.3 | - | - | 7.9 | - | - | 47 | - | - |
| ulnar | - | | | - | | | - | | |
| wrist | 3.4 | - | - | 8.6 | - | - | - | - | - |
| below elbow | 8.7 | - | - | 7.6 | - | - | 47 | - | - |
| above elbow | 12.3 | - | - | 7.2 | - | - | 47 | - | - |
| deep peroneal | - | | | - | | | - | | |
| - | 2.7 | - | - | 42 | - | - | - | | |



| F-WAVE | | | | | | | | |
|---|--------------|----|--------------|------|-----|---------|-------|--------|
| # = number of stimuli P = persistence CD = chronodispersion F:M = ratio of average F-wave amplitude to M-wave amplitude | | | | | | | | |
| R/L | NERVE | # | LATENCY (ms) | | | CD (ms) | P (%) | F:M(%) |
| | | | min | mean | max | | | |
| R | tibial nerve | 16 | 61.4 | - | - | - | - | - |

- **On the basis of both the clinical and electrophysiologic evaluations, formulate your diagnostic impression. List the most likely diagnosis first and follow in order with the other possibilities that are not excluded by the data. Eliminate those diagnoses not supported by the data.**
- **Are there additional electrophysiologic data that you feel would further delineate the diagnosis? (Remember, collecting data that are not needed for the diagnosis is costly and uncomfortable for the patient.)**

No further electrophysiologic data were collected.

DIAGNOSTIC IMPRESSION

1. Acute myopathy probably 2° to amiodarone toxicity.
2. Peripheral sensorimotor polyneuropathy (axonopathy), diffuse, possibly 2° to colchicine toxicity, possibly aggravated by amiodarone toxicity

DISCUSSION

This study shows evidence of acute myopathic changes in the motor unit potentials recorded in the proximal muscles of the upper and lower limb. Large amounts of abnormal spontaneous activity including fibrillations, positive sharp waves and myotonic discharges indicate a major disturbance in the stability of the muscle fiber membrane potential and membrane electrical properties. This would be most consistent with an acute, destructive, myopathic process. In addition, there is evidence of a distal axonal-type mixed sensorimotor peripheral neuropathy primarily noted in the distal lower limbs where the sensory nerve action potentials cannot be recorded and the compound muscle action potentials show reduced amplitude.

The motor unit potentials in the proximal muscles show decreased amplitude, decreased duration and an increase in polyphasic form. These changes in motor unit potential parameters in the proximal muscles are consistent with muscle fiber drop-out from the motor unit which would be expected to result in a significant reduction in motor unit twitch tension, thus explaining the clinical weakness. There is also an 'increased' recruitment pattern noted where motor units are rapidly recruited as the muscle is starting to contract, with a full interference pattern quickly achieved with voluntary effort. A rapidly-established full recruitment pattern showing generally reduced amplitude is an electrodiagnostic finding consistent with the presence of a primary myopathy.

Superimposed on the primary myopathy involving the proximal muscles, there is also evidence of a peripheral neuropathy. The sensory nerve action potentials should be normal



in a primary myopathy reflecting the sparing of sensory nerve afferents. However, the absence of recordable sensory nerve action potentials in the feet and the reduction in amplitude of the tibial and peroneal compound muscle action potentials in this patient indicate the presence of a concomitant peripheral neuropathy. The changes in motor unit potentials seen in the extensor hallucis longus also suggest a chronic primary neuropathic process with an *increase* in motor unit potential amplitude and duration, the exact opposite of what was noted in the proximal muscles. These changes reflect compensatory motor fiber sprouting with enlargement of motor units within this muscle, a change that can be seen in muscles that have lost some of their innervating motor fibers as the result of a chronic axonopathy.

- **What other diagnostic procedures (laboratory tests, etc.), if any, are needed?**
- **What treatment would you recommend?**

COMMENTARY

The patient underwent a muscle biopsy of the left deltoid muscle which was not examined during the needle EMG studies. Histological preparation showed a severe vacuolar myopathy with fibers containing single large and multiple small vacuoles. Adenosine triphosphatase staining showed that the vacuoles were present in both type 1 and type 2 fibers. There was an abnormal variability of muscle fiber size. No inflammatory response was seen.

Amiodarone had been stopped. Colchicine was also subsequently discontinued because of its associated neurotoxicity. The patient made a slow but steady recovery of strength and function and was discharged walking with a walker and able to do most of his self-care independently.

Medications and toxins can be responsible for significant iatrogenic and environmentally-associated pathology affecting the neuromuscular system. Not only colchicine, but other medications such as phenytoin, disulfiram, nitrofurantoin, amitriptyline, lithium, nitrous oxide, and metronidazole, among others, can produce a mixed sensorimotor polyneuropathy characterized by distal axonal loss. A similar picture can also be seen in heavy metal poisoning with arsenic, mercury, thallium or gold. Exposure to a variety of toxic substances such as acrylamide, organophosphorus esters, hexacarbons and carbon monoxide, can also result in an axonopathy. In the differential diagnosis for this type of neuropathy are a number of other conditions, including alcoholism, amyloidosis, necrotizing angiopathy/connective tissue disorders, HIV infection, critical illness polyneuropathy, carcinomatous axonal sensorimotor polyneuropathy, myotonic muscular dystrophy, chronic liver disease and several other clinical conditions.

Myopathies are not an uncommon problem that complicate drug therapy. The major findings are increasing proximal muscle weakness with or without muscle pain, increased muscle enzyme levels, histologic abnormalities and electromyographic changes. Drug-induced myopathies can also be associated with polyneuropathy, this combination being sometimes referred to as a 'neuromyopathy'.

The drug-induced myopathies can be classified according to whether or not there is associated muscle pain and/or associated neuropathy. Painless myopathies can be divided into myopathies without neuropathy (e.g. corticosteroids), myopathy with neuropathy (colchicine, chloroquine and hydroxychloroquine) and myasthenic syndromes (D-penicillamine, beta-blockers, antibiotics). A similar classification is used for painful



myopathies which include drug-induced polymyositis (D-penicillamine, cimetidine, zidovudine) and other myopathies without evidence of muscle inflammation.

Combinations of drugs can induce severe myopathies, which may well have been possible in the patient presented here who was on both amiodarone and colchicine, each of which has been associated with a vacuolar myopathy, although by different mechanisms. Colchicine is felt to induce myopathy through the disruption of the microtubules, while amiodarone is felt to produce myopathy through a lysosomal storage disorder. With discontinuation of the amiodarone and subsequent discontinuation of colchicine, the patient described here was noted to eventually have a nearly complete clinical recovery. Roth et al (1990) have described a case of a patient who had been taking colchicine for many years and developed a severe myopathy after 1 month of anti-arrhythmic therapy with amiodarone. The patient in this report also developed a significant peripheral neuropathy with this combination of drugs. The combination of cyclosporin and colchicine is also known to be associated with the precipitation of a severe myopathy. When such drug combinations must be used, there should be great care taken to carefully check for any signs of an incipient myopathy or neuropathy.

Drug-induced myopathies can also be subclassified histologically into vacuolar, mitochondrial and necrotizing forms. The exact mechanisms whereby drugs can cause such myopathies are not known. Possibilities include metabolic or structural disruption and autoimmunity. Challenge with the offending medication after resolution of the myopathic symptoms following withdrawal of the medication should not be attempted because of the significant risk of a serious relapse. Clinically, the most important issue is that the connection between the presence of the myopathy and the offending drug(s) be recognized so that the drug(s) can be stopped. Generally, the myopathy gradually resolves after the precipitating medications have been discontinued.

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