Iatrogenic Neuromuscular Disorders

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Iatrogenic Neuromuscular Disorders

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Dr. Bolton was born in Outlook, Saskatchewan, Canada. He received his medical degree from Queen’s University and trained in neurology at the University Hospital, Saskatoon, Saskatchewan, Canada, and at the Mayo Clinic. While at Mayo Clinic, he studied neuromuscular disease under Dr. Peter Dyck, and electromyography under Dr. Edward Lambert. Dr. Bolton has had academic appointments at the Universities of Saskatchewan and Western Ontario, at the Mayo Clinic, and currently at Queen’s University. He was also recently received the AANEM Distinguished Physician Award. His special interests are investigations of neuromuscular problems in the intensive care unit, and of neuromuscular respiratory insufficiency.

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The ideas and opinions expressed in this publication are solely those of the specific authors and do not necessarily represent those of the AANEM.
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OBJECTIVES  After attending this session, participants will be able to (1) recognize iatrogenic neuromuscular disorders such as medication induced peripheral neuropathies, myopathies, and neuromuscular transmission disorders, and (2) manage patients with acute ventilatory failure in the ICU related to the use of steroids and neuromuscular blocking agents and patients with failure to wean due to underlying neuromuscular disease.

Prerequisite  This course is designed as an educational opportunity for physicians.

Accreditation Statement  The AANEM is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education (CME) for physicians.

CME Credit  The AANEM designates this activity for a maximum of 3.25 AMA PRA Category 1 Credit(s).™ If purchased, the AANEM designates this activity for 2 AMA PRA Category 1 Credit(s).™ This educational event is approved as an Accredited Group Learning Activity under Section 1 of the Framework of Continuing Professional Development (CPD) options for the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada. Each physician should claim only those hours of credit he or she actually spent in the educational activity. CME for this course is available 10/09 - 10/12.
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Iatrogenic Neuropathies

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INTRODUCTION

Iatrogenic as defined by Dorland’s Illustrated Medical Dictionary (24th Edition) is a condition resulting from the activity of physicians. Thus, it is any activity of physicians and other healthcare providers that injures or harms a patient. Iatrogenesis when applied to neuropathies includes untoward effects resulting from prescribed medications and chemotherapeutic agents, as well as procedures that lead to mononeuropathies, plexopathies, or radiculopathies.

This manuscript will focus on commonly prescribed medications, immunosuppressants, and chemotherapeutic drugs that can cause iatrogenic polyneuropathies.

MEDICATION-INDUCED NEUROPATHIES

With a few exceptions, the presentation of patients with drug-related or induced polyneuropathy does not differ from that of most chronic length-dependent neuropathies. The peripheral nervous system (PNS) reacts to toxins in a limited manner. Spencer and Schaumburg hypothesized that most toxins, including medications, produce damage in one of four regions of the peripheral nerve: (1) the distal sensory and motor axon (axonopathy), (2) the Schwann cell, leading to a demyelinating neuropathy, (3) the dorsal root ganglion (ganglionopathy or neuronopathy), and (4) the anterior horn cell or motor neuron.

In keeping with this classification, most medication-induced neuropathies can be categorized into one of four groups depending on the region of the PNS where the primary pathologic process occurs (Table 1). As is true of most classifications, not all drugs fit perfectly into one category; some can cause pathology in more than one site, as well as in the central nervous system (CNS). The Table groups medication-induced neuropathies by the major confirmed or presumed anatomic site of pathology. Several drugs, listed in more than one grouping, can cause both an axonopathy or a demyelinating neuropathy.

Amiodarone

The most common neurological adverse effects of amiodarone are tremor, optic neuropathy, and peripheral neuropathy. The neuropathy typically begins between 5 and 12 months after amiodarone is first prescribed. Unlike most drugs, amiodarone gives rise to more than one type of neuropathy. These may be primarily axon loss, demyelinating, or a combination as reflected in nerve conduction studies (NCSs). Nerve biopsy shows severe loss of large and small myelinated fibers as well as unmyelinated fibers.

Amitriptyline

Amitriptyline is a tricyclic antidepressant that has become a well-accepted treatment for neuropathic pain. Ironically, amitriptyline has been associated with the development of a peripheral neuropathy in several case reports. Zampollo reported a man who developed lower limb paresthesias, distal hypesthesia, and reduced ankle reflexes after taking 150 mg of amitriptyline uninterrupted for 2 years. Motor and sensory amplitudes were reduced, latencies were normal or prolonged, and conduction velocities were slowed, consistent with diffuse axon loss. When amitriptyline was discontinued, symptoms,
signs, and the electrophysiologic abnormalities resolved within 3 years. Meadows and colleagues\textsuperscript{37} reported a woman who developed an amitriptyline-induced neuropathy. Her symptoms remitted when treated with 500 mg per day of pyridoxine. The authors hypothesized that amitriptyline produces a polyneuropathy in the same way as isoniazid, by depleting the availability of pyridoxal phosphate.\textsuperscript{37}

### Colchicine

Riggs and colleagues\textsuperscript{53} first described a relationship between colchicine and neuropathy and myopathy in 1986. Their patient had taken large doses of colchicine for 5 years and the neurological examination was consistent with a severe sensory and motor neuropathy and a mild proximal myopathy. The muscle biopsy showed an increased variability in myofiber size, rounded and atrophic myofibers, muscle fibers containing small vacuoles and subsarcolemmic deposits, and uneven staining of central muscle fibers. Except for persistent gait ataxia and distal hand weakness, the patient recovered after discontinuation of colchicine.

In a larger of study of 12 patients with colchicine myopathy and neuropathy, Kuncl and colleagues\textsuperscript{31} found similar abnormalities on nerve conduction testing. Sural nerve biopsy in one patient identified mild loss of large myelinated axons, degenerating axons, and regenerating axon clusters. Biopsies of proximal muscles showed a distinctive vacuolar myopathy, in which the vacuoles were distributed either centrally or in the region of the subsarcolemma. Except for symptoms and signs of a mild neuropathy, the patient's neurologic function returned to normal within 4 weeks after discontinuation of colchicine. The authors associated the neuropathy and myopathy to renal dysfunction, as the adverse effect only occurred in patients with elevated serum creatinine.

### Dapsone

Dapsone is commonly used to treat distinct dermatologic disorders, such as dermatitis herpetiformis, pyoderma gangrenosum, acne conglobata, alopecia mucinosa, and leprosy. Several patients have developed a motor greater than sensory, distal greater than proximal polyneuropathy after taking the drug.\textsuperscript{51,62} The neuropathy has been found in patients taking dosages ranging from 100-600 mg per day for several weeks to 16 years. Greater involvement in the hands than in the feet is an atypical feature for neuropathy. NCs typically show normal to low normal conduction velocities, normal to prolonged distal latencies, and reduced compound muscle action potential (CMAP) amplitudes.\textsuperscript{20} Data from Gutmann and colleagues\textsuperscript{20} suggest that dapsone has its primary effect on the motor soma and axons of the motor neuron.

Marked improvement has occurred in all patients after discontinuation of dapsone. Similar to isoniazid, the drug is metabolized by acetylation.\textsuperscript{19} Slow acetylation and accumulation of toxic blood and tissue levels have been implicated as the initiating steps in the development of the neuropathy.\textsuperscript{29,62}

### Table 1 Drug-induced neuropathies

<table>
<thead>
<tr>
<th>Anatomic Site of Pathology</th>
<th>Axonopathy</th>
<th>Dorsal Root Ganglion</th>
<th>Anterior Horn Cell</th>
<th>Schwann Cell</th>
<th>Fiber Sheath Pathology</th>
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* isolated case reports

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**Iatrogenic Neuropathies**

**AANEM Course**
Disulfiram

Disulfiram has been used since the 1940s as an agent to help chronic alcoholics remain sober. Mokri and colleagues reported four patients with disulfiram-induced motor and sensory symmetric polyneuropathy, varying from mild to severe.40 The initial symptoms developed several weeks to 4 months after beginning the drug. NCSs showed absent sensory nerve action potentials (SNAPs), reduced amplitude of CMAPs, and slightly diminished nerve conduction velocities. In one patient, repeat NCSs 1 year later showed partial recovery of the SNAP in the median nerve and normalization of the conduction velocity in the motor fibers of the median and ulnar nerves. The investigators reported a decrease of both large and small myelinated fibers and axon degeneration in the sural nerve biopsy.40

Ethambutol

Ethambutol is a medication used with other antimycobacterial agents to treat tuberculosis. Optic neuritis is a well-known adverse effect of ethambutol therapy. Tugwell and James60 described 3 patients who developed a polyneuropathy 5 to 9 months after initiation of therapy. The timing of the evolution of the polyneuropathy was similar to the interval delay for optic neuritis. All patients had features consistent with a sensory greater than motor neuropathy.

NCSs showed reduced SNAP amplitudes and slightly prolonged sensory distal latencies. Motor amplitudes were normal and motor conduction velocities were either normal or slightly reduced. All three patients improved when the ethambutol was discontinued. An unpublished series of over 1000 patients taking ethambutol found 15 who complained of numbness in the extremities at some time while taking the medication.

Gold

In 1950, Doyle and Cannon14 reported the first extensive description of polyneuritis as an adverse reaction to gold therapy. They described a man who developed features of a severe motor and sensory polyneuropathy after receiving a cumulative dose of 900 mg of Myochrysine (450 mg of gold). At the peak of the neuropathy, the patient could not feed himself and complained of paresthesias from the feet to the rib cage. Physical examination revealed findings consistent with a severe motor and sensory polyneuropathy as well as marked incoordination, dysmetria, writhing movements of the hands, and gait ataxia. The patient improved rapidly once the gold injections were discontinued.

Walsh63 was the first to provide nerve conduction data on gold neuropathy. He reported a woman who developed a polyneuropathy after receiving a total of 85 mg of gold. All sensory responses were absent. Motor latencies and conduction velocities were normal except for an ulnar nerve conduction velocity of 40 m/s. A sural nerve biopsy showed loss of large and small diameter myelinated fibers. Teased fiber preparations demonstrated that most fibers were undergoing active axon degeneration. Only rare fibers showed segmental demyelination.

Katrak and colleagues27 reported electrophysiologic and nerve biopsy results in three patients with gold-induced peripheral neuropathy (PN). In one, NCSs were normal, whereas in the other two patients, abnormalities were recorded in almost all nerves tested. Many of the conduction rates (prolonged latencies and slowed conduction velocities) were sufficiently severe to suggest a demyelinating process. Nerve biopsy findings in two patients confirmed axon degeneration. In the third patient, nerve pathology revealed a striking increase in internodes and a 50% or greater reduction in myelin thickness. All patients improved when the gold therapy was discontinued.

Hydralazine

Hydralazine is a chelating agent and a carbonyl reagent that forms complexes with sulfhydryl groups. It inhibits enzymes involved in pyridoxine metabolism, and it is this capability that accounts for the development of peripheral neuropathy in some patients. Although infrequently used for the treatment of hypertension, hydralazine was a mainstay therapy several decades ago. In 1962, Kirkendall and Page28 reported two patients who developed symptoms and signs of a polyneuropathy after taking hydralazine for 3 to 8 months.

In one patient, the neuropathy appeared to be primarily sensory. In the other, the neurologic deficits were a left foot drop and pronounced sensory symptoms and signs distally in the legs. In both patients, stopping the hydralazine and adding pyridoxine led to improvement in symptoms and strength within 2 to 4 weeks. Raskin and Fishman52 reported two additional patients with hydralazine-induced polyneuropathy. One developed symptoms after 7 days; the other, after 10 years.

Isoniazid

Isoniazid is a hydrazide of isonicotinic acid. Its major route of metabolism is through acetylation to acetyl isoniazid.5 The drug has been one of the mainstays of tuberculosis treatment for 5 decades. Isoniazid is another medication that causes PN through its effect on pyridoxine metabolism.

Studies show a large bimodal variation in human metabolism of isoniazid. Patients can be categorized into rapid or slow inactivators, a bimodality that is genetically determined.16 Hughes and colleagues22 identified a polyneuropathy in 6 of 17 subjects taking the drug, 4 of whom were slow inactivators. Although the number of patients was small, the investigators proposed the hypothesis that slow inactivators are more predisposed than rapid ones to the development of polyneuropathy after treatment with isoniazid. Other research demonstrates that metabolism of the drug is inherited as an autosomal recessive trait.2 Slow acetylators are unable to metabolize isoniazid quickly, which leads to high blood levels and a greater propensity to develop a toxic neuropathy.

In 1959, Money41 reported 84 patients with pulmonary tuberculosis who were receiving antituberculous therapy with isoniazid and para-aminosalicylic acid. Polyneuropathy was the most common adverse
neurological effect. In almost all cases, the neuropathy did not develop until 6 months after the onset of isoniazid therapy. Sensory symptoms and signs were more common than weakness, and the lower extremities were more affected than the upper. Most patients improved when prescribed vitamin B supplementation despite the maintenance of isoniazid therapy. Ochoa described neuropathological findings in nine patients with isoniazid neuropathy. He observed a marked reduction in the number of myelinated fibers, the presence of denervated Schwann cell bands, and regenerated myelinated fibers. Six of the nine patients had mild slowing of nerve conduction velocities in the ulnar and peroneal nerves.

Lithium

It is well-known that lithium in toxic doses can cause tremor, but it can also lead to a severe polyneuropathy. Vanhooren and colleagues reported two patients who developed an acute motor and sensory polyneuropathy as a result of lithium intoxication. Both initially presented with CNS manifestations, including coma, hypertension, conjugate eye deviation, Babinski signs, hemiparesis, and extrapyramidal signs. When the patients regained consciousness, one had proximal weakness and the other flaccid paralysis in the legs and areflexia. Motor NCSs showed reduced CMAP amplitudes and either normal or diminished conduction velocities. In one patient, the sural response was absent. Several months after clearing of the intoxication, sensory and motor amplitudes improved. Sural nerve biopsy in one patient identified a moderate loss of myelinated fibers, mild endoneural fibrosis, and scattered vacuolated macrophages with myelin debris. Both patients improved from lithium intoxication, but not completely.

Metronidazole

Metronidazole is a 5-nitromidazole antimicrobial used for the treatment of protozoan infections (trichomoniasis, giardiasis, and amoebiasis), as a bactericidal agent in anaerobic infections, and for Crohn’s Disease. Several authors have reported a sensory neuropathy or neuronopathy in patients receiving metronidazole for the treatment of Crohn’s Disease. Patients typically complain of paresthesias in the feet and hands. Sensory examination shows a distal gradient loss to small fiber more than large fiber perception in the setting of preserved strength. NCSs show absent to reduced SNAP amplitudes and normal motor conduction studies. Sural nerve biopsy in the patient reported by Bradley and colleagues identified a loss of many myelinated fibers and axonal degeneration in all of the remaining sensory fiber sizes. Coxon reported three patients taking metronidazole. When the drug was discontinued, the sensory neuropathy improved completely in one, partially in another, and remained static in the third.

Misonidazole

Misonidazole is a 2-nitromidazole used as a red blood sensitizing agent prior to radiation therapy. Melgaard and colleagues reported on eight patients who developed a severe subacute sensory polyneuropathy after treatment with misonidazole for 3 to 5 weeks. The total dose of misonidazole varied between 17-22 g. All but one patient complained of severe pain and paresthesias in the feet and hands. Strength was rarely affected and deep tendon reflexes were preserved. On sensory testing, touch, pain sensation, vibration, and joint position sense were affected more in the feet than in the hands. Three to five months after discontinuation of the misonidazole, four patients were improved; three had died from the underlying carcinoma, and one patient’s condition was unchanged. NCSs were consistent with a severe primarily sensory neuropathy.

Nitrofurantoin

Nitrofurantoin is a synthetic bacteriostatic antimicrobial. In years past, it was used to treat a wide range of gram positive and gram negative organisms. Currently, it is frequently prescribed for urinary tract infections. Several authors described a toxic neuropathy temporally related to the use of nitrofurantoin in 1956. The neuropathy can present as early as 1 to 2 weeks after initiation of nitrofurantoin therapy. The major manifestations are distal paresthesias, loss of sensory perception in the hands and feet, mild to moderate distal weakness, and areflexia. The neuropathy may resolve over time or it may be irreversible. Ellis reported six patients who developed an acute form of nitrofurantoin-induced polyneuropathy. Three of them died from complications of the polyneuropathy; the relationship to nitrofurantoin was not recognized, and nitrofurantoin was continued until death. The other three patients made partial recoveries. All six had renal insufficiency, an observation also noted by Loughridge and other authors. This observation led to the recommendation that nitrofurantoin be used with caution in patients with renal insufficiency.

Craven described five patients who developed a polyneuropathy after receiving treatment with nitrofurantoin. All had normal blood urea nitrogen levels when the drug was first prescribed, but had mild renal insufficiency at the time the neuropathy developed clinically. Paul and colleagues demonstrated in vitro that nitrofurantoin reversibly inhibits the formation of citrate at the stage of generation of acetyl coenzyme A from pyruvate and coenzyme A. Inhibition should be greater when the blood level of nitrofurantoin is higher, a condition that exists in renal insufficiency.

Toole and Parrish reviewed the world literature on nitrofurantoin neuropathy in 1973. They noted that most patients experienced the onset of neuropathic symptoms within the first 6 weeks of treatment. The daily dosage prescribed ranged from 100-800 mg. Available follow-up information revealed that once nitrofurantoin was stopped, approximately 33% experienced complete resolution of symptoms and signs, 50% had residual disease, and approximately 17% remained unchanged. NCS findings in nitrofurantoin-induced polyneuropathy are scant. A nerve biopsy by Morris found atrophy of the peripheral nerves.
Nitrous Oxide

In 1978, Layzer and colleagues\(^3^4\) reported three patients—two dentists and a hospital technician—who presented with symptoms of numbness and the sensation of an electric shock passing from the toes to the neck after flexion of the neck. All had a common history of excessive recreational use of nitrous oxide. In the same year, Layzer\(^3^3\) described 15 additional patients with the same condition. He characterized the clinical presentation as a myeloneuropathy because of the combination of peripheral and CNS findings.

All but one of his patients were dentists. Except for two who were exposed to the inhalant professionally, the others had abused nitrous oxide recreationally. In each case, the patients improved after cessation of the nitrous oxide. Five of the 15 continued to have moderate disability 6 weeks to 3 years after discontinuation. Because of its similarity to subacute combined degeneration, Layzer speculated that nitrous oxide might interfere with vitamin B\(_{12}\) metabolism.

This hypothesis was advanced when Amess and colleagues\(^2\) found that nitrous oxide in patients undergoing cardiac bypass surgery produced an identical deoxycytidine suppression test result to that found in patients with vitamin B\(_{12}\) deficiency. Since all of their patients had normal vitamin B\(_{12}\) concentrations, the data suggested that nitrous oxide interferes with vitamin B\(_{12}\) function. In these patients, NCSs showed normal results in motor nerves and mild slowing of conduction velocities in sensory nerves. Sural nerve biopsy showed a normal number of nerve fibers, varying degrees of myelin ovoid formation, and rare fibers with focal areas of axon swelling and denuded myelin.

Phenytoin

Phenytoin has been commonly prescribed for epilepsy since its introduction in 1938. Lovelace and Horwitz\(^3^6\) identified 26 of 50 patients taking phenytoin who manifested a peripheral neuropathy by clinical examination and electrophysiological study; no other etiology could be found for the neuropathy. All patients had absent deep tendon reflexes in the lower extremities. Conduction velocities in the lower extremities ranged from 30-40 m/s in most affected patients, and the sensory and motor amplitudes were often low in amplitude, long in duration, and complex. The authors determined that the neuropathy was more likely to occur in patients who had taken phenytoin for more than 10 years. There was no correlation between the dosage of the drug and the development of a polyneuropathy.

Shorvon and Reynolds\(^5^6\) followed 51 epilepsy patients prospectively for 5 years who were prescribed either phenytoin or carbamazepine monotherapy. None of those who received carbamazepine developed either clinical or electrophysiologic features suggestive of a diffuse polyneuropathy. In the phenytoin group, none who took therapeutic doses developed clinical evidence of a neuropathy. In the patients taking phenytoin who developed polyneuropathy, review of the medical records uncovered recurrent toxic drug levels and low folic acid levels.

Pyridoxine

Pyridoxine is an essential vitamin that has been consumed in large doses by individuals to aid in bodybuilding. It has also been prescribed as a treatment for premenstrual syndrome, carpal tunnel syndrome, schizophrenia, fibromyalgia, autism, and hyperkinesis. Schaumburg and colleagues\(^3^4\) reported two patients who began to experience ascending numbness 3 and 11 months after consuming large doses of pyridoxine (2 and 3 g) daily. Neurological examination demonstrated normal strength, loss of ankle reflexes, and a distal gradient loss of vibration, pin prick, temperature, and touch sense. Neither patient improved when the pyridoxine was discontinued nor after 1 year of follow-up. Motor NCSs were normal.

The same authors\(^5^5\) reported a larger cohort of patients who developed a severe sensory neuropathy after taking 2-6 g of pyridoxine daily for 2 to 40 months. All patients showed profound loss of most sensory modalities and were areflexic; all improved when pyridoxine was stopped, and two experienced almost complete recovery after 2 to 3 years of follow-up. The authors concluded that vitamin B\(_{6}\) in high doses was probably toxic to the dorsal root ganglia.\(^5^4\) In 1980, Krinke and colleagues\(^3^0\) showed that large doses of pyridoxine produced a sensory neuronopathy in dogs; spinal cord pathology showed widespread neuronal degeneration in the dorsal root ganglia, the sensory nerve fibers in the peripheral nerves, dorsal columns of the spinal cord, and the descending spinal tract of the trigeminal nerves.

Although pyridoxine sensory neuronopathy is most common in individuals taking large doses of the vitamin, toxicity can also be observed in those who consume much smaller doses. Of the 16 patients reported by Parry and Bredesen,\(^4^6\) 3 had been taking less than 1 g per day, and 1 had taken only 100-200 mg for 3 years.

Statins

The statins are inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, an enzyme that regulates the synthesis of cholesterol. In 1994, Jacobs\(^2^4\) reported the development of a sensory polyneuropathy in a patient treated with lovastatin for 2 years. The patient’s symptoms abated when lovastatin was discontinued, but returned within 2 weeks when pravastatin was substituted for lovastatin. The following year, Ahmad\(^1\) reported two patients with lovastatin-induced neuropathy.

Phan and colleagues\(^4^9\) published NCS results in four patients with a polyneuropathy caused by simvastatin. CMAP amplitudes were reduced in all but one of them, and each had absent or reduced SNAP amplitudes. Motor and sensory conduction velocities were either normal or slightly slowed. The authors proposed that the simvastatin might produce toxicity through an adverse reaction on mitochondrial function. Inhibitors of HMG-CoA reductase block cholesterol synthesis and interfere with synthesis of dolichol and ubiquinone. A deficiency of ubiquinone, a key enzyme in the mitochondrial respiratory chain, might interfere with the energy utilization of the neuron, and in turn, produce a reversible polyneuropathy.
Jeppesen and colleagues reported similar electrophysiologic results to those of Phan and colleagues in seven patients who developed a polyneuropathy after taking one of the following statin medications: lovastatin, fluvastatin, pravastatin, or simvastatin. Four of their patients had an irreversible neuropathy, a finding that the authors attributed to a longer exposure to the statins (4 to 7 years compared to 1 to 2 years).

Substitution of one statin for another that causes a polyneuropathy may not prevent the reoccurrence of a drug-induced neuropathy. Ziajka and Wohrheimer reported a patient who developed a neuropathy after taking lovastatin and whose symptoms returned when treated individually with simvastatin, pravastatin, and atorvastatin.

Some physicians have challenged the relationship between statins and the development of polyneuropathy. They consider it low risk and acknowledge that long-term exposure increases the chances for the neuropathy. One study estimated the incidence of statin-induced neuropathy to be approximately 1 case per 10,000 patients; another put the estimate at 60 cases per 100,000.

**Thalidomide**

Thalidomide was manufactured as a sedative and hypnotic. In 1961, it was withdrawn from use because of its teratogenicity and propensity to cause phocomelia in neonates. The drug is now undergoing resurgence as an effective treatment for several dermatologic conditions, such as complex aphthous ulcers, Behcet’s Disease, prurigo nodularis, discoid lupus erythematosus, and erythema nodosum leprosum.

Thalidomide was first described as causing a sensory and motor polyneuropathy in the early 1960s. The neuropathy is often associated with erythema of the hands and brittle fingernails. The incidence varies greatly from one study to another, with some authors reporting a neuropathy in 100% of patients exposed to thalidomide. The occurrence is not related to the daily dose of the drug or the duration of treatment.

Data show that women and the elderly are most prone to developing neuropathy, as are those who are slow drug acetylators. Most patients complain of paresthesias, hypesthesias, and leg cramps that are greater distally than proximally, and more in the legs than in the upper extremities. Coasting, a phenomenon of worsening of the neuropathy when the offending drug is stopped, is commonly observed for a month when thalidomide is discontinued. Small fiber modalities are often more affected than large fiber. Nerve conduction results are consistent with a sensory polyneuropathy. Approximately 25% of patients recover completely, whereas 30% improve partially, and 45% do not recover.

**ANTIRETROVIRAL MEDICATIONS**

Antiretroviral medications are categorized as nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, chemokine coreceptor antagonists, and integrase inhibitors. PN is associated with the use of NRTIs: didanosine (ddl), zalcitabine (ddC), and stavudine (d4T). All three agents cause a polyneuropathy that is sensory greater than motor. The neuropathy typically presents with burning, paresthesias, and pain in the calves. Common signs on neurologic examination are loss of small and large fiber sensory functions and absent ankle reflexes. The neuropathies are clinically indistinguishable from those of human immunodeficiency virus (HIV)-associated distal sensory neuropathy, yet the acute or subacute onset and rapid progression in parallel with the use of the NRTIs are strong clues as to the cause of the neuropathy. The toxic neuropathies are dose dependent and, in the case of ddC, coasting may occur. In one study of ddC, all patients who received a high dose (0.12-0.24 mg/kg/day) developed a distal sensory polyneuropathy. Because of the common neurotoxicity of NRTIs, lower doses are often used to initiate therapy.

Even low doses of ddL, ddC, and d4T may cause a neuropathy in older patients, and those with preexisting subclinical neuropathy, inherited neuropathies, and poor nutrition. The incidence of neuropathy may increase substantially if the NRTIs are used in a therapeutic regimen with hydroxyurea, which is itself neurotoxic. The mechanism of neurotoxicity from the NRTIs is unknown, but may relate to their inhibition of mitochondrial deoxyribonucleic acid gamma polymerase.

**PERIPHERAL NEUROPATHIES ASSOCIATED WITH CHEMOTHERAPEUTIC AGENTS**

Several of the commonly prescribed chemotherapeutic agents can cause polyneuropathy. Those include the vinca alkaloids, platinum agents, taxanes, suramin, ara-C, etoposide, and ifosfamide.

**Vinca Alkaloids**

Vinca alkaloid is derived from the extraction of the agent from the periwinkle plant. The vinca alkaloids consist of vincristine, vinblastine, vindesine, and vinorelbine. In a rank order of toxicity, vincristine is the most toxic, and the development of neuropathy is widely recognized by oncologists and neurologists. Vincristine causes a dose-dependent sensory greater than motor and autonomic polyneuropathy.

The neuropathy typically presents with paresthesias of the feet and hands and loss of ankle reflexes. Distal weakness that may be present on examination is less often of clinical significance to the patient. Unlike other chemotherapeutic agents, vincristine gives rise to an autonomic neuropathy that may manifest as abdominal pain, constipation, and sometimes an ileus. Fortunately, the neuropathy induced by vincristine is usually reversible once the chemotherapy is stopped, and complete recovery occurs in about 80% of patients. NCSSs confirm the findings expected in an axon loss sensory greater than motor neuropathy. Vincristine must be avoided in patients with preexisting inherited neuropathies; the resulting cumulative neuropathy can be devastating and relatively permanent.
Vinorelbine, which is less toxic than vincristine, causes a distal sensory neuropathy in 20-30% of treated patients; few have severe neuropathy.

**Taxanes**

The taxanes consist of paclitaxel and docetaxel. The latter is a semisynthetic analogue of paclitaxel. The major toxicity of paclitaxel is myelosuppression, but it becomes neurotoxic when used with granulocyte colony stimulating factor. The polyneuropathy of paclitaxel is primarily sensory. Its severity depends on the cumulative dose and dose intensity per cycle. A large number of patients develop a polyneuropathy when doses of 135-200 mg/m² every 3 weeks are prescribed. The neuropathy typically develops after the third to seventh cycle. Neuropathy invariably develops when single doses larger than 250 mg/m² are used.

As expected in a sensory polyneuropathy, the initial symptoms are numbness, paresthesias, and pain in the feet and ankles. In severe cases, the hands may become numb and ataxia may arise. Severe neuropathy often develops when the cumulative dose exceeds 1500 mg/m². It also occurs in patients with preexisting diabetes, alcoholic neuropathy, and inherited neuropathies. When paclitaxel is stopped, the neuropathy may progress for up to 4 weeks. It resolves in mild cases, but up to 40% of patients are left with permanent sensory symptoms in the toes and feet, and some may have weakness below the knees and ataxia. Findings from electrophysiologic testing are consistent with a sensory polyneuropathy.

Because of its semisynthetic relationship to paclitaxel, docetaxel-induced neuropathy shares many of the clinical characteristics of that induced by paclitaxel. Fortunately, clinically significant neuropathy is less common with typical dosing of docetaxel. Slightly fewer than 50% of patients who receive docetaxel will develop a neuropathy. Severe neuropathy is not common, but it tends to occur when cumulative doses of greater than 600 mg/m² are prescribed. Similar to paclitaxel-induced neuropathy, it presents with numbness in the feet and hands after the third to fifth treatment. When docetaxel is stopped, coating may take place for several months. Fortunately, the majority of patients improve or are left with mild residual sensory symptoms. Approximately 5% of patients exposed to docetaxel will develop a proximal myopathy superimposed on the distal neuropathy.

**Suramin**

Suramin is a hexasulfonated naphthylurea used to treat prostate cancer, adenocortical, ovarian, and renal cell carcinoma, malignant thymomas, and non-Hodgkins lymphoma. Suramin toxicity causes two types of neuropathy: (1) a length-dependent, sensory greater than motor axon loss neuropathy, and (2) a subacute motor greater than sensory demyelinating neuropathy resembling chronic inflammatory demyelinating polyneuropathy (CIDP) or a prolonged case of Guillain-Barre Syndrome (GBS). The incidence of neuropathy ranges from 25-90% and neurotoxicity appears to be dependent on the peak suramin blood level rather than the cumulative dose.

The length-dependent sensory greater than motor neuropathy is more common after treatment with suramin and is slowly reversible in most patients once chemotherapy is stopped. The motor demyelinating polyneuropathy is observed in about 10% of patients, and may not occur until 1 to 5 months after suramin is first used as a treatment. As with CIDP and GBS, patients can become bedridden from the polyneuropathy, and some may require ventilatory support. The cerebrospinal fluid (CSF) protein is elevated, furthering the resemblance to CIDP and GBS. Most patients improve over 3 to 6 months.

**Cytosine Arabinoside**

Acute cerebellar dysfunction is one of the most recognized toxicities of high dose Ara-C. Ara-C toxicity causes several types of neuropathies, including a pure sensory polyneuropathy, an acute motor and sensory neuropathy similar to GBS, and bilateral brachial plexopathy. The neuropathy may begin within hours to 3 weeks after the Ara-C treatment is initiated. Fortunately, toxicity to Ara-C is rare.

**Etoposide**

Etoposide is a semisynthetic derivative of podophyllotoxin and is used to treat a wide variety of neoplasms, including lymphoma, leukemia, testicular cancer, and small cell carcinoma of the lung. The polyneuropathy that develops after treatment with etoposide is primarily sensory and is most likely related to the effect of the drug on the dorsal root ganglion. The polyneuropathy from etoposide develops in up to 10% of patients who receive the drug; it tends to resolve completely once therapy is discontinued.

**Efosfamide**

Efosfamide is used to treat lymphomas, testicular and cervical carcinomas, sarcomas, and lung cancers. A neuropathy occurs in about 4% of patients who receive the chemotherapy and is typically sensory in manifestation. Symptoms begin within 10 days to 2 weeks after therapy is initiated, and resolve within 2 weeks of stopping the drug.

**NEUROPATHIES FROM IMMUNOSUPPRESSANT AGENTS**

**Tacrolimus**

Tacrolimus is an immunosuppressant that interferes with T-cell function and is primarily prescribed to prevent rejection after solid organ transplantation. Tacrolimus-associated neuropathies include a chronic demyelinating polyneuropathy that resembles CIDP or a more asymmetric form that begins approximately 2 to 10 weeks after initiation of therapy. Similarities with CIDP include areflexia, greater involvement of large than small fibers, and an elevated CSF protein. The nerve conduction abnormalities also resemble CIDP as patients have slowed conduction velocities, prolonged distal latencies, reduced CMAPs, and temporal dispersion of proximal CMAP amplitudes. Patients have improved after receiving...
intravenous immunoglobulin (IVIg) and plasma exchange, suggesting that the pathogenesis of this neuropathy is autoimmune and inflammatory.

Another presentation of a tacrolimus-induced polyneuropathy is an acute, predominantly motor axon loss neuropathy that begins 1 to 2 weeks after the start of therapy. The polyneuropathy can be devastating, producing facial weakness and quadriparesis. Most patients improve once tacrolimus is stopped. A similar drug-induced polyneuropathy has been described in patients receiving cyclosporin, beginning 1 to 8 weeks after treatment is started.

**TUMOR NECROSIS FACTOR-ALPHA ANTAGONISTS**

Tumor necrosis factor-alpha antagonists (TNF-alpha antagonists) are used to treat patients with refractory autoimmune disorders, including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn’s disease, and ulcerative colitis. The drugs work at several levels of inflammation and immunogenesis to block or reduce damage at the vascular endothelium and blood nerve barrier, and to prevent access of immunoglobulins, cytokines, complement, macrophages, nitrogen oxide metabolites, and proteases to the sites of pathology. Three TNF-alpha antagonists are presently marketed: infliximab, etanercept, and adalimumab.

Several presentations of peripheral neuropathy have been reported in patients receiving TNF-alpha antagonists. These vary in manifestation from GBS, Fisher syndrome, multifocal motor neuropathy, mononeuritis simplex or multiplex, to an axonal sensory or sensorimotor polyneuropathy. Timing and dosing of TNF-alpha antagonists vary greatly in each patient for each condition. In some patients, the neuropathy develops within 8 hours of the first dose; in others, after 2 years.

Many patients improve once the TNF-alpha is stopped, and treatment with corticosteroids, IVIg, or plasma exchange may not be necessary. The pathogenesis of TNF-alpha antagonist-induced neuropathy has been hypothesized as resulting from enhanced T-cell proliferation and cytokine production when the TNF-alpha antagonist modifies the antigen-presenting cell function, T-cell receptor signaling, and decreasing apoptosis of autoreactive T cells.

**SUMMARY**

Many medications have been implicated in polyneuropathy and the list grows each year. The medications can induce neuropathy by acting on the peripheral axon, the anterior horn cell, the dorsal root ganglion, or the Schwann cell. Commonly prescribed medications can cause neuropathies, as can chemotherapeutic agents, antiretroviral HIV drugs, and most recently, immunosuppressants and TNF-alpha antagonists. Recognition of medication-induced neuropathy requires good knowledge of the neurologic literature, high clinical suspicion, and review of the patient’s present and prior therapy when no other cause for neuropathy is evident.
Toxic Myopathies

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INTRODUCTION

Although many drugs are known to cause myopathies, the pathophysiological bases vary.1−9 These agents can have adverse effects on muscles that are either direct or indirect. The direct effect can be generalized or focal, the latter might occur secondary to a drug being injected into tissue. Indirect toxic effects may result from the agent creating an electrolyte imbalance or inducing an immunological reaction. Muscle fibers may undergo necrosis as a result of the drug directly disrupting the sarcolemma, nuclear function, mitochondria function, or that of other organelles. Classifications of the toxic myopathies according to their presumed pathogenic mechanisms will be presented in this manuscript (Table 1).

NECROTIZING MYOPATHIES

A number of drugs can cause a generalized necrotizing myopathy. Affected individuals may complain of myalgias or weakness, or may just have asymptomatic elevations of their serum creatine kinase (CK) levels. Severe necrotizing myopathy may be complicated by myoglobinuria. The serum CK is elevated and is dependent upon the amount of muscle that is damaged.

Cholesterol Lowering Agents

Cholesterol lowering medications including 3-hydroxy-3 methyl-glutaryl-coenzyme A (3-HMG-CoA) reductase inhibitors,10−18 fibric acid derivatives,15,19−29 niacin,30,31 and ezetimibe32−35 can cause a toxic myopathy. Most patients just have mild elevations in serum CK without further symptoms. Others have myalgias and less frequently, weakness. Myoglobinuria is a rare event, but may lead to death. With discontinuation of the offending agent medication, the myalgias, weakness, and elevated serum CK levels tend to completely resolve in several days to months.

HMG-CoA Reductase Inhibitors

Clinical Features. Statin agents inhibit 3-HMG-CoA reductase, the rate controlling enzyme in cholesterol synthesis. Symptoms or signs of a toxic myopathy including asymptomatic hyper-CK-emia, myalgias, proximal weakness, and less commonly, myoglobinuria, occur with all of the major HMGCoA reductase inhibitors: lovastatin,12,15,17,18,31,36,37 simvastatin,11,13,14,37,38 provastatin,16,37 atorvastatin,10,37,39 fluvastatin,37 and cerivastatin.37,40,41 The nomenclature regarding statin induced toxic myopathies in the published literature is unfortunately quite unsatisfactory, listing “myalgias,” “myositis,” and “myopathy” as three independent types of muscle disorders caused by statin use, when in fact the definitions of these three subtypes may just reflect the spectrum of severity of the myopathy.42−46

General reviews of statin myopathies cite a 2 to 7% incidence of myalgias and 0.1 to 1.0% incidence of weakness or elevated CK, with myoglobinuria developing in <0.5% of patients.1,42,45,46 The incidence of severe myopathy is estimated by a National Heart Lung and Blood Institute advisory panel at approximately 0.08% for lovastatin, simvastatin, and pravastatin.43 The risk of toxic myopathy increases with the concomitant use of fibric acids,17,18,26,30,31,5 niacin,31 erythromycin,47 cyclosporine,17,18 and ezetimibe32−35 as do renal insufficiency and hepatobiliary dysfunction. In this regard, 5% of patients taking both lovastatin and gemfibrozil developed a severe myopathy,26 while a severe myopathy complicated as many as 30% of patients receiving both lovastatin and cyclosporine.12,17,18 Although the term “myositis” has been used to denote cases associated with markedly elevated serum CK levels, histopathological confirmation is lacking in most such cases. “Myositis” denotes an autoimmune attack on muscle. Rare cases of myositis have been described in association with statin use.16,48−55,55a

Laboratory Features. Asymptomatic elevation of serum CK is common in patients taking statin medications. Marked elevations of CK occur in patients with severe weakness and myoglobinuria.
Routine motor and sensory nerve conduction studies (NCSs) are normal. Fibrillation potentials, positive sharp waves, and myotonic discharges with early recruitment of small duration motor unit action potentials (MUAPs) are apparent in weak muscles. Electromyography (EMG) in patients with asymptomatic serum CK elevations is often normal.

**Histopathology.** Muscle biopsies reveal muscle fiber necrosis with phagocytosis and small regenerating fibers in patients with elevated serum CKs and weakness or myalgias. Cytochrome oxidase negative myofibers may be appreciated, but these are not consistent findings.

Pathogenesis. The pathogenesis of the myopathy secondary to HMGCoA reductase inhibitors is unclear, as several pathways may potentially be interrupted downstream. Mevalonate is the immediate product of HMGCoA reductase metabolism. Subsequently, mevalonate is metabolized to farnesol, which is converted to either squalene or geranylgeraniol. Squalene is the first metabolite committed to the synthesis of cholesterol. In contrast, geranylgeraniol is important in the biosynthesis of coenzyme Q10 (a mitochondrial enzyme important in the production of adenosine triphosphate [ATP]), dolichol (important in glycoprotein synthesis), isopentyladine (a component of transfer ribonucleic acid [tRNA]), and in the activation of regulatory proteins (G-proteins). It is possible that statins could diminish cholesterol within muscle membranes, thereby predisposing the muscle fibers to rhabdomyolysis. However, it is the depletion of metabolites of geranylgeraniol, and not the inhibition of cholesterol synthesis, that may be the primary cause of myotoxicity. In this regard, HMG-CoA reductase inhibitors decrease the levels of coenzyme Q, which could impair energy production.

There are several reports of patients treated with statins who developed dermatomyositis (DM), polymyositis (PM), and immune-mediated necrotizing myopathy. The most common, myositis, which has been seen in patients on a statin medication, is a necrotizing myopathy. Unlike PM, there are many necrotic fibers without much endomysial inflammation except within the necrotic fibers. In many instances, the myositis did not improve following discontinuation of the statin medication (after 6 months or more) and did so only after treatment with an immunosuppressant medication. In addition, the myopathy worsened after discontinuation of the immunosuppressant agent and improved once again upon reinstating immunotherapy. Thus, it seemed that these cases did not simply represent delayed improvement of a “toxic” myopathy. Further, occasional patients have been known to develop DM when on a statin medication or experience a flare of DM when started on a statin medication. Whether or not the DM or necrotizing was coincidental or triggered by statin medication is unclear at this point.

A recent genomewide association study was performed in 85 subjects with definite (CK 10 x upper limited of normal [ULN] with symptoms) or incipient myopathy (CK 3 x ULN or 5 x baseline) and 90 controls, all of whom were taking 80 mg of simvastatin daily as part of a trial involving 12,000 participants. Replication was tested in a trial of 40 mg of simvastatin daily involving 20,000 participants. These studies found a single strong association of myopathy with the rs4363657 single nucleotide polymorphism (SNP) located within SLCO1B1. This gene encodes a protein that regulates the hepatic uptake of statins. More than 60% of these myopathy cases could be attributed to the C variant. No SNPs in any other region were clearly associated with myopathy, including those genes that encode metabolic enzymes associated with rhabdomyolysis. Genotyping SNPs in the SLCO1B1 may be used to predict which patients may be more at risk for developing a statin induced toxic myopathy. However, the risk is very low and may not be cost effective at this time. The study does dispel the suggestion that statin myopathy is due to unmasking of metabolic genetic defects.

**Fibric Acids**

Clinical Features. Clofibrate and gemfibrozil are branched chain fatty acid esters used to treat hyperlipidemia. Fibric acid derivatives have been associated with a myopathy that typically presents within 2 or 3 months after starting the drug. However, onset of the myopathy has been reported up to 2 years following initiation of treatment. Patients may develop generalized weakness, myalgias, cramps, and occasionally, myoglobinuria. Patients with renal insufficiency, those taking both clofibrate and gemfibrozil, and especially also receiving an HMG-CoA inhibitor, are predisposed to developing a severe myopathy.

Laboratory Features. Elevated serum CK levels are usually noted. Motor and sensory NCSs are normal. Needle EMG demonstrates fibrillation potentials, positive sharp waves, complex repetitive discharges, myotonic discharges, and small duration, low amplitude polyphasic MUAPs in affected muscle groups.

**Histopathology.** Muscle biopsies demonstrated scattered necrotic muscle fibers. In animal models, clofibrate is also known to result in a non inflammatory necrosis of muscle tissue with fiber size variation and groups of small atrophic muscle fibers.

Pathogenesis. The pathogenic mechanism of the myopathy associated with fibric acid derivatives is not known. It has been postulated that these medications somehow destabilize the lipophilic muscle membrane leading to muscle fiber degeneration.

**Niacin**

Rarely, niacin may cause myalgias and cramps of the lower extremities (LEs). Serum CK levels can be elevated as much as ten-fold. The symptoms improve and CK levels normalize after discontinuation of niacin. Electrodagnostic (EDX) studies and muscle biopsies were not performed. In the only other report in which the authors are aware of, rhabdomyolysis occurred in a patient who was taking both lovastatin and niacin. Of note, niacin can inhibit HMG-CoA reductase; therefore, the pathogenic mechanism of the myopathy is likely similar to that of the statins.
### Table 1 Toxic Myopathies

<table>
<thead>
<tr>
<th>Pathogenic Classification</th>
<th>Drug</th>
<th>Clinical Features</th>
<th>Laboratory Features</th>
<th>Histopathology</th>
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<tbody>
<tr>
<td><strong>Necrotizing Myopathy</strong></td>
<td>Cholesterol lower agents</td>
<td>Acute or insidious onset; Proximal weakness; Myalgias</td>
<td>Elevated serum CK; EMG: fibrillation potentials, Myotonia (statins, cyclosporine), myopathic MUAPs</td>
<td>Many necrotic fibers; No evidence of endomysial inflammatory cell infiltrate involving non-necrotic muscle fibers</td>
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<td></td>
<td>Cyclosporine</td>
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<td><strong>Amphiphilic</strong></td>
<td>Chloroquine</td>
<td>Acute or insidious onset; Proximal and distal weakness; Myalgias; Sensorimotor neuropathy; Hypothyroid (amiodarone)</td>
<td>Elevated serum CK; EMG: fibrillation potentials, Myotonia (Chloroquine), myopathic MUAPs; NCS: axonal sensorimotor neuropathy</td>
<td>Autophagic vacuoles and inclusions are apparent in some muscle fibers and in Schwann cells</td>
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<td>Hydroxychloroquine</td>
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<td><strong>Antimicrotubular</strong></td>
<td>Colchicine</td>
<td>Acute or insidious onset; Proximal and distal weakness; Myalgias; Sensorimotor neuropathy</td>
<td>Normal or elevated CK; EMG: fibrillation potentials, myopathic MUAPs; NCS: axonal sensorimotor neuropathy</td>
<td>Autophagic vacuoles and inclusions are evident in some muscle fibers; Nerve biopsies demonstrate axonal degeneration</td>
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<td>Vincristine</td>
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<td><strong>Mitochondrial Myopathy</strong></td>
<td>Zidovudine</td>
<td>Acute or insidious onset; Proximal weakness; Myalgias; Rhabdomyolysis; Painful sensory Neuropathy</td>
<td>Normal or elevated CK; EMG: normal or myopathic; NCS: axonal sensory neuropathy</td>
<td>Muscle biopsies reveal red fibers, COX-negative fibers; May also see inflammatory cell inclusions, cytoplasmic bodies, nemaline rods</td>
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<td>Other HIV-related anti-retrovirals?</td>
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<td><strong>Inflammatory Myopathy</strong></td>
<td>L-tryptophan</td>
<td>Acute or insidious onset; Proximal weakness; Myalgias</td>
<td>Elevated serum CK; EMG: fibrillation potentials, myopathic MUAPs</td>
<td>Perivasculary, perimysial, or endomyosial inflammatory cell inclusions</td>
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<td>D-penicillamine</td>
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<td><strong>Hypokalemic Myopathy</strong></td>
<td>Diuretics</td>
<td>Acute proximal or generalized weakness; Myalgias</td>
<td>Serum CK may be elevated; Low serum potassium</td>
<td>May see scattered necrotic fibers and vacuoles</td>
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<td>Laxatives</td>
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<td>Amphotericin</td>
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<td>Toluene abuse</td>
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<td>Corticosteroids</td>
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<td>Alcohol Abuse</td>
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<td><strong>Critical Illness Myopathy</strong></td>
<td>Corticosteroids</td>
<td>Acute generalized weakness including respiratory muscles</td>
<td>Serum CK can be normal or elevated; NCS: low amplitude CMAPs with relatively normal SNAPs; EMG: fibrillation potentials, myopathic MUAPs or no voluntary MUAPs</td>
<td>Atrophy of muscle fibers, scattered necrotic fibers; absence of myosin thick filaments</td>
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<td>Non-depolarizing neuromuscular blocking agents</td>
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<td><strong>Unknown</strong></td>
<td>Omeprazole</td>
<td>Acute or insidious onset; Proximal weakness; Myalgias</td>
<td>Normal or slightly elevated serum CK; EMG: myopathic MUAPs; NCS: axonal sensorimotor neuropathy</td>
<td>Type II muscle fiber atrophy may be seen</td>
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<td>Isoetinoin</td>
<td>Acute or insidious onset; Proximal weakness; Myalgias</td>
<td>Normal or slightly elevated CK</td>
<td>Atrophy of fibers</td>
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<td>Finasteride</td>
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<td>Serum CK is normal; EMG: myopathic MUAPs</td>
<td>Variability in fiber size, type II fiber atrophy, increased internalized nuclei</td>
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<td></td>
<td>Emetine</td>
<td>Acute or insidious onset; Proximal weakness; Myalgias</td>
<td>Serum CKs mild to moderately elevated</td>
<td>Myofibrillar Myopathy</td>
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CK = creatine kinase; COX = cytochrome c oxidase; EMG = electromyography; fibr = fibrillation potentials; HIV = human immunodeficiency virus; MUAPs = motor unit action potentials; NCS = nerve conduction study; PSWs = positive sharp waves

Ezetimibe

Ezetimibe is a new class of lipid lowering drugs referred to as the 2-azetidinones, which selectively inhibit the absorption of intestinal cholesterol. A few reports of ezetimide induced myopathy have been reported. Similar to other cholesterol lowering agents, patients may develop hyper-CK-emia with or without myalgias or weakness. Most cases occur in patients who are already on a statin agent, but some occur with ezetimibe being used as monotherapy.

OTHER DRUGS ASSOCIATED WITH NECROTIZING MYOPATHY

Cyclosporine and Tacrolimus

Clinical Features. The immunophilins (i.e., cyclosporine and tacrolimus) are commonly used as immunosuppressive agents, especially in patients requiring transplantation. Generalized myalgias and proximal muscle weakness can develop within months after starting these medications. Myoglobinuria can also occur, particularly in patients receiving cyclosporine or tacrolimus concurrent with cholesterol lowering agents or colchicine. Tacrolimus has also been associated with hypertrophic cardiomyopathy and congestive heart failure. Myalgias, muscle strength, and cardiac function improve with reduction or discontinuation of the offending cyclophilin.

Laboratory Features. Serum CK is usually elevated. NCSs are normal. EMG is remarkable for evidence of increased muscle membrane instability with fibrillation potentials, positive sharp waves, and myotonic potentials. Early recruitment of small amplitude, short duration MUAPs may be demonstrated in weak muscle groups.

Histopathology. Muscle biopsies demonstrate necrosis, vacuoles, and type 2 muscle fiber atrophy.

Pathogenesis. The pathogenic basis of cyclophilin induced myopathy and cardiomyopathy is not known. Perhaps, the agents destabilize the lipophilic muscle membrane leading to muscle fiber degeneration, similar to the cholesterol lowering agents. In this regard, cyclosporine itself has a cholesterol lowering effect. This may explain the increased risk of myopathy in patients receiving cyclosporine and the more classic lipid lowering agents (e.g., fibric acid derivatives and statins).

Other Agents

Labetalol and propofol have also been associated with necrotizing myopathy.

AMPHIPHILIC DRUG MYOPATHY (DRUG-INDUCED AUTOPHAGIC LYOSOMAL MYOPATHY)

Amphiphilic drugs contain separate hydrophobic and hydrophilic regions, which allow the drugs to interact with the anionic phospholipids of cell membranes and organelles. In addition to a myopathy, these agents can also cause a neuropathy that is even more severe than the direct toxicity on the muscle.

Chloroquine

Clinical Features. Chloroquine is used to treat malaria, sarcoidosis, systemic lupus erythematosus, and other connective tissue diseases. Some patients develop slowly progressive, painless, proximal weakness and atrophy, which are worse in the legs than in the arms. A cardiomyopathy can also occur. Sensation is often reduced as are muscle stretch reflexes, particularly at the ankle, secondary to a concomitant neuropathy. This “neuromyopathy” usually does not occur unless patients take 500 mg for a year or more, but has been reported with doses as low as 200 mg/d. The neuromyopathy improves after the chloroquine discontinuation.

Laboratory Features. Serum CK levels are usually elevated. Motor and sensory NCSs reveal mild to moderate reduction in the amplitudes with slight slow velocities in patients with a superimposed neuropathy. Patients with only the myopathy usually have normal motor and sensory studies. Increased insertional activity in the form of positive sharp waves, fibrillation potentials, and myotonic discharges are seen primarily, but not exclusively, in the proximal limb muscles. Early recruitment of small amplitude, short-duration polyphasic MUAPs are appreciated in weak proximal muscles. Neurogenic appearing units and reduced recruitment may be seen in distal muscles more affected by the toxic neuropathy.

Histopathology. Autophagic vacuoles are evident in as many as 50% of skeletal and cardiac muscle fibers. Type 1 fibers appear to be preferentially affected. The vacuoles stain positive for acid phosphatase, suggesting lysosomal origin. On electron microscope (EM), the vacuoles are noted to contain concentric lamellar myeloid debris and curvilinear structures. Autophagic vacuoles are also evident in nerve biopsies.

Pathogenesis. Chloroquine is believed to interact with the lipid membranes, forming drug lipid complexes that are resistant to digestion by lysosomal enzymes. This results in the formation of the autophagic vacuoles filled with myeloid debris.

Hydroxychloroquine

Hydroxychloroquine is structurally similar to chloroquine and can cause a neuromyopathy. The myopathy is usually not as severe as seen in chloroquine. Vacuoles are less appreciated on routine light microscopy, but EM still usually demonstrates the abnormal accumulation of myeloid and curvilinear bodies.

Amiodarone

Clinical Features. Amiodarone is an antiarrhythmic medication that can also cause a neuromyopathy. Severe proximal and distal weakness along with
distal sensory loss and reduced muscle stretch reflexes. The legs are more affected than the arms. Some patients develop a tremor or ataxia. Amiodarone can also cause hypothyroidism, which may also contribute to proximal weakness. Patients with renal insufficiency are predisposed to developing the toxic neuromyopathy. Muscle strength gradually improves following discontinuation of amiodarone.

**Laboratory Features.** Serum CK levels are elevated. Motor and sensory NCSs reveal reduced amplitudes, and slow conduction velocities particularly in the LEs. EMG demonstrates fibrillation potentials and positive sharp waves in proximal and distal muscles. In proximal muscles, MUAPs are typically polyphasic, short in duration, small in amplitude, and recruit early. Distal muscles are more likely to have large amplitude, long duration polyphasic MUAPs with decreased recruitment.

**Histopathology.** Muscle biopsies demonstrate scattered fibers with autophagic vacuoles. In addition, neurogenic atrophy can also be appreciated, particularly in distal muscles. EM reveals myofibrillar disorganization and autophagic vacuoles filled with myeloid debris. Myeloid inclusions are also apparent on nerve biopsies. These lipid membrane inclusions may be evident in muscle and nerve biopsies as long as 2 years following discontinuation of amiodarone.

**Pathogenesis.** The pathogenesis is presumably similar to other amphiphilic medications (e.g., chloroquine).

### ANTIMICROTUBULAR MYOPATHIES

**Colchicine**

**Clinical Features.** Colchicine is commonly prescribed for individuals with gout. Colchicine can also cause a generalized toxic neuromyopathy. It is weakly amphiphilic, but its toxic effect is believed to arise secondary to its binding with tubulin and prevention of tubulin's polymerization into microtubular structures. The dose limiting side effect of vincristine is a toxic axonal sensorimotor polyneuropathy associated distal muscle weakness and sensory loss. Proximal muscle weakness and myalgias are less common.

**Laboratory Features.** Serum CK level is elevated, up to fifty-fold, in symptomatic patients. Serum CK may also be mildly elevated in asymptomatic patients taking colchicine. NCSs reveal reduced amplitudes, slightly prolonged latencies, and mildly slow conduction velocities of motor and sensory nerves in the arms and legs. Needle EMG demonstrates positive sharp waves, fibrillation potentials, and compound muscle action potentials (CMAPs), while the distal latencies are slightly prolonged and conduction velocities are mildly slow. Needle EMG demonstrates positive sharp waves, fibrillation potentials, and neurogenic appearing MUAPs in the distally located muscles of the upper extremity and LE.

**Histopathology.** Biopsies of distal muscles demonstrate evidence of neurogenic atrophy and, occasionally, the accumulation of lipofuscin granules. Proximal muscle biopsies reveal scattered necrotic fibers. A superimposed toxic neuropathy leads to distal sensory loss as well as diminished reflexes. The neuromyopathy weakness resolves within 4 to 6 months after discontinuing the colchicine.

**Vincristine**

**Clinical Features.** Vincristine is a chemotherapeutic agent which disrupts RNA transcription and also promotes the polymerization of tubulin into microtubules. The dose limiting side effect of vincristine is a toxic axonal sensorimotor polyneuropathy associated distal muscle weakness and sensory loss. Proximal muscle weakness and myalgias are less common.

**Laboratory Features.** Serum CK levels have not been reported in patients suspected of having a superimposed myopathy. NCSs demonstrate markedly reduced amplitudes of sensory nerve action potentials (SNAPs) and compound muscle action potentials (CMAPs), while the distal latencies are slightly prolonged and conduction velocities are mildly slow. Needle EMG demonstrates positive sharp waves, fibrillation potentials, and neurogenic appearing MUAPs in the distally located muscles of the upper extremity and LE.

**Histopathology.** Biopsies of distal muscles demonstrate evidence of neurogenic atrophy and, occasionally, the accumulation of lipofuscin granules. Proximal muscle biopsies reveal scattered necrotic fibers. On EM, there is prominent myofibrillar disarray and subarcosomal accumulation of osmiophilic material. In addition, some myonuclei contain membrane bound inclusions. Autophagic vacuoles with spheromembranous debris have been noted in research animals but have not been appreciated in humans.

**Pathogenesis.** The pathogenic basis of the neuromyopathy is presumably similar to that of colchicine.

### DRUG-INDUCED MITOCHONDRIAL MYOPATHY

**Zidovudine (Azidothymidine)**

**Clinical Features.** Azidothymidine (AZT) myopathy usually presents with insidious onset of progressive proximal muscle weakness and myalgias. However, these clinical features do no help distinguish AZT myopathy from other human immunodeficiency virus– (HIV) related myopathies. Myopathies related to HIV infection are heterogeneous and include inflammatory myopathy, microvasculitis, noninflammatory necrotizing myopathy, type 2 muscle fiber atrophy, secondary to disuse and wasting due to their chronic debilitated state, and a toxic myopathy secondary to AZT. Further, weakness in an HIV-infected patient can also be secondary to PN (e.g., chronic inflammatory demyelinating polyneuropathy[CIDP]) or myasthenia gravis (MG). Clinically, AZT myopathy and the other
myopathic disorders associated with HIV infection are indistinguishable, compounding the diagnostic difficulty.

Regardless of etiology of the myopathy, patients can present with progressive proximal muscle weakness and myalgias. In addition, muscle weakness may be multifactorial: an individual patient can have an HIV-associated myositis, nemaline rod myopathy, AZT-induced mitochondrial myopathy, and type 2 muscle fiber atrophy (not to mention an HIV-related or drug-induced PN).

**Laboratory Features.** Serum CK levels are normal or only mildly elevated in AZT myopathy. However, similar elevations are evident in other forms of HIV-related myopathy. A markedly elevated serum CK (e.g., greater than five times the upper limits of normal) is more suggestive of an HIV-associated myositis. Motor and sensory NCSs are normal, unless there is a concomitant PN from the disease. Needle EMG may demonstrate positive sharp waves and fibrillation potentials and early recruitment of short duration, small amplitude polyphasic MUAPs. In addition, small polyphasic MUAPs with early recruitment but no abnormal spontaneous activity was reported in patients with autoimmune deficiency syndrome, with ultrastructural mitochondrial abnormalities but no inflammation or nemaline rods on biopsy.

**Histopathology.** Muscle biopsies are remarkable for the presence of ragged red fibers (RRFs), suggesting mitochondrial abnormalities in AZT myopathy. The number of RRFs correlates with the cumulative dose of AZT. In addition, necrotic fibers, cytoplasmic bodies, nemaline rods, and fibers with micruracluotation may be seen in addition to RRFs. In contrast to HIV-associated inflammatory myopathy, significant endomysial inflammation and invasion of non-necrotic fibers should not be present in cases of pure AZT myopathy. EM reveals abnormalities of the mitochondria and myofilaments. In AZT, RRFs suggestive of abnormal mitochondria are evident on modified Gomori trichrome stain.

**Pathogenesis.** AZT acts as a false substitute for the viral reverse transcriptase, thereby inhibiting its enzymatic activity and replication of the HIV virus. However, AZT also inhibits the activity of mitochondrial deoxyribonucleic acid (mtDNA) polymerase, which probably accounts for the mitochondrial abnormalities. When treated with AZT, patients with HIV have a decrease in quantity of mitochondrial mtDNA and decline in respiratory chain enzymatic activity, compared to untreated infected patients. The histological and molecular abnormalities on repeat muscle biopsies resolve, coinciding with clinical improvement following discontinuation of AZT. However, the fact that AZT is responsible for the mitochondrial abnormalities is evident on muscle biopsy, the contribution of these mitochondrial abnormalities to the muscle weakness remains controversial.

**Other Antiviral Agents**

It has been suggested that the risk of mitochondrial myopathy with other nucleoside reverse transcriptase inhibitors, lamivudine (3TC), zalcitabine, didanosine, is less than that of AZT. However, these agents are clearly associated with mitochondrial toxicity, and patients may develop associated hyperlactemia and hepatic steatosis while taking these medications. The AIDS Clinical Trial group randomized 2467 patients to receive one of four single or combination regimens with AZT, didanosine, zalcitabine, and their respective placebo. Approximately 10% of patients had myalgias prior to treatment, and 7% developed myalgias during treatment. There was no significant difference between treatment arms and the rate of myalgias or muscle weakness in any group. Five patients (0.5%) had elevated serum CK (≥4× normal) prior to treatment, and 52 (5%) developed increased CK during treatment. Serum CK levels were significantly higher in the AZT zalcitabine group, but this did not correlate with symptoms of myopathy. Unfortunately, there was no comment on muscle biopsies, and thus it is unclear whether the myopathies were secondary to mitochondrial toxicity or myositis.

The main treatment of HIV infection currently is with highly active antiviral therapy (HAART) consisting of a combination of nucleoside reverse transcriptase inhibitors and a protease inhibitor. Rare cases of rhabdomyolysis and myoglobinuria occur in patients taking other HAART medications, including tenofovir and ritonavir. A review of 563 patients receiving HAART in Essen, Germany, between 1995 and 1998 demonstrated a prevalence of HIV-associated myopathy in 1.5% of patients treated with HAART. It was not clearly stated how the myopathy was defined (e.g., clinical symptoms or signs, elevated serum CK, EMG, or biopsy). Additionally, it wasn’t stated whether the myopathy was felt to be due to mitochondrial toxicity, myositis, or wasting syndrome.

**Drug-Induced Inflammatory Myopathies**

A number of drugs have been associated with inflammatory myopathy (Table 1). These are now very rare conditions. In some cases, the myopathy was not due to the drug itself, but to an adulterant in the formulation. Also, the myositis may be due to the effect of the drug on the immune system as in the case of alpha interferon.

**Myopathies Secondary to Impaired Protein Synthesis or Increased Catabolism**

**Corticosteroid Myopathy**

**Clinical Features.** Steroid myopathy manifests as proximal muscle weakness and atrophy, affecting the legs more than the arms. The distal extremities, oculobulbar, and facial muscles are normal, as are sensation and muscle stretch reflexes. Most patients exhibit a “Cushingoid appearance” with facial edema and increased truncal adipose tissue. Prednisone at doses of 30 mg/d or more (or equivalent “Cushingoid appearance” with facial edema and increased truncal adipose tissue. Prednisone at doses of 30 mg/d or more (or equivalent doses of other corticosteroids) is associated with an increased risk of myopathy. Any synthetic glucocorticoid can cause the myopathy, but those that are fluorinated (triamcinolone > betamethasone > dexamethasone) are more likely to result in muscle weakness than the nonfluorinated compounds. Women appear to be at a higher risk than men (approximately 2:1) to developing a steroid myopathy.
Alternate day dosing may reduce the risk of corticosteroid induced weakness. Muscle weakness can develop within several weeks following the administration of corticosteroids; however, it more commonly occurs as a complication of chronic administration of oral high-dose corticosteroids. Acute onset of severe generalized weakness can occur in patients receiving high dosages of intravenous corticosteroids with or without concomitant administration of neuromuscular (NM) blocking agents.

**Laboratory Features.** Serum CK is normal. Serum potassium can be low as a result of glucocorticoid excess and can cause some degree of weakness. Motor and sensory NCSs are normal in steroid myopathy. Repetitive stimulation studies should not demonstrate a significant decrement or increment. Needle EMG is normal as well. The paucity of abnormalities is understandable, as corticosteroids preferentially affect type 2 muscle fibers. The first recruited motor units are comprised of type 1 muscle fibers. Because these are not affected as severely as type 2 fibers, the EMG is usually normal.

**Histopathology.** Muscle biopsies reveal atrophy of type 2 fibers, especially the fast twitch, glycolytic type 2B fibers. There may also be a lesser degree of atrophy of type 1 muscle fibers. Lipid droplets are commonly noted in type 1 fibers, and rare mitochondrial abnormalities have been seen on EM.

**Pathogenesis.** Corticosteroids bind to receptors on target cells and are subsequently internalized into the nuclei, where these regulate the transcription of specific genes. How corticosteroids cause a myopathy is not known, but it could be the result of decreased protein synthesis, increased protein degradation, alterations in carbohydrate metabolism, mitochondrial alterations, and reduced sarcolemmal excitability.

**Treatment.** Major modes of therapy include: reduction in the dose, tapering to an alternate day regimen, or switching to a nonfouri-nated steroid, and exercise to prevent concomitant disuse atrophy. Of particular concern is distinguishing steroid myopathy from an exacerbation of underlying immune-mediated NM disorders (e.g., inflammatory myopathy, MG, and CIDP) in a patient being treated with corticosteroids. If the weakness occurred while the patient was tapering the corticosteroid, relapse of the underlying disease process would be most likely. In contrast, if weakness developed while the patient was on chronically high doses of steroids, a steroid myopathy should be considered. In the case of an inflammatory myopathy, an increasing serum CK and an EMG with prominent increase in insertional and spontaneous activity would point to an exacerbation of the myositis. In some cases, it is impossible to state with certainty whether the new weakness is related to a relapse of the underlying disease or secondary to the corticosteroid treatment. In such cases, the corticosteroid medication can be tapered and the patients must be closely observed. If muscle strength improves, it is presumed that the patient had a steroid myopathy. If patient’s strength declines, it is more likely the weakness is caused by an exacerbation of the underlying autoimmune disease and requires increased doses of corticosteroids or other immunosuppres-sive medications.

**Finasteride**

**Clinical Features.** Finasteride is used to treat prostatic hypertrophy. It is a 4-azasteroid that blocks dihydrotestosterone production and androgen action in the prostate and skin. One patient developed severe proximal greater than distal weakness and atrophy while being treated with finasteride (5 mg qd).

**Laboratory Features.** Serum CK levels were normal. NCSs were normal, while the EMG showed small polyphasic MUAPs.

**Histopathology.** Muscle biopsy revealed only mild variability in fiber size, type 2 muscle fiber atrophy, and increased central nuclei.

**Pathogenesis.** The pathophysiologic mechanism for the myopathy is not known. Finasteride is one of the 4-azasteroids and its parent compound, as well as the metabolites, has structural similarity to corticosteroids. Thus, the pathogenic mechanism may be similar to that seen of steroid myopathy.

**Emetine (Ipecac)**

**Clinical Features.** Emetine hydrochloride is an emetic agent that has been abused, particularly in patients with anorexia nervosa and bulimia. A severe proximal myopathy and cardiomyopathy can occur with overuse of emetine (500 to 600 mg/d for over 10 days). Patients also complain of muscle pain, tenderness, and stiffness. Deep tendon reflexes are usually diminished, but the sensory examination is completely normal. The myopathy is reversible following discontinuation of the medication.

**Laboratory Features.** The serum CK levels may be mildly to moderately elevated. Sensory and motor NCSs are normal. Needle EMG examination can be normal, although positive sharp waves and fibrillation potentials are usually apparent. There is early recruitment of small amplitude, short duration MUAPs.

**Histopathology.** Muscle biopsies reveal that scattered necrotic fibers, small atrophic and regenerating fibers, as well as many fibers contain cytoplasmic bodies. Oxidative enzyme stains demonstrate targetoid or moth eaten structures. On EM, there is evidence of myofibrillar degeneration in addition to compacted myofibrillar debris (cytoplasmic bodies). The histological appearance of light and EM is similar to myofibrillar myopathy or desmin myopathy.

**Pathogenesis.** The exact pathogenic basis for the disorder is not known, but it is postulated that emetine might inhibit the synthesis of important muscle proteins.

**TOXIC MYOPATHIES WITH MULTIFACTORIAL OR UNKNOWN PATHOGENIC MECHANISM**

**Critical Illness Myopathy**

Patients in the intensive care unit (ICU) may develop generalized weakness due to critical illness polyneuropathy and prolonged...
The myopathy can also develop from high dose intravenous corticosteroids and/or nondepolarizing NM blockade. Numerous reports of AQM usually developing in patients who received high dose intravenous corticosteroids and/or nondepolarizing NM blockers. The myopathy can also develop in patients with sepsis or multiorgan failure who never received either corticosteroids or nondepolarizing NM blocking agents. A patient's status, post recent organ transplantation, appears to be at increased risk of AQM, perhaps due to the high doses of intravenous corticosteroids for prevention of rejection and NM blocking agents in the perioperative period. Because of their immunosuppressed state, patients undergoing transplant are also prone to infection and sepsis, which also predisposes them to AQM. The incidence of AQM is uncertain because there have been only a few prospective series published on the subject. In a study of 25 consecutive patients requiring mechanical ventilation for severe asthma, myopathy developed in 9 of 25 patients (36%), and elevated serum CK levels in 19 of 22 (76%) patients tested. The patients were treated with dexamethasone 10 mg every 8 hours or hydrocortisone 250 mg every 6 hours; 22 of the 25 patients also received vecuronium. Mechanical ventilation lasted an average of 3.1 +/- 3.1 days in patients without myopathy and 12.9 +/- 6.6 days in those with myopathy. In a prospective study of 100 consecutive adult patients undergoing liver transplantation, 7 patients developed AQM. Patients were treated with nondepolarizing NM blocking agents and high-dose steroids in the perioperative period. Three of six patients tested had elevated serum CK levels, as high as 10 times the upper limit of normal 25 days post operation. Four patients had muscle biopsies demonstrating necrosis and selected loss of myosin. Three patients later died from sepsis and multiorgan failure. The remaining patients slowly regained strength and the ability to ambulate over 1 to 3 months. Patients with AQM exhibit severe generalized weakness of the trunk, extremities, and respiratory muscles, and can rarely involve the extraocular muscles. The myopathy is usually initially recognized by the inability to wean the patient from the ventilator. Sensory examination is usually normal, but this can be difficult to determine in an intubated patient with altered mental status. Deep tendon reflexes are decreased or absent. The mortality is high at approximately 30% in one large series, secondary to multiple organ failure and sepsis, rather than the myopathy. The morbidity and mortality in AQM and critical illness neuropathy appear to be similar. In patients who survive, muscle strength recovers slowly over several months.

Clinical Features. The first reported case of AQM was a 24-year-old woman with status asthmaticus who developed severe generalized weakness following treatment with high doses of intravenous corticosteroids and NM blockade. Subsequently, there have been numerous reports of AQM usually developing in patients who received high dose intravenous corticosteroids and/or nondepolarizing NM blockers. The myopathy can also develop in patients with sepsis or multiorgan failure who never received either corticosteroids or nondepolarizing NM blocking agents. A patient's status, post recent organ transplantation, appears to be at increased risk of AQM, perhaps due to the high doses of intravenous corticosteroids for prevention of rejection and NM blocking agents in the perioperative period. Because of their immunosuppressed state, patients undergoing transplant are also prone to infection and sepsis, which also predisposes them to AQM. The incidence of AQM is uncertain because there have been only a few prospective series published on the subject. In a study of 25 consecutive patients requiring mechanical ventilation for severe asthma, myopathy developed in 9 of 25 patients (36%), and elevated serum CK levels in 19 of 22 (76%) patients tested. The patients were treated with dexamethasone 10 mg every 8 hours or hydrocortisone 250 mg every 6 hours; 22 of the 25 patients also received vecuronium. Mechanical ventilation lasted an average of 3.1 +/- 3.1 days in patients without myopathy and 12.9 +/- 6.6 days in those with myopathy. In a prospective study of 100 consecutive adult patients undergoing liver transplantation, 7 patients developed AQM. Patients were treated with nondepolarizing NM blocking agents and high-dose steroids in the perioperative period. Three of six patients tested had elevated serum CK levels, as high as 10 times the upper limit of normal 25 days post operation. Four patients had muscle biopsies demonstrating necrosis and selected loss of myosin. Three patients later died from sepsis and multiorgan failure. The remaining patients slowly regained strength and the ability to ambulate over 1 to 3 months. Patients with AQM exhibit severe generalized weakness of the trunk, extremities, and respiratory muscles, and can rarely involve the extraocular muscles. The myopathy is usually initially recognized by the inability to wean the patient from the ventilator. Sensory examination is usually normal, but this can be difficult to determine in an intubated patient with altered mental status. Deep tendon reflexes are decreased or absent. The mortality is high at approximately 30% in one large series, secondary to multiple organ failure and sepsis, rather than the myopathy. The morbidity and mortality in AQM and critical illness neuropathy appear to be similar. In patients who survive, muscle strength recovers slowly over several months.

Laboratory Features. Serum CK levels can be normal but are moderately elevated in about 50% of patients. NCSs reveal marked reduced amplitudes of CMAPs with normal distal latencies and conduction velocities. In contrast, SNAP amplitudes should be normal or mildly reduced (<80% of the lower limit of normal). Markedly reduced amplitudes of SNAPs should lead to the consideration of CIM. However, the SNAPs may be affected if the patient has a baseline (unrelated neuropathy), and many of these patients have illnesses that are associated with neuropathy (diabetes mellitus and renal or liver failure). Thus, reduced SNAP amplitude in and of itself does not exclude AQM; in the author's opinion, most cases of weakness developing in the ICU are due to AQM and not CIM. Direct muscle stimulation may help to distinguish AQM from CIM, but these studies are fraught with possibilities of technical error. Direct muscle stimulation bypasses the distal motor nerve and neuromuscular junction (NMJ). In critical illness neuropathy or prolonged NM blockade, the muscle membranes should retain its excitability, and direct muscle stimulation CMAP (dmCMAP) should be near normal despite a low or absent nerve stimulation evoked CMAP (neCMAP). In contrast, if the muscle membrane excitability is reduced, as seen in AQM, both the neCMAP and the dmCMAP should be very low. Theoretically, the ratio of neCMAP to dmCMAP should be close to 1:1 in a myopathy, and should approach zero in a neuropathy or NMJ disorder. In this regard, absent or reduced amplitudes of the dmCMAP with neCMAP/dmCMAP ratios >0.9 were demonstrated in 11 patients with AQM, while neCMAP/dmCMAP ratios were 0.5 or less in patients with severe neuropathy.

EMG usually demonstrates prominent fibrillation potentials and positive sharp waves; however, abnormal spontaneous activity is not always evident. Early recruitment of short duration, small amplitude, polyphasic MUAPs may be seen if the patient has sufficient strength to generate any MUAPs; patients with severe weakness may be unable to volitionally recruit any MUAP. The inability to quantitate MUAP morphology and recruitment can make it difficult to distinguish AQM from CIM in patients who may have abnormal sensory conduction studies. Sequential EMG studies have reported profuse spontaneous activity and inability to actively recruit MUAPs early, followed by the appearance of small polyphasic MUAPs with early recruitment during the recovery period.

Histopathology. Muscle biopsies reveal a wide spectrum of histological abnormalities. Type 2 muscle fiber atrophy with or without type 1 fiber atrophy is common. Scattered necrotic muscle fibers may be seen. Focal or diffuse loss of reactivity for myosin adenosine triphosphatase (ATPase) activity in type 1 fibers more than type 2 fibers corresponding to the loss of thick filaments (myosin) apparent on EM is typically observed, but not in all cases. Other structural proteins (actin, titin, and nebulin) are relatively spared.

Pathogenesis. The variable laboratory, histologic, and electrophysiologic features suggest that the pathogenesis is multifactorial. Some biopsies demonstrate widespread necrosis, which certainly can
account for the muscle weakness observed in patients. The mechanism of muscle fiber necrosis is not known, and, importantly, not all patients have significant necrosis on biopsy. Myosin is selectively lost in some, but not in all patients. Calcium activated proteases (calpains) may be responsible for proteolysis of myosin. Perhaps glucocorticoids, nondepolarizing NM agents, or the milieu of critical illness induces the expression of calpains. In addition, the enhanced expression of cytokines during sepsis may, in turn, lead to a catabolic state in muscle with breakdown of proteins, glycogen, and lipid. The reduced muscle membrane excitability may be the result of a combination of factors: (1) partial depolarization of the resting membrane potential, (2) reduced muscle membrane resistance, and (3) decreased sodium currents.185,186,196,197

Omeprazole

**Clinical Features.** Omeprazole inhibits the H+/K+ ATPase enzyme system (the proton pump) at the secretory surface of the gastric parietal cell and is used for the treatment of gastric and duodenal ulcers and refluxes. Rare cases of a neuromyopathy have been reported with the use of omeprazole.180,198,199 Patients developed proximal weakness and myalgias along with paresthesias and a stocking distribution of sensory loss, predominantly in the legs. Deep tendon reflexes are diminished or absent.

**Laboratory Features.** Serum CK levels were normal or mildly elevated. NCSs were consistent with an axonal sensorimotor polyneuropathy.198 EMG revealed small polyphasic MUAPs in one patient.199

**Histopathology.** Muscle biopsies in the two reported patients revealed only type 2 muscle fiber atrophy.198,199 Superficial peroneal nerve biopsy in one patient demonstrated axonal degeneration.198

**Pathogenesis.** The pathogenic mechanism for the neuromyopathy is unknown.

Isoretinion (Accutane)

**Clinical Features.** Isoretinion is used for treatment of severe acne. Myalgias, usually in the setting of exercise, are common.200 In addition, there are a few reports of patients developing proximal muscle weakness.202

**Laboratory Features.** Serum CK levels can be normal or mildly elevated. Decreased serum carnitine levels have been reported.200 EMG revealed small polyphasic MUAPs in one patient.202

**Histopathology.** Muscle biopsy in a single patient reported demonstrated only atrophy of muscle fibers.202

**Pathogenesis.** The basis for the myopathy is not clear. The diminished carnitine levels and response to L-carnitine in some patients suggest that a perturbation of lipid metabolism may be contributory.

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**DRUG INDUCED HYPOKALEMIC MYOPATHY**

Hypokalemia can be a complication of a variety of medications (e.g., diuretics, laxatives, mineralocorticoids, amphotericin, and lithium). Further, excessive eating of licorice may have an aldosterone-like effect and cause hypokalemia. Hypokalemic myopathy has also been associated with alcohol abuse and inhalation of toluene. The clinical, laboratory, histopathological, and electrophysiologic features of hypokalemic myopathy are similar, regardless of the etiology of the hypokalemia.

**MYOPATHIES ASSOCIATED WITH ANESTHETIC AGENTS AND CENTRALLY ACTING MEDICATIONS**

Malignant Hyperthermia

**Clinical Features.** Malignant hyperthermia (MH) is caused by a genetically heterogeneous group of disorders and is characterized by severe muscle rigidity, myoglobinuria, fever, tachycardia, cyanosis, and cardiac arrhythmias precipitated by depolarizing muscle relaxants (e.g., succinylcholine) and inhalational anesthetic agents (e.g., halothane).203 The incidence of MH ranges from 0.5% to 0.0005%.203 At least 50% of patients had previous anesthesia without any problems. The signs of MH usually appear during surgery, but can develop in the postoperative period. Rarely, attacks of MH have been triggered by exercise, ingestion of caffeine, and stress.204

**Laboratory Features.** Serum CK can be normal or mildly elevated between attacks in patients susceptible to MH. During attacks of MH, serum CK levels are markedly elevated and myoglobinuria can develop. Hyperkalemia is also usually present. Metabolic and respiratory acidosis is evident with lactic acidosis, hypoxia, and hypercarbia. NCSs and EMG are usually normal. EMG shortly after an attack of MH would be expected to demonstrate increased spontaneous activity and, perhaps, small polyphasic MUAPs recruiting early. The in vitro muscle contracture test can be performed to assess the susceptibility of MH in individuals who may be at risk (i.e., family members with history of MH).203 However, the test is not routinely available. Varying concentrations of halothane and caffeine are applied to strips of muscle that are stimulated at 0.1 to 0.2 Hz for 1 to 5 seconds, while tension is measured by a strain gauge. In patients susceptible to MH, much lower concentrations of caffeine and halothane produce muscle contractions than needed in normal muscle tissue.

**Histopathology.** Muscle biopsies demonstrate nonspecific myopathic features including fiber size variability, increased internal nuclei, moth eaten fibers, and necrotic fibers after an attack of MH.

**Pathogenesis.** Some cases of MH arise secondary to excessive calcium release by the sarcoplasmic reticulum calcium channel. Increased intracytoplasmic calcium leads to excessive muscle contraction, increased use of oxygen and ATP, and overproduction of heat. Why various anesthetic agents and depolarizing muscle relaxants trigger this exaggerated release of calcium from the sarcoplasmic reticulum in predispose individuals is not known.
MH susceptibility is genetically very heterogeneous, as families have been linked to different chromosomes and genes. The first mutations were discovered in the ryanodine receptor gene located on chromosome 19q13.1 (MHS1).132,205,206 The ryanodine receptor bridges the gap between the sarcoplasmic reticulum and the T tubule. Mutations in the ryanodine receptor may result in a functional alteration of the associated calcium channel such that there is an excessive release of calcium into the cytoplasm upon activation. Of note, mutations in this gene also cause the congenital myopathy, the central core disease. Mutations in the ryanodine receptor gene account for only a minority of patients with MH; other genetic loci have been identified. MHS2 localizes to chromosome 17q11.2–q24 (possibly the gene for the alpha subunit of the sodium channel).207 Thus, MHS2 may be allelic to potassium sensitive periodic paralysis, paramyotonia congenita, and related disorders. MHS3 has been linked to chromosome 7q21–q22 (possibly to a gene encoding a subunit of the calcium channel).208 MHS4 localizes to chromosome 3q13.1, but the gene has yet to be identified.209 Mutations in the dihydropyridine receptor gene on chromosome 1q31 (allelic to hypokalemic periodic paralysis) are the cause of MHS5.210 Linkage to chromosome 5p has been demonstrated in still other families (MHS6).211 In addition, patients with dystrophinopathies are susceptible to developing MH.212 Thus, it appears that MH may occur in various myopathic disorders, affecting the structural proteins of the muscle membrane or ion channels.

Treatment. Patients at risk of MH should not be given known triggering anesthetic agents whenever possible. MH is a medical emergency, requiring several therapeutic steps.203 The anesthetic agent must be discontinued while 100% oxygen is delivered. Dantrolene 2 to–3 mg/kg every 5 min for a total of 10 mg/kg should be administered. The stomach, bladder, and lower gastrointestinal tract are lavaged with iced saline solution, and cooling blankets are applied. Acidosis and hyperkalemia are treated with sodium bicarbonate, hyperventilation, dextrose, insulin, and occasionally calcium chloride. Urinary output must be maintained with hydration, furosemide, or mannitol. The patient must be monitored and treated for cardiac arrhythmias.

MYOPATHIES SECONDARY TO DRUGS OF ABUSE

Alcohol

Chronic alcohol abuse is more often attributed to causing neuropathy than myopathy.9 However, several forms of a toxic myopathy due to alcohol have been described: (1) acute necrotizing myopathy, (2) acute hypokalemic myopathy, (3) chronic alcoholic myopathy, (4) asymptomatic alcoholic myopathy, and (5) alcoholic cardiomyopathy.2,8,9 An acute necrotizing myopathy manifests as acute muscle pain, tenderness to palpation, cramping, swelling, and weakness following or during a recent particularly intense drinking binge. The severity of the myopathy is highly variable. Severe cases can be associated with myoglobinuria and acute renal failure. The muscle cramps resolve over the course of several days, while the remainder of symptoms may last several weeks. Serum CK levels are markedly elevated during these attacks. Muscle biopsies reveal widespread muscle fiber necrosis and occasionally fibers with tubular aggregates. Disorganizing of the sarcomeres and degeneration of mitochondria may be appreciated on EM. Patients require appropriate supportive medical care and nutritional supplementation, as many are malnourished.

Alcohol abuse can lead to acute hypokalemia, which can cause generalized weakness. Muscle weakness evolves over the time period of 1 or 2 days. Serum potassium is very low, <2 meq/L, and the CK levels are elevated. Muscle biopsy performed in the acute time frame may reveal vacuoles with the muscle fibers. The myopathy resolves with correction of the serum potassium. Some alcoholics develop an insidious onset of primarily proximal limb girdle weakness, especially of the lower limbs, which has been attributed to a chronic alcoholic myopathy. Muscle biopsy may reveal scattered muscle fiber atrophy, necrosis, and regeneration. It is unclear whether the muscle weakness is caused by a toxic influence of alcohol on muscle, a toxic PN, or malnutrition.

An asymptomatic alcoholic myopathy has been suggested in some patients on the basis of elevated serum CK levels found coincidentally. There is no complaint of weakness, and the physical examination does not reveal striking evidence of a myopathic disorder. Histologic findings are not available for this class of patients, and the true nature of this presumed form of alcoholic myopathy is questionable. The elevated serum CK may be related to subclinical necrotizing myopathy, hypokalemia, or muscle trauma.

Laboratory Features. Serum CK levels may be normal or slightly elevated and potassium levels may be reduced or normal. Reduced amplitudes of the sensory and, occasionally, motor NCSs may be seen if patients have a concomitant alcoholic neuropathy. Needle EMG may reveal positive sharp waves, fibrillation potentials, and early recruitment of short duration, low amplitude MUAPs firing at high rates with minimal force production in weak muscles in patients with a necrotizing alcoholic myopathy.67,215–217

Pathogenesis. The pathogenic basis for the various forms of alcoholic myopathies is not known. The metabolism of alcohol may lead to the accumulation of toxic metabolites (e.g., acetaldehyde) or free radicals that may be toxic to lipid membranes.9

Illicit Drugs

Illicit drugs and controlled narcotics (e.g., heroin, meperidine, cocaine, pentazocine, piritramide, amphetamines, etc.) may be myotoxic.2,8,218–221 Muscle injury can be related to direct muscle trauma (e.g., needle injury), rhabdomyolysis secondary to pressure, and ischemic necrosis related to prolonged loss of consciousness, ischemia due to vasocstriction, rhabdomyolysis caused by generalized status epilepticus, or the direct toxic effects of the drugs (or adulterants) on muscle tissue. Serum CK levels should be markedly elevated, and muscle biopsies reveal widespread necrosis in such cases.

Inhalation of volatile agents (e.g., toluene) can also cause generalized muscle weakness, and occasionally, myoglobinuria. Toluene causes distal renal tubular acidosis with associated severe hypokalemia, hypophosphatemia, and mild hypocalcemia. Muscle strength returns
after correction of the electrolyte abnormalities and abstaining from inhaling volatile agents.

**SUMMARY**

Various drugs can cause muscle damage and from a variety of different mechanisms. It is imperative to take a good medical history including current and previous medication history (as well as history of illicit drug use and alcohol abuse), as stopping the offending agent usually leads to improvement of the myopathy. However, continued use can be associated with significant morbidity and even death (e.g., from myoglobinuria). The most common toxic myopathy is associated with statin use, given how frequently these medications are prescribed. With that said, most individuals treated with statin medications and other medications known to cause toxic myopathy have no complications.

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INTRODUCTION

The iatrogenic disorders of neuromuscular transmission (NMT) occur as the result of synaptic neurotoxicity. Unlike the brain, spinal cord, and nerve that are protected by their respective blood brain and blood nerve barriers, the neuromuscular junction (NMJ) is uniquely sensitive to the effects of neurotoxins because there are no barriers to protect the NMJ from the deleterious effects of circulating toxins. Neurotoxins directed to the NMJ may occur as natural substances of plants or animals, prescribed pharmaceutical compounds, environmental hazards, or weapons of terror. These agents reduce the safety factor of NMT by interfering with either the presynaptic or postsynaptic function of the NMJ, or both. The clinical features of the toxicity produced by these agents vary, as many have toxic effects on other parts of the central, peripheral, or autonomic nervous systems. Many have other systemic effects as well.

Worldwide, the most common NMT toxicity results from envenomation. However, of more concern to the clinician are the effects of pharmacologic agents that produce weakness in patients with known or preclinical disorders of NMT. All forms of NMJ neurotoxicity are characterized by progressive, typically symmetrical muscle weakness. Muscles of eye movement or the eyelids are most often involved, as are the muscles of neck flexion and the pectoral and pelvic girdles. More severe toxicity may affect bulbar or respiratory muscles, or both. Cognition and sensation are usually spared unless other parts of the nervous system are also involved. Muscle stretch reflexes are often preserved or only minimally diminished, particularly during the early phases of the illness, but may be lost if muscle weakness is severe.

PHARMACOLOGICAL BLOCKADE OF NMT

Drugs that produce worsening of NM function are classified into four categories. First, are drugs that have a direct effect on NMT in otherwise normal individuals; second, are drugs that disturb the immune system and result in the development of myasthenia gravis (MG); third, are drugs that unmask subclinical MG, or worsen muscle strength in patients with disorders of NMT (e.g., MG, Lambert-Eaton myasthenic syndrome [LEMS], botulism); and fourth are drugs that delay recovery of strength, particularly respiratory function, following general anesthesia during which NM blocking agents have typically been used.

Altered drug clearance due to renal or hepatic disease, concomitant drug administration, electrolyte disturbances, or direct toxicity may predispose patients to NM weakness in the first situation. The most common example of the second situation is the induction of MG by d-penicillamine (D-P). In the third situation, persistence of NM dysfunction after a drug has been discontinued implies that a subclinical disease had been unmasked by the drug. This is seen when previously asymptomatic patients given D-P develop weakness that does not resolve following discontinuation of the drug.

The adverse effects of drugs on synaptic transmission may be classified in three ways. They may act presynaptically, reducing acetylcholine (ACh) release by a local anesthetic like effect on the nerve terminal, by impairing calcium influx into the nerve terminal, or by reducing the synthesis of ACh in the nerve terminal, similar to the effect of hemicholinium. They may act postsynaptically, producing a curare like blockade of ACh receptors or potentiating the effects of depolarizing or nondepolarizing NM blocking
agents. Some drugs have both pre- and postsynaptic effects. Other than several reviews of adverse effects of various drugs on patients with MG or other diseases of NMT, much of the literature on this subject is anecdotal, often involving individual case reports (www.myasthenia.org/docs/MGFA_MedicationsandMG.pdf). The adverse effects of these potentially neurotoxic medications must be taken into consideration when deciding which drugs to use in patients with MG or related conditions. For most drugs, the actual incidence of adverse effects is unknown because it is impossible to determine how many at risk patients have used each drug without complication. Additionally, in vitro and animal studies may suggest an adverse drug effect that does not correlate with clinically significant side effects. While it is most desirable for these patients to avoid all drugs that may adversely affect NMT, in certain instances, they must be used for the management of other illness. In such situations, thorough knowledge by the physician regarding the deleterious side effects can minimize potential danger. When possible, it is wise to use the drug within each class that has been shown clinically, or at least experimentally, to have the most minimal effect on NMT.

Telithromycin is the only drug with a Food and Drug Administration black box warning for use in patients with MG. There are no other drugs that are absolutely contraindicated in patients with MG and LEMS with the possible exceptions of D-P, botulinum toxin (BTX), and interferon alpha. However, there are many drugs that can exacerbate weakness in these patients or prolong the active duration of muscle relaxants.

Drugs that perturb NMT produce varying degrees of ptosis, ocular, facial, bulbar, respiratory, and generalized muscle weakness, similar to MG. Treatment includes discontinuing the offending drug and potentially reversing the NM blockade with intravenous calcium, potassium, or cholinesterase inhibitors. The most frequently encountered problems in the author’s experience were the result of an administration of antibiotics (macrolides, fluoroquinolines, and aminoglycosides) and β-adrenergic blocking agents to patients with MG.

This manuscript will focus on the selected common iatrogenic causes of NMJ failure and direct the reader to a more comprehensive review.16

Antibiotics

Antibiotics are one of the most common causes of synaptic failure. Earliest reports date back to the 1940s. Currently, there are several hundred reports of purported NM weakness attributed to the use of antibiotics. Some patients were otherwise normal, others were receiving NM blocking agents or drugs with known effects on the NMJ, some had MG, and others had diseases that alter the pharmacokinetics of the drug.

Aminoglycoside antibiotics are well recognized for producing NM weakness, irrespective of the route of administration.31 The weakness is related to dose and serum levels and can be reversed in part by cholinesterase inhibitors, calcium infusion, and aminopyridines. At the NMJ, aminoglycosides may have pre- or postsynaptic effects, or both.3 For example, tobramycin has a predominantly presynaptic action that inhibits ACh release, whereas netilmicin acts predominantly postsynaptically, blocks ACh binding to the receptor similar to curare. Specific NM blocking effects have been demonstrated for amikacin, gentamicin, kanamycin, neomycin, netilmicin, streptomycin, and tobramycin. Neomycin is the most toxic of these, while tobramycin is the least toxic.

In the author’s observations, macrolide and ketolide antibiotics may acutely exacerbate myasthenic weakness.34 These include the macrolides erythromycin and azithromycin. More recently, abrupt worsening in MG has also been reported with the new ketolide, telithromycin.39 This drug was not identified as potentially dangerous to myasthenic patients until after 21,000,000 patient exposures (author’s observation).

Cardiovascular Drugs

After antibiotics, cardiovascular drugs, particularly the beta adrenergic blocking agents and calcium channel blockers, produce most of the adverse drug reactions in patients with NM disorders. The β-adrenergic blocking agents oxprenolol, propranolol, practolol, and timolol have all been implicated in causing a worsening of strength in patients with MG. Several cases have been reported of transient diplopia in patients receiving one of several ophthalmic β-blockers. Exacerbation of oculomotor weakness may occur even with β-blockers applied topically on the eye. The author has observed abrupt worsening of weakness in several MG patients after parenteral or ophthalmically applied β-blockers; other patients have had onset of myasthenic symptoms shortly after beginning one of these drugs. Studies examining the effects of various β-blockers on muscle twitch tension demonstrate a reduction in twitch tension following the application of these drugs. Repetitive nerve stimulation (RNS) studies have not shown ill effects of β-blockers given intravenously to MG patients. However, microphysiologic studies show a dose dependent reduction in the efficacy of NMT in normal rat skeletal muscle and human myasthenic muscle bathed in atenolol, labetolol, metoprolol, nadolol, propranolol, or timolol.17 Different β-blockers have reproducibly different pre- and postsynaptic effects. The reduction in miniature end-plate potential (MEPP) amplitude caused by all of these drugs suggests a postsynaptic site of action. Additional presynaptic effects are suggested by the relatively large reductions in EPP amplitude compared to MEPP amplitude, alterations in MEPP frequency caused by all except timolol, and reduction in quantal content caused by metoprolol and propranolol. Of the drugs examined, propranolol has the greatest effect on NMT; atenolol has the least. The effects of calcium channel blockers on myocardial muscle have been extensively characterized, but their effects on skeletal muscle are less understood. Studies to date have produced conflicting results: some have demonstrated postsynaptic curare-like effects, while others have shown presynaptic inhibition of ACh release or both pre- and postsynaptic effects. Oral administration of calcium channel blockers to cardiac patients without NM disease did not produce any evidence of altered NMT by...
single-fiber electromyography (SFEMG). Acute respiratory failure after beginning oral verapamil has been seen in a patient with LEMS, and in a patient with moderately severe, generalized myasthenia (Howard, JF, unpublished observations). Elderly myasthenic patients have experienced worsening of strength after receiving felodipine and nifedipine for hypertension. Low doses of verapamil or its timed release preparation have been used without problems in patients with MG (author’s observation).

Cholesterol Lowering Agents

Several published works suggest that the statin cholesterol lowering agents may be causal in the exacerbation of myasthenic weakness. The mechanism for this worsening is not clear. Statins have immunomodulatory properties, with the ability to induce production of the Th2 cytokines interleukin (IL)-4, IL-5, and IL-10. Therefore, it is possible that up regulation of Th2 cytokine production could lead to worsening of MG. Statin-induced mitochondrial failure in the nerve terminal has been proposed as a mechanism to impair NM transmission, given the high content of mitochondria in the nerve terminal. There is no evidence to suggest that HMG-CoA reductase is known to directly interfere with NM transmission. A recent editorial has suggested caution with their use in patients with MG after realizing that further study is necessary.

Immune Modulators

Generalized MG may occur after starting interferon alpha for leukemia, during interferon alpha-2b treatment for malignancy, and during treatment for chronic active hepatitis C. Recent reports have also suggested that MG may occur independently in association with hepatitis C, bringing into question the role of interferon in these patients. Expression of interferon gamma at motor endplates of transgenic mice produces abnormal NMJ function and generalized weakness that improves with cholinesterase inhibitors.

Clostridial Neurotoxins

Complications from BTX have become more frequent as the toxin has become increasingly used in treatment of focal dystonias and spasticity and most recently, for cosmetic purposes. In addition to local effects at the site of injection, BTX also has remote NM blocking effects. Dysphagia is a frequent side effect of botulinum injection for laryngeal dysphonia, and typically lasts for about 2 weeks. A prospective study of complications of BTX injection for cervical dystonia showed that prior to treatment, 11% of patients had symptoms of dysphagia, and 22% had radiologic evidence of abnormal esophageal peristalsis. After injections of BTX, new symptoms of dysphagia developed in an additional 33%, while 50% developed new peristaltic abnormalities. The dysphagia may be severe, especially when there is pretreatment dysphagia or when both sternocleidomastoid muscles are injected with large doses of the toxin. SFEMG studies of a forearm muscle following BTX injections for cervical dystonia and hemifacial spasm show abnormal increase in mean jitter. Studies performed 6 weeks after treatment also showed increased fiber density, indicating reinnervation. There may also be mild abnormalities of cardiovascular reflexes, suggesting distant effects on autonomic function. LEMS has been unmasked, and myasthenic crisis has been reported following therapeutic BTX injection. More tragic situations have also been reported. The amelioration of a profound retrocollis following BTX therapy led an inebriated and beligerant individual to murder his son by gunshot during an argument.

ENVENOMATION

Most biological toxins of animal origin affect the cholinergic system and either facilitate the release of neurotransmitter from the presynaptic nerve terminal, or block the ACh receptor. In general, bites from snakes, scorpions, and ticks are more common during summer months. In contrast, marine toxins may be encountered at any time, as they are usually acquired through ingestion and less often by injection or penetration. Specific animal envenomations occur in defined geographic areas. For example, tick paralysis occurs predominantly in states west of the Rocky Mountains, and in the western provinces of Canada and Australia. The geography of snake envenomation is species specific. Cobras are found in Asia and Africa, kraits in Southeast Asia, mambas in Africa, coral snakes in North America, and sea snakes in the Pacific near Australia and New Guinea.

Arthropods

Arthropod venoms have been known since antiquity when they were used to incapacitate prey or as a defense against predators. The few arthropod venoms that are toxic to the NMJ act by one of three mechanisms. In the first, there is an initial augmentation of ACh release followed by depletion of neurotransmitter. The second enhances ACh release without subsequent presynaptic neurotransmitter depletion. The third blocks ACh release. Untreated arthropod envenomation is fatal in 12 to 25% of cases, but with the improvement in critical care facilities in the last few decades, these intoxications are rarely fatal.

Spider Bites

Only a few spider venoms affect the NMJ. The funnel web spider and the redback spider of Australia are the most dangerous members of this group. In North America, only the bite of the black widow spider is of concern. The usual victim of a black widow spider bite is a small male child, perhaps due to their inquisitiveness in exploring nooks and crannies. Lathrotoxins in the venoms of spider genus Latrodectus (black widow spider) produce a marked facilitation in neurotransmitter release at all neurosecretory synapses including the NMJ by depolarizing the presynaptic nerve terminal and increasing Ca++ influx into the
nerve terminal.\textsuperscript{14} This depletes the neurotransmitter stores in the nerve terminal, resulting in a blockade of synaptic transmission. This toxin exerts its effects on the nerve terminal by several mechanisms. The toxin binds to neurexin and thereby activates the presynaptic protein complex of neurexin, syntaxin, synaptotagmin, and the N type calcium channel to facilitate massive ACh release. Neurotransmitter release in nerve muscle preparations, as measured by MEPP frequency, increases several hundred fold within a few minutes. There is a subsequent depletion of synaptic vesicles and disruption of the highly organized active zone region of the presynaptic nerve terminal, thus inhibiting the docking of synaptic vesicles to the terminal membrane and preventing effective recycling of vesicular membranes.\textsuperscript{15}

Symptoms begin within minutes after a black widow spider bite and reflect the massive release of neurotransmitter from peripheral, autonomic, and central synapses. Severe muscle rigidity and cramps are followed by generalized muscle weakness due to the depolarizing NM blockade. Death from cardiovascular collapse may occur in the elderly or in young children, but otherwise, black widow spider bites are rarely fatal. Treatment is primarily supportive.\textsuperscript{26} Calcium gluconate may help alleviate severe muscle cramps and rigidity. Magnesium salts may reduce neurotransmitter release if given soon after the bite. Equine serum antivenom is very effective and rapidly reverses the neurotoxic effects.\textsuperscript{6}

**Snakebites**

Venomous snakes fall into four major groups: Viperidae (true vipers), Crotalidae (rattlesnakes and pit vipers), Elapidae (American coral snake, cobras, kraits, mambas), and Hydrophiodae (sea snakes). NM blockade results primarily from the venom of Elapidae and Hydrophiodae species.\textsuperscript{25,36} One Crotalidae species, C. durissus terrificus, a South American rattlesnake, produces a potent NM blocking venom. Venoms from other rattlesnakes and pit vipers act through hematological and cardiovascular mechanisms. Venom is produced and stored in salivary glands and inoculation occurs through fangs or modified premaxillary teeth.\textsuperscript{4}

These toxins may act either presynaptically or postsynaptically. Presynaptic toxins, β-neurotoxins (β-bungarotoxin, notexin, and taipoxin) inhibit the normal release of ACh from the motor nerve terminal. There is often an initial augmentation of release followed by depletion of neurotransmitter. Presynaptic toxins tend to be more potent than the α-neurotoxins, which act postsynaptically by producing a curare mimic, nondepolarizing NM block that are variably reversible. They have a slower onset of action, a longer lasting effect, and are 15 to 40 times more potent than d-tubocurarine. Most venoms are a mixture of both types of neurotoxins, although one may predominate in a given venom. The venoms of the Hydrophiodae species are more toxic than those of land snakes and entail a lesser amount of toxin injected per bite.\textsuperscript{1} There are numerous subforms of α-neurotoxin. All suppress the release of ACh from the nerve terminal via several different mechanisms. Toxins from different species potentiate each other suggesting that they occupy different binding sites at the NMJ. Taipoxin from the Australian and Papua New Guinean taipan snake is unique. In addition to producing a potent presynaptic blockade of synaptic transmission, it also has a direct toxic effect on muscle that produces rapid muscle necrosis and degeneration. Different species vary in their susceptibility to snake toxins. For example, the venom of the Australian mulga snake is fatal in man, produces prossis in monkeys, and yet has no apparent NM blocking effect in rabbits.

The clinical course of snake envenomation follows a variable pattern. After envenomation by a pit viper or cobra, there is local pain. However, pain is often absent after bites by other Elapidae and Hydrophiodae. Swelling typically occurs within 1 hour following bites by Viperidae, Crotalidae, or the cobra, but is not seen following bites by other Elapidae (mambas, kraits, coral snakes), and Hydrophiodae. There is then a preparalytic stage with headache, vomiting, loss of consciousness, paresthesias, hematuria, or hemoptysis.\textsuperscript{3} These symptoms are not common after envenomation by cobras or mambas. The time between the snake bite and paralytic signs and symptoms varies from 0.5 to 19 hours. The first signs of NM toxicity are usually ptosis and ophthalmoparesis, although these are absent following the bite of the South American rattlesnake. Facial and bulbar weakness then develops over hours.\textsuperscript{32} Limb, diaphragmatic, and intercostal muscle weakness follows and may progress for up to 2 to 3 days. Without appropriate treatment cardiovascular collapse, seizures, and coma ensue. There is no sensory abnormality other than in the immediate area around the bite. Other systemic effects result from coagulation deficits. Cerebral and subarachnoid hemorrhage have been reported after bites from many snake species and are the leading cause of death following viper bites in several parts of the world.\textsuperscript{18}

Antivenoms are the most effective treatment for snakebites that do not contain significant amounts of phospholipase, a component of presynaptic neurotoxins. Antivenoms are used to shorten the duration of weakness. If the type of snake is known, a high titer specific monovalent antivenom is given. However, often the type of snake is not known and a polyvalent antivenom must be used. Respiratory, cardiovascular, and hematological support measures may be required. Supportive measures are the mainstay of treatment for most coral snake bite. Intensive care treatment and airway maintenance are similar to that used in MG. Cholinesterase inhibitors have been recommended when there is a predominantly postsynaptic abnormality; electrodiagnostic testing may be useful in determining whether these agents are likely to be effective.\textsuperscript{21}

**Marine toxins**

The rapid rise in marine pollution has spurred a renewed interest in marine toxins. Previously these toxins were only of interest to physiologists and pharmacologists who used them as tools for the investigation of biological systems. References to marine neurotoxins date to biblical times (Exodus 7:20–21). The reader is referred to Southcott’s review of this subject.\textsuperscript{35} Marine neurotoxins that affect the NMJ are rare and come primarily from poisonous fish, a few mollusks, and dinoflagellates. Unlike poisoning from arthropods and snakes, most marine toxins are ingested. Some marine toxins
are unique due to an increase in the concentration of toxin though successive predatory transvection up the food chain.

Conotoxins, a diverse group of toxins from predatory cone snails, inject their venom through a small harpoon like dart (Olivera and colleagues 1985). It is only the fish predatory species (Conus geographus, C. textile, C. marmoreus and C. omaria) of this mollusk that pose a danger to humans. The effects of these toxins vary among species and within a single species. Several have direct effects on the NMJ. The α-conotoxins block the binding of ACh to the ligand binding site similarly to the snake α-neurotoxins described earlier. The α-conotoxins block the voltage-gated calcium channel (VGCC) of the presynaptic nerve terminal. These α-conotoxins have played an important role in our understanding of LEMS and is used in the VGCC antibody assay for that condition. Injection of α-conotoxin is followed by intense local pain, then malaise and headache, and a progressive generalized weakness within 30 minutes. Respiratory failure often occurs within 1 to 2 hours. Most cone snail bites are preventable. These snails should be handled carefully with forceps and thick gloves. The proboscis protrudes from the small end of the shell, but is flexible and long enough to sting the holder at the other end. Live cone snails should never be placed in a pocket, as the dart can penetrate cloth. Treatment is directed toward respiratory and cardiovascular support. There is no antivenom available. There is no published information about the potential efficacy of cholinesterase inhibitors. More than 60% of reported cone snail stings have been fatal.

The most venomous fish is the stonefish, Synanceja horrida, S. trachynis, S. verrucosa found in the Indo-Pacific oceans and Red Sea, and the genus Inimicus found off the coast of Japan. The most venomous fish is the stonefish, Synanceja horrida, S. trachynis, S. verrucosa found in the Indo-Pacific oceans and Red Sea, and the genus Inimicus found off the coast of Japan.12 The toxin, stonustoxin, is inflicted by injection through 13 dorsal spines when the victim steps on the small fish buried in the sand. NM blockade occurs as the result of induced neurotransmitter release and depletion of ACh stores, similar to that of other presynaptic toxins. Envenomation produces immediate excruciating pain that may last for 1 to 2 days. Severe edema occurs due to the actions of hyaluronidase, which promotes the rapid spread of venom through the tissue. Tissue necrosis may also occur. In addition to gastrointestinal, autonomic, and cognitive difficulties, the victim may experience generalized muscle weakness due to the mechanism noted above. Death occurs from cardiotoxicity. Treatment is supportive; specific antitoxin may be helpful in some cases.

CONCLUSION

Both pharmacologic agents and evenomation can cause NMJ neurotoxicity symptoms. Clinical features of the toxicity vary and many have toxic effects on other parts of the central, peripheral, and autonomic nervous systems.

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INTRODUCTION

Neuromuscular complications of critical illness include sepsis and multiple organ failure. Critical illness occurs in many patients receiving mechanical ventilation for more than 1 week in major medical and surgical intensive care units (ICUs). The majority suffer both central nervous system and peripheral nervous system complications.1

Sepsis is defined as the systemic inflammatory response syndrome (SIRS) resulting from an infection that is bacterial, viral, fungal, or parasitic in nature. It may also occur secondary to major trauma in events such as automobile accidents, war injuries, or burns. SIRS includes the presence of one or more of the following manifestations; temperature > 38°C or < 36°C, heart rate greater than 90 beats per minute, respiratory rate greater than 20 breaths per minute, or hyperventilation as indicated by a partial pressure of carbon dioxide in the arterial blood (PACO2) less than 32 mmHg, white blood cell counts > 12,000 cells/mm3 or < 4,000 cells/mm3, or the presence of immature neutrophils.

Severe sepsis is associated with dysfunction of at least one organ, hypoperfusion, or hypotension. Septic shock occurs when sepsis induced hypotension persists, despite adequate fluid resuscitation. Multiple organ dysfunction occurs when two or more organs have altered function, in which homeostasis cannot be maintained without intervention.

The majority of these patients have the nervous system complications of septic encephalopathy,2 critical illness polyneuropathy (CIP),3 and critical illness myopathy (CIM).4 These complications appear as stupor or coma, difficulty weaning from mechanical ventilation, and limb weakness. As intensivists struggle to overcome the complex problems of sepsis and multiple organ failure, these nervous system complications are either overlooked or misdiagnosed. Stupor is attributed to sedation, weaning difficulties to diaphragmatic fatigue, and limb weakness to catabolic myopathy. With successful weaning, the patient is discharged to a general ward, where the patient experiences impaired cognition; difficulty dressing, eating, and rising from bed or toilet seat; difficulty standing and walking; shortness of breath; and fatigue. A prolonged stay in a rehabilitation center may become necessary. Without further investigation, the nature of these symptoms remains unexplained and puzzling to the patient, family, and caregivers.

Comprehensive neurological assessments will identify these nervous system complications in the ICU. Computed tomography (CT) head scans and cerebral spinal fluid examination are unremarkable in septic encephalopathy, but an electroencephalography (EEG) shows abnormalities consistent with a diffusive encephalopathy.2 Electromyography (EMG) and nerve conduction studies of the limbs, measurement of creatine kinase, and an occasional muscle biopsy, will disclose the presence and severity of CIP or CIM, or as is often the case, a combination of both conditions.1 The knowledge gained will assist in determining the need and type of sedation, adjustments in weaning procedures tailored to respiratory insufficiency, and early rehabilitation.

The least sedating method involves briefly discontinuing sedation each day and then determining the level of alertness. It is now used as a guide in managing sedation in ICUs.5 When the patient becomes alert enough, limb strength can be tested through voluntary
activation, with grading according to the Medical Research Council scale. De Jonghe and colleagues of France, utilized this method and identified 28 patients who had sepsis and multiple organ failure. These patients were also thought to have CIP and CIM, as demonstrated by subsequent electrophysiological studies and muscle biopsy. The weak patients had a longer duration of weaning from mechanical ventilation than patients who were not weak.

An early sign of CIP or CIM is observed when testing the level of consciousness in a patient who is stuporose or comatose; nail bed pressure will evoke only weak or absent limb movements, but facial grimacing will be obvious. Loss of tendon reflexes that were previously present is an early sign of these conditions.

Once respiratory or limb muscle weakness has been identified and there is improvement, no further studies are needed. However, if there is persistence or deterioration, CT head scans, electrophysiological studies, EEG, EMG, and possibly muscle biopsies are performed.

CONCLUSION

It is important to realize that only one quarter of patients with CIP and CIM would be identified by clinical examination alone, while others would be identified by electrophysiological studies. Not only do these studies identify CIP and CIM, they are also valuable in ruling out other conditions. For example, myasthenia gravis, Lambert-Eaton myasthenic syndrome, and amyotrophic lateral sclerosis may present for the first time as acute respiratory insufficiency, requiring mechanical ventilation and admission to an ICU. Thus patients with long-term neuromuscular disability and those “stuck on a ventilator” end up being managed in chronic care facilities and remain undiagnosed.

Recent electrophysiological studies have provided new insights into the pathophysiology of these conditions. Measurements of nerve excitability in CIP indicate that motor axons are depolarized through raised extracellular potassium and hypoperfusion. Excitability studies of muscle in CIM have revealed reduced muscle fiber conduction velocity and conduction block.

In the future, electrophysiological monitoring may be particularly useful. EEG monitoring would disclose the varying affects of sedation, septic encephalopathy, or a combination of both. The simple recording of the compound muscle action potential (CMAP) of the thenar muscle by stimulating the median nerve at the wrist would detect a drop in amplitude as an early sign of CIP and CIM. Park and colleagues, as well as Allen and colleagues have shown that a characteristic increase in the duration of CMAP in addition to a drop in amplitude, is specific for CIM. For research purposes, these methods would be sensitive to changes induced by interventions designed to elevate sepsis and its nervous system complications.

REFERENCES

It Hurts Everywhere But My Shoulder
A Collaborative Approach to Upper Extremity Pain

David B. Shuster, MD
Douglas A. Gordon, MD, FRCSC
Marc Trzeciak, DO
Rannie Al Samkari, MD
Michael A. Herbenick, MD
John C. Kincaid, MD

2009 COURSE H
AANEM 56th Annual Meeting
San Diego, California
It Hurts Everywhere But My Shoulder
A Collaborative Approach to Upper Extremity Pain

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Dr. Shuster received his Baccalaureate from the University of California, San Diego where he developed and taught a gymnastics class for people with disabilities thus inspiring his interest in Physical Medicine and Rehabilitation. Shuster received his medical degree from Creighton University School of Medicine and completed his residency and masters degree at the University of Washington Department of Rehabilitation Medicine.

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Dr. Shuster served as USA Team Physician at the World Maccabiah Games in Israel and has given numerous international presentations on musculoskeletal problems in athletes who use wheelchairs and more recently the Patient Centered Practice. He helped develop, and currently teaches in, the musculoskeletal course at the Boonshoft School of Medicine, Wright State University which integrates electrodiagnostic medicine and spinal cord injury medicine into the second year curriculum.

Presently, Dr Shuster is in the private practice of Electrodiagnostic Medicine focusing on patient centered care that optimizes the experience of the patient and referring physician.

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Please be aware that some of the medical devices or pharmaceuticals discussed in this handout may not be cleared by the FDA or cleared by the FDA for the specific use described by the authors and are “off-label” (i.e., a use not described on the product’s label). “Off-label” devices or pharmaceuticals may be used if, in the judgement of the treating physician, such use is medically indicated to treat a patient’s condition. Information regarding the FDA clearance status of a particular device or pharmaceutical may be obtained by reading the product’s package labeling, by contacting a sales representative or legal counsel of the manufacturer of the device or pharmaceutical, or by contacting the FDA at 1-800-638-2041.
Goals—After attending this session, participants will (1) understand the differential diagnosis of musculoskeletal problems affecting the hand, wrist, forearm, and elbow, (2) understand the anatomy and clinical examination relevant to these disorders, (3) be able to conceptualize the diagnostic approach to these disorders, (4) understand the pathophysiology and treatment strategies for these disorders, and (5) understand the value of the integration of these disorders into the electrodiagnostic medicine consultation. This course has been structured as an interactive experience with questions and discussion playing prominently in the process.

Prerequisite—This course is designed as an educational opportunity for physicians.

Accreditation Statement—The AANEM is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education (CME) for physicians.

CME Credit—The AANEM designates this activity for a maximum of 3.25 AMA PRA Category 1 Credit(s). If purchased, the AANEM designates this activity for 2 AMA PRA Category 1 Credit(s). This educational event is approved as an Accredited Group Learning Activity under Section 1 of the Framework of Continuing Professional Development (CPD) options for the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada. Each physician should claim only those hours of credit he or she actually spent in the educational activity. CME for this course is available 10/09 - 10/12.
### 2008-2009 AANEM COURSE COMMITTEE

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### 2008-2009 AANEM PRESIDENT

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INTRODUCTION

Physicians specializing in electrodiagnostic (EDX) medicine are asked to examine patients who are experiencing numbness, tingling, pain, and weakness. Pain and apparent weakness may be due to the musculotendinous unit exclusively, or may be caused in combination with the joint that it crosses to provide function. It is the responsibility of the physician to understand the differential diagnoses affecting these structures. Of equal importance is the occurrence of bony or musculotendinous pathology which may coexist with nerve pathology. Musculotendinous disorders and bone and joint disorders may influence nerve disorders and be the direct cause of apparent weakness and pain, or may be associated with nerve pathology.

Although electrodiagnosis primarily involves the lower motor neuron, EDX physicians should also understand the musculotendinous and bony problems that affect patients seen in consultation. This will also help the patient better understand and differentiate the various causes of symptoms, as well as assist the referring physician in determining appropriate care for the patient.

Knowledge of the neuromusculoskeletal system as the unit of function provides clinicians with a more educated clinical impression and helps them determine whether or not symptoms are due to a nerve problem. Physiologic evidence of nerve pathology including demyelination, conduction block, and axonal loss is often found. It is the physician’s responsibility to determine how these findings correlate with symptoms experienced by patients. Doing so reinforces the need for physicians to perform EDX consultations. It is important for EDX medicine physicians to go above and beyond the realm of the lower motor neuron.

These thoughts are echoed in the American Association of Neuromuscular and Electrodiagnostic Medicine’s (AANEM) position statement Proper Performance and Interpretation of Electrodiagnostic Studies. It emphasizes the need for synthesis of the patient’s history and physical examination with the nerve conduction study (NCS) and needle electromyography (EMG) data to reach the diagnosis.

The AANEM believes that training should include clinical aspects of neurologic and musculoskeletal conditions and strongly recommends that EDX procedures be performed by physicians with comprehensive knowledge of neurological and musculoskeletal disorders to assure accurate interpretation and diagnosis.¹

Dillingham² emphasizes the importance of differentiating musculoskeletal problems from entrapments, plexopathies, and radiculopathies and states, “It is often useful to the referring physician if the electrodiagnostician comments on other clinical conditions that were identified during the work up, such as shoulder impingement syndrome or lateral epicondylitis. Such observations can reveal other treatment alternatives in addition to addressing the electrodiagnostically confirmed disorders.”

Clairmont³ also includes musculoskeletal diagnoses in the differential for patients presenting for EDX medicine consultation.

Building a Better EMG: Integration of Musculoskeletal Problems in Electrodiagnostic Medicine Consultation

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INTRODUCTION

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Clairmont³ also includes musculoskeletal diagnoses in the differential for patients presenting for EDX medicine consultation.
Electrodiagnosis, however, is not just a simple test. It involves clinical diagnoses that may include non-nerve disorders. The EDX physician must be skilled in interpreting individual results and integrating those interpretations into the patient’s clinical picture. O’Dell emphasizes the overlap between the examination and clinical presentation of the neurologic and musculoskeletal systems and includes the neurologic and musculoskeletal systems as essential elements of the physiatric history and physical examination. NCSs and EMG are best considered an extension of the clinical examination.

Dillingham found that in patients referred with a questionable cervical radiculopathy, non-nerve diagnoses commonly explained some component of the complaint, and that 68% of patients with a negative EMG had non-neurologic diagnoses.

The idea of a unifying diagnosis for all of the patient’s complaints is appealing, but often unrealistic. As EDX medicine physicians, the ability to differentiate which symptom is caused by which pathology is of utmost importance.

Phalen, an orthopaedic specialist, emphasized the neurologic differential diagnoses in his original work on carpal tunnel syndrome. As EDX medicine physicians, it is vital to address the multiple causes of upper extremity pain and the overlap of neurologic, musculotendinous, and bony pathology that is so commonly seen in patients. Any findings must be interpreted with regard to the patient’s symptoms.

Expertise in diagnosing the problems that patients present with and the ability for EDX medicine physicians to provide clinical direction, is proportion to the value of the referring physician, the payor, and most importantly, the patient.

Since many patients present with musculoskeletal disorders as a component of their symptoms, it is incumbent upon the physician to have the expertise to diagnose these problems.

REFERENCES

INTRODUCTION

Common pathologies, especially those suggested by objective testing, present some special diagnostic challenges and pitfalls that are not often identified and discussed. Carpal tunnel syndrome (CTS) is one of these pathologies, as it is by far the most common neurological condition seen in the upper extremities (UEs) and therefore, is the one addressed most frequently by the electrodiagnostic (EDX) physician. While most agree that CTS is a clinical diagnosis supported by positive test results, this distinction often becomes clouded or forgotten in today’s fast paced and market-driven practice of medicine. It becomes easy to bypass elements of the patients’ history and physical examination and infer the diagnosis based on EDX studies alone. This process is what I have labeled “tunnel vision.” This can affect physicians of all specialties unless there is constant awareness of its influence and vigilance asserted in its prevention.

CASE PRESENTATION

Many years ago, during my first year of practice, I became acquainted with the case of a 39-year-old white male who was right-hand dominant and in good general health. He presented to the emergency room (ER) with sudden onset of painful cramping and diffuse paresthesias in the left UE. The ER physician performed a full cardiac work up, but all testing was negative. The patient was told he might have CTS and was sent home with analgesics and a cock-up wrist splint. He was directed to follow up with his family physician.

After the occurrence of several additional episodes, the patient’s primary care physician examined him, then referred him to a neurologist for EDX studies to “rule out CTS.” The study showed a mild increase in both motor and sensory latencies in the median nerves at both wrists, with the left side slightly worse than the right. There was no axonal loss, but the EDX physician noted some minimal increased diffuse insertional activity in several muscle groups. The report returned to the family physician read “bilateral median neuropathy at the wrist consistent with CTS, left greater than right.” The patient was told to wear the cock-up wrist splint for an additional 10 days. When no improvement was noted, he was sent to a surgeon for carpal tunnel release.

The surgeon examined the patient and reviewed a copy of the EDX study. He was able to elicit a mildly positive Tinel sign and positive Phalen test bilaterally. Surgery was scheduled for the following week. The intervention was uneventful and there were no complications. Although the wound healed well, the patient continued to experience episodes of pain and paresthesias exclusively in the left UE, and felt that he was losing strength. At one postoperative visit, he was noted to have facial asymmetry and was thought to have developed Bell’s palsy.

The surgeon referred the patient to an ear, nose, and throat (ENT) specialist who concurred with the diagnosis of Bell’s palsy, but to rule out any compressive lesion of the facial nerve, a computed tomography (CT) scan of the base of the skull was ordered. The X-ray technician performing the scan misread the requisition and...
included the entire head. A large right intracranial parietal mass, consistent with a glioblastoma, was identified. This ultimately proved to be the correct diagnosis.

What went wrong in this case? An ER physician had diligently ruled out acute coronary problems and other life-threatening conditions and had suggested CTS, knowing that it was a common condition causing paresthesias in the UEs. Providing the patient with a splint was a benign method of providing treatment in the acute setting, thinking that the patient would undergo a more complete evaluation when he saw his primary care physician. However, knowing that the patient had just presented to the ER, the primary care physician assumed that he had undergone a detailed physical examination. The ER physician had concluded that the patient suffered from CTS and provided him with a splint for treatment. His symptoms were, in fact, paresthesias in the UE, thus it all seemed very clear. The fact that the splint had not helped to improve his symptoms was viewed as an indication of severity.

Referring the patient to an EDX physician to “rule out CTS” seemed to be the next logical step in confirming the diagnosis. If it had been effectively ruled out by EDX testing, then some other evaluation would have become necessary. The physician did exactly as requested and checked the patient for CTS. This seemed to be entirely reasonable, given the results of the EDX study. The report was carefully worded, noting that the findings were consistent with CTS, yet not specifically stating that the patient actually had the condition. This distinction was not appreciated, however, and for the primary care physician, the diagnosis was now clearly established. When symptoms did not resolve with conservative measures, sending the patient to a surgeon seemed to be the next logical step.

The surgeon saw a patient referred with an established and documented diagnosis that had failed conservative protocols and needed symptom relief. With a positive Tinel sign and Phalen test, further proof seemed unnecessary. The need for surgery was clearly indicated and was performed with expertise. When the patient was seen to have sudden onset facial paralysis in the postoperative period, Bell’s palsy, a common condition causing sudden facial paralysis, was immediately evoked. When the ENT specialist was asked to see a patient with Bell’s palsy, there was no reason to doubt the diagnosis, but for comprehensive measures, the CT scan was ordered. Each specialist involved responded diligently and responsibly to the physician who referred the patient to him or her with an established diagnosis. Oddly enough, it was the technician, by accident, that enabled the actual diagnosis to be made.

In summarizing this case, the patient’s heart was fine, his asymptomatic carpal tunnel was cured, and there was no compressive neuropathy of the facial nerve. However, he died from glioblastoma within 6 months of the onset of his symptoms. None of his physicians were at fault, except in their unquestioning acceptance of their predecessor’s diagnoses. Knowing the real diagnosis earlier probably would have changed nothing in the evolution of the patient’s disease, but he might have spent his last few months of life more comfortably than in having and recovering from a carpal tunnel release.

While this was not my patient, I could picture myself as being any one of the competent physicians who had simply accepted the common diagnoses that had been provided to them. It was at that time that I made a personal decision and commitment to consistently complete a detailed history and physical examination relative to the head, neck, and UEs on all patients referred with a diagnosis of CTS or those presenting with complaints of numbness or paresthesias.

QUANTIFYING THE PROBLEM

In 1986, Chaplin and associates1 looked at 175 consecutive patients referred for hand pain, numbness, or weakness and found that 100 (57%) had CTS clinically, while 75 (43%) did not, and were diagnosed with some other problem. Nathan2 found in 1988 that 17% of the workers he studied had abnormal nerve conduction studies (NCSs). In that group, only 62% had signs and symptoms of CTS, while 38% had none. Bingham and associates3 reported in 1996 on 1021 industrial applicants with an average age of 30.1 years. Of these, 17.5% had abnormal NCSs in at least one hand, however, only 10% acknowledged any CTS symptoms.

Approximately 5 years after this case, in a presentation for the Quebec Orthopedic Association, I presented an informal and retrospective look at 370 patients who had been referred for CTS4 and had undergone a detailed examination. All of the patients had EDX studies that were suggestive of median nerve compression at the carpal canal.

Of the 370 patients, four groups (Table 1) were identified from the detailed examination, additional testing that was performed, and follow up visits. Group 1 patients (N=103, 28%) were found to have CTS as their only diagnosis, and as the only source of their symptoms in the UEs. Group 2 patients (N=177, 48%) were found to have CTS as an important part of their presentation, but also had one or more additional pathologies that contributed significantly to their symptoms. Group 3 patients (N=27, 7%) had either occasional mild symptoms of CTS at some point in their lives, or had positive provocative tests, but these elements had played no part in their decision to seek medical attention. Any presenting symptoms could be entirely accounted for by some other pathology. Finally,

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients referred for Carpal tunnel syndrome (CTS), N=370</th>
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</thead>
<tbody>
<tr>
<td>Group 1: CTS only clinical pathology</td>
<td>N = 103 (28%)</td>
</tr>
<tr>
<td>Group 2: CTS + one or more additional pathologies</td>
<td>N = 177 (48%)</td>
</tr>
<tr>
<td>Group 3: No CTS symptoms but history or (+) provocative tests</td>
<td>N = 27 (7%)</td>
</tr>
<tr>
<td>Group 4: No CTS</td>
<td>N = 63 (17%)</td>
</tr>
</tbody>
</table>
Proximal compression of the radial nerve, posterior interosseous syndrome or pronator syndrome, was present in 5% of patients. Nerve proximally, either in the form of anterior interosseous nerve coidosis, and others. Compressive neuropathy of the median nerve was common in 5% of patients. These included a wide variety of pathologies such as idiopathic ganglion cysts, stroke, multiple sclerosis, focal dystonia, isolated Raynaud's disease, syringomyelia, Parsonage-Turner syndrome, Charcot-Marie-Tooth disease, and many others. The figures add up to 129%, meaning that about one third of the patients had more than one additional pathology generating their symptoms.

**Table 2** Other pathologies contributing to, or responsible for, patients’ symptoms

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Compressive neuropathy, ulnar nerve</td>
<td>37%</td>
</tr>
<tr>
<td>Tenosynovitis</td>
<td>21%</td>
</tr>
<tr>
<td>Cervical radiculopathy/neuralgia</td>
<td>14%</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>12%</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>9%</td>
</tr>
<tr>
<td>Pain dysfunction/hypersensitivity</td>
<td>8%</td>
</tr>
<tr>
<td>Epicondylitis</td>
<td>6%</td>
</tr>
<tr>
<td>Systemic inflammatory/metabolic disease</td>
<td>5%</td>
</tr>
<tr>
<td>Compressive neuropathy prox. median nerve</td>
<td>5%</td>
</tr>
<tr>
<td>Compressive neuropathy prox. radial nerve</td>
<td>4%</td>
</tr>
<tr>
<td>Other/diverse</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>129%</strong></td>
</tr>
</tbody>
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Thus, approximately one out of three patients had more than one non-carpal tunnel syndrome pathology.

Group 4 patients (n=63, 17%) had never experienced any symptoms of CTS, nor did they have any positive provocative tests. All of their symptoms could be explained by some other entity.

Group 2, 3, and 4 patients (N=267, 72%) all had other conditions that either contributed to or were entirely responsible for their symptoms (Table 2). Compressive neuropathy of the ulnar nerve (37%) was the most common, with most cases located at the cubital tunnel and a few others at the ulnar tunnel and Guyon's canal. Tenosynovitis was frequently present (21%) and most commonly involved the digital flexor sheaths, but also the first and second wrist extensor compartments (deQuervain's disease and intersection syndrome), and the fourth and sixth compartments. Cervical radiculopathy, or cervical neuralgia, was part of the presentation in 14% of these patients. Osteoarthritis generated significant symptoms in 12%, with the basal thumb at the carpometacarpal joint the most common site, but also with the wrist, fingers, shoulder, and elbow sometimes involved. Peripheral neuropathy was significant in 9%, mostly in diabetic and alcoholic patients, but also with a few idiopathic cases. Pain dysfunction was present in 8%, typically in the form of hypersensitivity from a previous injury or in some cases, complex regional pain syndrome (CRPS). Some of these patients had also been diagnosed with fibromyalgia. Epicondylitis was seen in 6%, and included both the medial and lateral sides. The medial side was often associated with cubital tunnel syndrome in which case both conditions were counted separately. Previously undiagnosed or uncontrolled systemic inflammatory and metabolic diseases contributed significantly in 5% of patients. These included rheumatoid arthritis, lupus, diabetes, gout, hypothyroidism, sarcoidosis, and others. Compressive neuropathy of the median nerve proximally, either in the form of anterior interosseous nerve syndrome or pronator syndrome, was present in 5% of patients. Proximal compression of the radial nerve, posterior interosseous nerve syndrome, and radial tunnel syndrome, were seen in 4% of patients. In 8%, other diverse and more unusual conditions were found to be important contributors to the patients' symptoms. These included a wide variety of pathologies such as idiopathic ganglion cysts, stroke, multiple sclerosis, focal dystonia, isolated Raynaud's disease, syringomyelia, Parsonage-Turner syndrome, Charcot-Marie-Tooth disease, and many others. The figures add up to 129%, meaning that about one third of the patients had more than one additional pathology generating their symptoms.

**DISCUSSION**

Most physicians have an ultimate goal of helping patients find relief of their symptoms following carpal tunnel release. If the decision to operate on patients is based on the results of EDX studies alone, only the patients in Group 1 (28%) would have been expected to experience complete relief of their symptoms post-operatively. If patients from Group 2 are included, 76% would be expected to find significant improvement following surgery, though 48% would be expected to have some residual symptoms due to other sources. This leaves 24% of patients (Groups 3 & 4) without expected gains of clinical improvement from the surgical intervention. Avoiding surgery on patients who don’t display signs or symptoms of CTS while simultaneously treating or identifying and separating out secondary pathologies would potentially improve the success rate dramatically. Using this model, one would predict that reported success rates for carpal tunnel release could vary between 28% and 100%, depending on how attentive one was to elements independent of the positive EDX studies.

In searching the literature for the highest and lowest published success rates for carpal tunnel release, the results are predictably variable. In 2004, Manktelow and associates\(^5\) reported on 984 workers' compensation cases. Only 14% of patients were symptom free 4 years after carpal tunnel release. In 2006, Schmelzer and associates\(^6\) studied 486 patients, most having had bilateral surgeries (753 hands), stating that 100% obtained symptom relief. Clearly, until tunnel vision has been overcome, optimal care can not be offered to patients, and CTS research will remain seriously flawed.

The case of the patient described earlier raises the question as to how five competent and conscientious physicians from five different specialties, who had the knowledge and experience necessary to orient the patient’s investigation appropriately on their first encounter, accepted their predecessors' diagnoses without question. A likely answer is each physician perceived their role to be that of a consultant applying his or her technical expertise within their field of specialization to an existing pathology. Each physician, in responding to the requests of colleagues, performed tests and services required of them and assumed that the patient had either been or would be questioned and examined at length by another physician.

The ER physician’s perceived role was to rule out and treat urgent life-threatening conditions. The family physician’s perceived role was to be responsible for referring the patient to the appropriate specialists for diagnosis and treatment. The EDX physician's...
perceived role was to perform and interpret a complex test. The hand surgeon's perceived role was to perform a delicate operation. The ENT specialist perceived his role as confirming the presence of a typically idiopathic and benign condition. Although each fulfilled their perceived roles impeccably, none of them viewed themselves as the patients’ physician, seeking the true source of his symptoms.

If the implications of inferring the existence of a common condition from a test result combines with a tendency to accept an existing diagnosis without question, it is clear that a nearly automated system of patient evaluation based on test results alone has been created. It bypasses the wealth of true expertise held by physicians in clinical diagnosis. With diminishing reimbursements for patient care and increased legal scrutiny of the results, there is constant pressure to spend less time with patients, yet generate legally correct documentation. The physician who takes the time to listen to and clarify a patient’s complaints, while asking and obtaining answers to the appropriate questions and thoroughly examining that patient, must be willing to accept financial punishment.

Furthermore, automated nerve conduction devices have gained popularity and may bypass the EDX physician’s expertise altogether. Certainly these devices generate objective data, however they also are consistent in attaching appropriate legal disclaimers. NCSs have been, and will continue to be, the gold standard in diagnosing chronic compressive neuropathy of the median nerve at the wrist. However, automated devices can neither question nor examine patients relative to other pathologies in the UEs, and thus can never be the gold standard for diagnosing CTS. By using these devices as “screening” tests and applying the principles of “tunnel vision”, the number of unnecessary surgeries will continue to increase while the overall success rate for carpal tunnel release decreases.

Having taught orthopedic residents for over 20 years, a trend toward reliance on objective testing and the “tunnel vision” that accompanies it proves to be one of the great challenges facing the future of the medical profession. The motivation to learn how to perform a good extremity examination requires the conviction that it holds value in the decision making process. When residents observe experienced physicians moving rapidly on to the next patient after performing only a cursory examination and requesting orders for a magnetic resonance image (MRI) or EDX study, they see little reason to spend time and energy learning how to perform a detailed examination, ultimately making them even more dependent on test results in their own future practices. As a new generation of future professors, this trend becomes irreversible. As stated in the case previously described, technicians respond to the requests of colleagues’ by ordering or performing additional tests or procedures, whereas physicians respond to their patients’ needs by seeking the underlying source of symptoms. Sadly, in acting as technicians, physicians not only lose sight of the patients’ needs, but are also deprived of the intellectual process that is an intense and rewarding part of a career in medicine.

**REASONS FOR THIS SESSION**

Throughout a career as a hand surgeon, evaluating and treating patients with UE problems and operating on many patients with CTS, it has been a privilege to enjoy the collaboration of expert and conscientious EDX physicians in a local practice environment. In patients who clinically present with symptoms of CTS, that expertise is relied upon to quantify the extent of involvement and to identify and clarify coexisting nerve pathologies. Although they are not asked to make a diagnosis, any suggestions in regards to findings that may point to contributing pathologies are always welcome. This type of collaboration has been highly effective through the years in finding the source of patients’ symptoms. As a physician, the final responsibility for confirming CTS as a correct diagnosis lies with me, and personal success and failure rates must be accounted for. In an ideal scenario, this model of collaboration would be the rule rather than the exception.

However, in personal experience, 80 to 90% of patients referred for paresthesias in the UEs have already undergone EDX studies prescribed by their primary care physicians and have been “diagnosed” with CTS. EDX physicians are most often the first specialists to see patients referred for CTS and provide the report that is often pivotal in further investigation and treatment. As suggested in the case described, these patients may not have complained of anything more specific than UE pain or paresthesias, but are being screened, often with the words “rule out CTS” simply because it is a common condition. The referring physician often believes that he or she is sending the patient for diagnosis and believes that if the test is positive for CTS, then the quest is over. If, as suggested, only 62 to 76% of patients with positive NCSs actually suffer from CTS, and if the majority of those also have major symptoms from other pathologies then the role as a clinical diagnostician becomes equally as important as the role as an EDX physician.

One may wonder why this has to be your task? Why not simply generate a strong generic disclaimer such as “other conditions not detected by these studies may be present and should be thoroughly evaluated by the referring physician”? The answer would be that you have no more to offer than an automated nerve conduction device. These devices are programmed to generate similar disclaimers because they have no capacity to clinically evaluate patients, not because their measurements are inaccurate. The role of the disclaimer is not provided to generate better patient care, but is simply stated to protect the manufacturer from legal action. Instead of addressing a patient’s specific needs, only those of the legal system are included. The omission of personal observations in a specific patient represents the essence of why professional expertise cannot be replaced by a computerized device.

While there are many highly specialized fields of expertise, the role of physician and patient advocate requires those practicing in the medical field to become familiar enough with other pathologies to be able to orient patients toward appropriate investigation and treatment. Though it is unnecessary to have detailed knowledge of all conditions affecting the UEs, it is important to recognize the more common pathologies, with the concentration on clinical diagnostic findings, rather than on treatment.
SUMMARY

In today's medical climate, objective testing is favored over clinical evaluation. Objective testing takes a fraction of the time to accomplish and offers legal protection in the case of poor outcomes. It also favors the expedient assumption that a positive test result establishes a clinical diagnosis and may propagate a chain of decisions that no longer have bearing on the patient’s needs. This process is what the author has labeled “tunnel vision”. CTS is the most common cause of paresthesias in the UEs and is easily “diagnosed” with objective testing. Evidence shows that chronic median nerve compression at the carpal canal may be present without generating symptoms, or at least not those that prompt the patient to seek medical care. Even competent and conscientious physicians can be enticed onto this path if they perceive themselves as providers of technical expertise rather than as clinical investigators. By paying particular attention to signs and symptoms unrelated to the positive EDX, the diagnosis of CTS can be confirmed or assist in establishing appropriate alternatives. Consideration of other pathologies in the UEs can help avoid the pitfalls of tunnel vision.

REFERENCE

INTRODUCTION

Primary idiopathic osteoarthritis (OA) describes the degeneration of articular cartilage without clear etiology. Accurate characterization of pain by patients can help lead to the source of pathology and appropriate treatment. It is crucial to differentiate pain due to nerve pathology from that of bone, joint, or tendon.

This manuscript deals with common types of joint pain caused by AO, including related structures in the differentials. It describes the pathologies, clinical presentations, and examinations.

THUMB CARPOMETACARPAL JOINT ARTHRITIS

Thumb carpometacarpal (CMC) joint arthritis, also called trapeziometacarpal (TM) or basal joint arthritis, has an increased prevalence in postmenopausal women. The distal interphalangeal joint is the most commonly involved site of disease, followed by the TM joint. However, the latter can cause far more significant functional disability secondary to painful, weakened pinch and grip.

Symptoms include pain at the base of the thumb, particularly with pinch and grip. Forceful lateral pinch (e.g., brushing teeth, turning a key, opening a jar, or picking up a book) often exacerbates pain; it is frequently associated with a sensation of movement or "slipping" within the joint. History may include pain with pinching and gripping activities. Difficulty turning keys, opening jars, and gripping doorknobs are classic complaints.

Radiographically, 25% of postmenopausal women show degenerative changes in the TM joint, but only 1 in 3 has symptoms. In general, symptoms of AO may not correspond to the level of radiographic disease.

Yao and Park recently demonstrated the importance of differential diagnoses, including DeQuervain's tenosynovitis, flexor carpi radialis tendonitis, extensor carpi radialis longus and brevis tendonitis, scaphoid pathology, scapho-trapezial-trapezoid (STT) joint pathology, flexor tenosynovitis, and carpal tunnel syndrome (CTS).

RADIAL SIDE HAND AND WRIST PAIN

Pain on the radial side of the hand and wrist can be due to soft tissue and bony disorders.

Differential diagnoses associated with such pain include:

1. Intersection syndrome (tendinopathy of the wrist extensors in the distal radial forearm)
2. DeQuervain's tenosynovitis (tendinopathy of the tendons within the first dorsal compartment of the wrist)
3. Scaphoid injury (acute or chronic)
4. AO of the STT joint
5. Instability, synovitis, or AO of the CMC joint (CMCJ)
6. Instability, synovitis, or AO of the metatarsophalangeal joint (MPJ)
7. Stenosing (or nonstenosing) tenosynovitis of the thumb (trigger thumb or non-triggering trigger thumb)
8. AO of the interphalangeal joint (IPJ) of the thumb
BASAL JOINT ARTHRITIS

The patient who presents with basal joint arthritis may complain of palmar-sided pain at the base of the metacarpal. On inspection, he or she may have the “shoulder sign”—a prominence at the base of the metacarpal, with a step off between the thumb metacarpal and the more proximal trapezium, typically in a dorsoradial direction. Enlarging prominence or “shoulder sign” inevitably develops at the base of the thumb metacarpal. It is the clinical manifestation of dorsal metacarpal subluxation on the trapezium and metacarpal adduction.

This prominence may be due to inflammation, subluxation of the metacarpal on the trapezium, or osteophytes. In most cases, swelling around the joint is visible in patients with symptomatic degenerative disease. In some, the thumb MPJ may be hyperextended. The base of the metacarpal may be stiff or contracted in an adducted position.

Most patients present with insidious onset of pain at the basal joint of the thumb or thenar eminence, with weakness and activity-related pain, particularly with pinch and grip maneuvers.

Pain with pressure is a classic complaint from those with arthritic changes in the joint. In CMCJ arthritis, patients have pain with palpation of the volar side of the CMCJ, directly proximal to the thenar eminence.

Clinical Examination

Accurate diagnosis is essential. Effective treatment, based on that diagnosis, should be directed specifically at the area of pathology.

The “grind test” increases the contact stress on the CMCJ, causing pain when an axially directed force is applied to the thumb metacarpal. Patients with MPJ and IPJ arthritis also have tenderness on palpation. The grind test is performed by applying axial compression, flexion, extension, and circumduction; if positive, these cause pain, and possibly, crepitus.

Further examination demonstrates tenderness along the thumb TM joint. Pinch strength testing shows decreased strength. Range of motion is almost always limited, and correlates with the degree of degenerative joint change.

A careful neurologic examination should be performed as part of the complete physical evaluation. Florack and colleagues found an association between CTS and CMJC arthritis; 43% of patients evaluated or treated for CMJC degenerative changes also met the criteria for CTS.

STT ARTHRITIS

STT arthritis produces a more subtle, aching pain, not always associated with grasp. Pain is increased with extremes of wrist motion, more so in flexion and extension, but can occur in all planes. STT arthritis is rarely isolated; it is usually associated with CMC arthritis.

Clinical Examination

Because TM and STT arthritis often occur together, patients commonly present with complaints of basilar thumb pain. Pressure applied one thumb breadth proximal to the CMC joint causes pain. The extremes of passive wrist range of motion do as well. If arthrosis of both joints is present, it may be difficult to clinically differentiate between the two conditions.

In isolated STT arthritis, pain is often localized as more medial, within the thenar eminence. It is described as a deep ache, not necessarily associated with thumb motion.

ULNAR SIDED WRIST PAIN

More common causes of ulnar sided wrist pain include pisotriquetral (PT) joint arthritis and flexor carpi ulnaris (FCU) tendonitis.

PT Joint Arthritis

The pisiform is a sesamoid bone that acts as a lever (much like the patella and quadriceps muscle) to enhance the function of the FCU muscle. PT joint AO is a degenerative disease that involves the articular surfaces of the pisiform and triquetrum. Early recognition of the pathologic process is important.

Primary AO of the PT joint is uncommon. The typical pathophysiology involves posterior lateral corner (PLC) component injury that leads to PT joint instability, with subsequent arthrosis. Ryan calls injury-related ulnar palmar wrist pain in the vicinity of the pisiform the pisiform ligament complex syndrome.

Many arthritic disorders of this joint are posttraumatic and preceded by chronic PT joint instability. In some cases of pisiform instability, neurologic symptoms may be present. Of important note is that the medial wall of Guyon canal is formed by the pisiform putting it in proximity to the ulnar nerve. Therefore, neurologic symptoms may be present in some cases of pisiform instability.

FCU Tendinopathy

FCU tendinopathy is probably caused by degenerative changes within the FCU tendon near its insertion in the pisiform. Paley and colleagues found that FCU tendinopathy is the cause of symptoms in 44% of patients with ulnar palmar wrist pain. It is often associated with other conditions as well, including PT joint arthritis.

Clinical Presentation

Ulnar palmar wrist pain may radiate distally toward the hypothenar area or proximally along the FCU and ulnar aspect of the forearm. The pain can be vague and poorly defined, but is often located in the hypothenar area. It can also be deep, and occasionally radiates dorsally. It is aggravated by wrist motion or activities of daily living. In severe cases, pain may occur when the patient is at rest.
Examination reveals tenderness over and around the pisiform. Tenderness can also be elicited over the PT joint immediately dorsal to the pisiform. Snapping or popping sensation in the ulnar palmar area may be produced with active wrist motion because of pisiform subluxation. Tenderness and pain proximal to the pisiform area can be caused by FCU tendinopathy.

**Clinical Tests**

Ulnar palmar pain due to PT arthritis can be provoked by full passive wrist extension.

The pisiform tracking test is a provocative maneuver that elicits pain, and possibly crepitation and is performed by flexing the wrist to relax the FCU tendon and moving the pisiform ulnarly and radially in a grinding like motion against the triquetrum.

**SUMMARY**

Common types of arthritic pain occur in the thumb CMC joint and the PT joint. Ulnar-sided wrist pain is typically caused by FCU tendinopathy. STT arthritis often presents with TM joint arthritis. It is essential to differentiate hand and wrist pain due to nerve pathology from that related to bones, joints, or tendons.

**REFERENCES**

INTRODUCTION

Hand and wrist pain are common reasons for visits to physicians. Patients present with general complaints of pain, numbness, tingling, and varying degrees of functional loss. Conditions that affect the tendons of the hand and wrist have a multitude of etiologies. Physicians are tasked with diagnosing and treating the different disorders while deciding what tests to perform and what referrals are necessary.

Tendinitis refers to inflammation of a tendon, while tenosynovitis refers to inflammation of the synovial lining of a tendon sheath. Causes include inflammatory conditions, such as rheumatoid arthritis (RA), amyloidosis, calcific tenosynovitis (gout), and pyogenic tenosynovitis (bacterial, mycobacterial, and viral). These can lead to tendon rupture. Tenosynovitis has also come to describe the reactive thickening that occurs with tendon entrapment.

Stenosing tenosynovitis (tendovaginitis) is characterized by narrowing or stenosis of the tendon’s retinacular sheath. This leads to tendon entrapment. The term tenosynovitis is misleading because of the lack of inflammatory tissue associated with tendon entrapment. Tendon entrapment occurs at the narrow fibro-osseous tunnels that act as fulcrums for acute angulation of wrist and digital tendons. Motion of the tendon through these tunnels causes hypertrophy and fibrosis of the retinacular sheath, resulting in edema, impeded gliding, and catching or locking of the swollen flexor tendon. In response, the sheath thickens over time with fibrocartilagenous metaplasia. Pathology findings show thickening, nodularity, and attritional changes within the tendon, with gross thickening of the overlying sheath. Patients present with both functional deficits and pain.

This manuscript discusses the etiology, pathophysiology, diagnosis, and treatment options for common causes of hand and wrist pain attributed to tendinitis and tenosynovitis of the hand and wrist.

ANATOMY OF THE TENDONS AND TENDON SHEATH

The dorsum of the wrist has six extensor compartments. The extensor retinaculum is a transverse band of thickened fascia 3 cm in width. This functions as a pulley for the extensor tendons that run in the six compartments beneath it. The compartments are numbered one through six from radial to ulnar. The first compartment contains the abductor pollicis longus (APL) and extensor pollicis brevis (EPB) tendons; the second contains the extensor carpi radialis longus and brevis (ECRL and ECRB) tendons; the third, the extensor pollicis longus tendons; the fourth, the extensor digitorum communis and extensor indicis proprius tendons; the fifth, the extensor pollicis longus tendons; the fourth, the extensor digitorum communis and extensor indicis proprius tendons; the fifth, the extensor digiti quinti tendon; and the sixth, the extensor carpi ulnaris (ECU) tendon. Each of the tendons within these compartments is surrounded by tenosynovium, which begins just proximal to the proximal edge of the retinaculum and continues distally to the level of the metacarpal bases.

On the palmar aspect of the wrist, flexor tendons and one nerve pass into the hand through the carpal tunnel. The tunnel is formed by two carpal bones on each side—the trapezium and scaphoid on the radial side, and the hamate and pisiform on the ulnar side. The roof is formed by a thick ligament, the flexor retinaculum. Nine flexor tendons traverse the tunnel. These include the flexor digitorum superficialis and flexor digitorum profundus (FDP) to the index, long, ring, and small fingers, as well as the flexor pollicis longus (FPL) to the thumb interphalangeal joint. The final structures to pass through include the median nerve as well as the tenosynovium that surrounds the flexor tendons. The FPL tendon runs in a separate tendon sheath.
The tendon sheaths of the index, middle, and ring fingers extend from mid-palm to the distal interphalangeal joints. The sheaths of the thumb and small finger continue proximally into the carpal tunnel. The flexor tendons within the digits are enclosed in a snug fibro-osseous canal that is lined by synovium.

Doyle described the flexor tendon sheath as a double-walled structure with two layers: visceral and parietal. The parietal layer is in contact with the pulley system, while the visceral layer adheres to the tendon as the epitenon. These two layers form a hollow tubular structure. The sheath begins at the metacarpal neck level at the A1 pulley and extends distally to just proximal to the distal interphalangeal joint. There are five annular and three cruciate pulleys for each digit, with two annular and one cruciate pulley for the thumb; these make up each fibro-osseous tunnel. In the thumb, the flexor sheath communicates with the radial bursa, while the small finger flexor sheath communicates with the ulnar bursa. The radial and ulnar bursa have a potential space of communication known as Parona's space. It lies between the fascia of the pronator quadrates and the FDP conjoined tendon sheath.

Vascular and nutrient supply to the flexor tendons arises from direct vessels and diffusion from the synovial fluid. Figure 1 depicts the flexor tendon sheath and the pulley system.

SPECIFIC DISORDERS

Stenosing Tenosynovitis

Stenosing tenosynovitis refers to mechanical impingement of a tendon in the hand or wrist caused by narrowing of its sheath. Inflammation and thickening of the sheath result in tendon entrapment. A size mismatch between the tendons and the tunnel they pass through creates this problem. The term tenosynovitis is misleading because of the lack of inflammatory tissue associated with tendon entrapment. Tendon entrapment occurs at the narrow tunnels that act as fulcrums for acute angulation of wrist and digital tendons. Motion of the tendon through these tunnels causes hypertrophy and fibrosis of the retinacular sheath, resulting in edema, impeded gliding, and catching or locking of the swollen flexor tendon. In response, the sheath thickens over time with fibrocartilaginous metaplasia.

De Quervain's tenosynovitis and trigger digit are the most common examples of stenosing tenosynovitis.

The etiology of tendon entrapment continues to be ill-defined. However, the condition tends to cluster among certain patients who have co-affliction with carpal tunnel syndrome, trigger digits, de Quervain's disease, and epicondylosis. Women are affected far more often than men. The age distribution has remained relatively the same despite an increase in tools that require repetitive motion, such as computer keyboards. Different causes have been proposed, but none have been confirmed. These include activities that involve repetitive finger flexion and forceful grip, such as welding and constant handheld tool work. A study by Trezies and colleagues found no significant difference between the occupational distribution of patients with trigger digits versus the general population.

Patients present with catching or locking of the digit in flexion, clicking, and pain, mainly at the palmar base of the digit. Also, the digit can lock in flexion and require passive manipulation into full extension. This creates significant reluctance to fully flex and extend the digit, leading to secondary contractures at the proximal interphalangeal joint. Inability to perform daily activities is common.

Treatment of trigger digits involves both conservative and surgical means. Conservative management involves activity modification, nonsteroidal anti-inflammatory drugs, splinting, and steroid injection. Surgical management involves release of the A1 pulley. If the patient's history shows that a specific activity is associated with the onset of triggering, then avoidance of that activity may result in spontaneous resolution. However, spontaneous resolution is rare.

For patients who do not have a contraindication, such as renal disease or peptic ulcer disease, nonsteroidal anti-inflammatory drugs may be added to an initial treatment regimen. Splinting is another conservative treatment option. This has shown some success in patients with mild triggering who refuse steroid injection.
or surgery. However, splinting can lead to stiffness and contracture. Steroid injection is the mainstay of conservative management. Results have been widely successful. However, positive outcome is reduced in patients with rheumatoid arthritis and diabetes mellitus. (See Table 1 for success rates of corticosteroid injections for trigger digit.11-13)

Surgical release of the A1 pulley is effective when nonoperative means have failed. An oblique or longitudinal incision distal to the metacarpophalangeal joint (MP) flexion crease centered over the MP joint is made. Neurovascular bundles are protected bilaterally. The A1 pulley is incised longitudinally for complete release. Patients begin digital range of motion exercises immediately8 Figure 2 describes the location of incision for A1 pulley release.

De Quervain's Tenosynovitis

The first dorsal compartment lies over the radial styloid and contains the APL and EPB tendons. These tendons pass through a tight fibrous tunnel that extends approximately 2 cm in length. Tendon entrapment leading to pain and disability is common. Activities that require frequent abduction of the thumb and ulnar deviation of the wrist cause tension on the tendons passing through the tunnel and create friction that leads to swelling and narrowing of the canal. Patients present with radial-sided wrist pain aggravated by movement of the thumb. De Quervain's tenosynovitis affects women six times more frequently than men. The average age is the fifth or sixth decade of life.

Physical examination reveals tenderness to palpation over the first dorsal compartment 1-2 cm proximal to the radial styloid, and pain with passive movement of the thumb into the palm and ulnar deviation of the wrist (Finkelstein's test). Treatment initially involves splinting of the thumb in radial abduction and the wrist slightly extended, as well as corticosteroid injection and anti-inflammatory medication. The success rate with injections of various corticosteroid formulations ranges from 62-93%.9

Table 1  Success rate of corticosteroid injection for the treatment of trigger digit

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Steroid Preparation</th>
<th>Findings</th>
<th>Number of Digits</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newport et al.10</td>
<td>1990</td>
<td>Betamethasone</td>
<td>1-3 injections: 77% overall success</td>
<td>338</td>
<td>Single digit and &lt; 6 month duration of symptoms showed favorable result.</td>
</tr>
<tr>
<td>Griggs et al.11</td>
<td>1995</td>
<td>Betamethasone</td>
<td>50% success in diabetics: 72% NIDDM 44% IDDM</td>
<td>121</td>
<td>Statistically significant increase in failure rate in IDDM patients.</td>
</tr>
<tr>
<td>Kolind-Sorensen12</td>
<td>1970</td>
<td>Hydrocortisone</td>
<td>67% overall success 78% in &quot;primary&quot; trigger digits</td>
<td>106</td>
<td>Only 50% success in patients with RA or DM</td>
</tr>
</tbody>
</table>

DM = diabetes mellitus; IDDM = insulin dependent diabetes mellitus (type 1); NIDDM = noninsulin-dependent diabetes (type 2); RA = rheumatoid arthritis.
Intersection Syndrome

Intersection syndrome involves stenosis of the second dorsal compartment. This compartment contains the tendons of the ECRL and ECRB. Intersection syndrome, a rarer form of stenosing tenosynovitis than de Quervain’s tenosynovitis, has been associated with similar activities, such as frequent repetitive motions of the wrist.

The patient presents with pain and swelling 4 cm proximal to the radiocarpal joint. Erythema and crepitus may be present. These symptoms are often confused with de Quervain’s tenosynovitis. Treatment is mainly conservative with activity modification, splinting, and steroid injections as described for de Quervain’s. Surgical management involves release of the second dorsal compartment.

ECU Tendinitis

Tenosynovitis involving the sixth dorsal compartment is not uncommon and usually presents as ulnar-sided wrist pain. Patients usually present with a history of twisting injury to the wrist. Dysesthesias along the course of the dorsal sensory branch of the ulnar nerve can be present. On examination, tenderness is elicited from palpation over the tendon sheath. It is not uncommon for this condition to present with other tendon entrapments, ligament injuries of the wrist, and carpal tunnel syndrome. To help distinguish ECU from ligamentous injury, lidocaine is injected into the sheath. If this results in immediate relief, it confirms the diagnosis. Referral to a hand surgeon is very important to help diagnose and treat this disorder. Treatment involves ice, splinting, anti-inflammatory medications, and steroid injection.

CONCLUSION

Tenosynovitis—whether acute, infectious and related to bacterial inoculation of the flexor tendon sheath, or stenosing, with mechanical impingement of the tendons that traverse fibro-osseous tunnels in the wrist and hand—is a highly common cause of pain in the hand and wrist. Patients do not typically present with neurological symptoms, but the condition can result in impaired function or debilitation. Proper diagnosis and treatment allow patients to continue a functional, pain-free lifestyle.

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Non-Neurologic Causes of Elbow Pain

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LATERAL ELBOW PAIN

Lateral Epicondylitis

Lateral epicondylitis is a common source of morbidity in the general population. The characteristic patient with lateral epicondylitis is an adult in their fourth or fifth decade of life. Men and women are affected equally, with symptoms typically seen in the dominant arm. Although nonsurgical measures and time usually provide relief, a greater number of patients than previously assumed may continue to experience symptoms. Approximately 80% of patients with newly diagnosed lateral epicondylitis report symptomatic improvement at 1 year.1 Although most patients may experience mild residual symptoms, only 4-11% who seek medical treatment will require surgical intervention.2-5

The extensor carpi radialis brevis (ECRB) origin is the most commonly cited anatomic location of lateral epicondylitis pathology. Histologic sections of this area show noninflammatory angiofibroblastic tendinosis with neovascularization, a disordered collagen scaffold, and mucoid degeneration.5 The overall presentation is consistent with a pattern of repetitive microinjury and healing attempts.

Pain over the lateral aspect of the elbow is the most consistent symptom of lateral epicondylitis. This pain is usually sharp and is exacerbated by activities involving active wrist extension or passive wrist flexion with the elbow extended. A characteristic complaint is pain in the lateral elbow that prevents patients from being able to hold items or pick them up with the forearm pronated.

The initial treatment of lateral epicondylitis remains nonsurgical; options for therapy are wide-ranging and well-published. No single approach has demonstrated superiority over any other. In fact, the literature suggests that the best predictor of outcome is the amount of daily physical strain as opposed to the specific treatment rendered. Rest, consisting of varying degrees and duration of activity limitations, and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to manage acute lateral epicondylitis. These simple interventions work on the tendon to reduce inflammation, relieve strain, and provide time for healing. Although lateral epicondylitis is characterized as a noninflammatory condition, NSAIDs may relieve pain from associated synovitis or acute inflammation in the surrounding supportive adipose, connective, and muscle tissue.6

Physical therapy is often prescribed for lateral epicondylitis. Since the literature supports more than one therapeutic philosophy, the most effective mode of therapy and treatment duration is a matter of debate.7-10 Prescribed orthotic devices include the proximal forearm band and the cock-up wrist splint. The goal of using these products is to reduce tension at the extensor origin, allowing time for the area to heal.

Steroid injections have been used to treat the acute pain of lateral epicondylitis, allowing patients to begin rehabilitation. Short-term data show that after a brief period of postinjection discomfort, pain relief with steroids is significantly better compared to other treatment methods. However, longer-term data indicate that those who receive steroid injections have the same, if not worse, outcomes than those in other treatment groups.11 Altay and colleagues12...
found no difference in results at 1 year in a comparison of lidocaine injection to lidocaine and steroid injection into the extensor origin. In addition to the common side effects of skin depigmentation and fat atrophy, steroids decreased collagen production and tenocyte replication, and were associated with common extensor tendon rupture. Botulinum toxin, platelet rich plasma (PRP), and extra-corporal shock waves are all being examined as possible nonoperative treatment regimens for epicondylitis.

Surgical treatment of lateral epicondylitis is considered only in the small number of patients who fail to improve after a prolonged attempt with nonsurgical management. Poor prognostic factors for successful nonoperative approaches include manual labor, dominant arm involvement, long duration of symptoms with high baseline pain levels, and poor coping mechanisms. Current data suggest that open and arthroscopic procedures are similarly effective.13,14

**POSTEROLATERAL ROTATORY INSTABILITY**

Posterolateral rotatory instability (PLRI) of the elbow is a clinical syndrome first described by O’Driscol and colleagues in 1991.15 PLRI usually results from a dislocation of the lateral ligamentous structures with subsequent failure to adequately heal. Patients commonly present with symptoms of clicking, snapping, clunking, locking, or even recurrent instability. These often occur in the extension half of the arc of motion, with the forearm in supination. Patients may report that the elbow feels loose or slides out of joint when they engage in activities, particularly weight bearing ones. They are often apprehensive about performing actions that precipitate the instability, such as pushing on armrests while getting up from a chair.

On initial examination, patients will appear to have a normal elbow. It is usually not tender and has a full pain-free ROM (ROM). Patients may have some degree of hyperextension, particularly with atraumatic PLRI. Although varus stress may feel uncomfortable, varus and valgus stress typically do not precipitate instability or much pain. The clinical examination is usually unremarkable except for the posterolateral rotatory instability test.15 Other tests include prone and chair pushups described by Regan and Morrey.16 Treatment options range from splinting to surgical repair or reconstruction of the torn lateral structures.16

**OTHER CAUSES OF LATERAL ELBOW PAIN**

The diagnosis of lateral elbow pain should exclude several conditions that produce similar symptoms to lateral epicondylitis. Radial tunnel syndrome, or compression of the posterior interosseous nerve (PIN), may be difficult to differentiate from lateral epicondylitis. Maximal tenderness in radial tunnel syndrome is typically noted 3-4 cm distal and anterior to the epicondyle over the mobile wad. Resisted wrist extension may not be painful in radial tunnel syndrome, but it is in lateral epicondylitis. Resisted thumb and index finger extension may be painful in radial tunnel syndrome, but not in lateral epicondylitis. Resisted forearm supination may be painful in radial tunnel syndrome because of compression of the PIN within the supinator muscle. Lateral epicondylitis and radial tunnel syndrome may coexist in up to 5% of patients.17

A careful examination is warranted to identify the patient with intra-articular pathology, such as radiocapitellar chondral lesions. Estimates of concurrent intra-articular pathology range from 11% to 69%.18,19 Ruch and colleagues reported on a group of patients with posterolateral plica causing refractory lateral elbow pain. The most suggestive physical examination findings included a painful clicking at terminal extension and forearm supination, as well as maximal tenderness over the posterior radiocapitellar joint.20

**MEDIAL ELBOW PAIN**

**Medial Epicondylitis**

Medial epicondylitis is far less prevalent than its lateral counterpart, with the latter occurring 7 to 20 times more frequently.21 The condition often occurs in baseball pitchers and in those who participate in a variety of other sports and occupational activities that create valgus force at the elbow.22 Medial epicondylitis is characterized by pain along the medial elbow that is worsened by resisted forearm pronation or wrist flexion. Tenderness is usually distal and lateral to the medial epicondyle, most often over the pronator teres and flexor carpi radialis. The ROM of the elbow and that of the wrist are usually complete. Normal strength and sensation are typically noted in the extremity. Concomitant ulnar neuropathy can exist with medial epicondylitis, causing varying degrees of diminished sensation in the ring and little fingers, as well as a Tinel sign at the elbow.

The basic principles of nonsurgical treatment for lateral epicondylitis apply to medial epicondylitis as well. After exclusion of any other pathologic causes for the pain, the indications for surgical treatment include persistent pain at the medial elbow that is unresponsive to a well managed nonoperative program lasting a minimum of 6 to 12 months. Open debridement and tendon repair is the surgical procedure of choice.23

**Valgus Instability**

Ulnar collateral ligament (UCL) injury has become a well recognized entity in overhead throwing athletes, with baseball pitchers identified as being at high risk. Jobe and colleagues24 developed the original UCL reconstruction, and described their repair technique and initial results in 1986.

Patients usually describe a gradual onset of localized medial elbow pain during the late-cocking or acceleration phase of throwing. Pain is typically located over the ulnar collateral ligament and can be differentiated from medial epicondylitis by the location of tenderness. Valgus instability testing and a Milking Test can help support the diagnosis of a UCL tear.
Surgical intervention is indicated for competitive athletes with acute complete ruptures of the UCL or chronic symptoms secondary to instability who show no significant improvement after at least 3 to 6 months of nonoperative management. UCL reconstruction techniques are effective in decreasing pain and returning high-level athletes to throwing.25

ANTERIOR ELBOW PAIN

Complete Distal Biceps Rupture

Once thought to be an uncommon injury, distal biceps tendon ruptures are being seen with increasing frequency. Most would agree that anatomic repair to the radial tuberosity is necessary to obtain strength and endurance in supination and flexion.26 Rupture of the distal biceps tendon can be disabling for individuals who require upper extremity strength for vocational and recreational activities.

The condition happens when an unexpected extension force is applied against a contracting biceps muscle. Rupture probably occurs through a tendon weakened by intrasubstance degeneration or external impingement. The history and physical examination are usually sufficient to make the diagnosis. The hallmark is a palpable defect in the distal biceps, which is accentuated by attempted elbow flexion. Weakness on supination is easily demonstrated; flexion weakness is more subtle. Magnetic resonance imaging (MRI) is usually not necessary, except when differentiating among biceps tendon degeneration (tendinosis), cubital bursitis, and partial distal tendon ruptures. Immediate surgical repair of the ruptured biceps tendon is advocated for optimal return of function.27 The results of late repair are less predictable for return of strength, but activity-related pain is diminished.

Partial Distal Biceps Rupture

The difficulty in treating patients with partial tears of the distal biceps tendon lies in proper diagnosis. Cubital bursitis, with or without concomitant bicipital tendinosis, and partial ruptures can both present with pain in the antecubital fossa; furthermore, both conditions may be present at the same time. Prior to the advent of MRI, pathologic changes within soft tissue could only be inferred from the history and physical examination. MRI allows direct assessment of these changes. This has helped define the pathology of the distal biceps tendon.

Partial distal biceps tendon ruptures that fail to respond to nonoperative treatment are best managed surgically. Most partial ruptures occur at the insertion into the radial tuberosity. The most successful surgical results for symptomatic partial ruptures have been achieved by releasing the remaining portion of the biceps tendon from the tuberosity, debriding the frayed tendon end, and anatomic reattaching the tendon to the radial tuberosity as if there were a complete rupture.28,29

POSTERIOR PAIN

Triceps Tendinitis/Tears

Triceps tendon ruptures are exceedingly rare and usually occur with a forceful eccentric contraction of the triceps that causes avulsion of the tendon from the olecranon. This is most commonly seen in weight lifters. Complete ruptures of the triceps tendons should be treated with surgical repair.

Triceps tendinitis is a common cause of posterior elbow pain centered on the tip of the olecranon at the triceps insertion. A chronic traction spur can be seen in patients on plain X-ray, but is not always present. Patients have reproduction of pain at the insertion site with resisted extension at mid-flexion (approximately 60 to 90 degrees). Treatment is usually supportive as most patients respond to nonoperative management. Partial excision of the degenerative tendon and repair is performed on those who fail to improve after 6 to 12 months of nonoperative treatment.

Valgus Extension Overload/Posterior Impingement

Posterior elbow impingement of the olecranon against the ulna is commonly related to olecranon osteophyte formation posteriorly. This pathologic entity is associated with the end result of valgus extension overload, commonly seen in the throwing athlete with chronic medial instability.

Repeated impaction of the posteromedial olecranon in the olecranon fossa leads to chondromalacia and subsequent hypertrophic spur and osteophyte formation, especially in the medial aspect of the ulnar notch.31 Postero medial impingement results in pain during throwing at the terminal phase of extension and during activities requiring forced extension.

These hypertrophic osteophytes and traction spurs can frequently be observed on X-ray, especially on the axial olecranon view. Patients commonly complain of posterior pain with passive or active extension, and typically have a loss of extension relative to the contralateral side. Treatment is aimed at decreasing pain nonoperatively, with NSAIDs and rest. Persistent symptoms are treated with arthroscopic or open resection of the posteromedial olecranon and scar tissue. Ulnar nerve dysfunction can commonly coexist.32
OTHER CAUSES OF ELBOW PAIN

Primary Osteoarthritis of the Elbow

Primary osteoarthritis (OA) of the elbow is a relatively rare disease, affecting < 2% of the population. Unlike OA of other joints, OA of the elbow is characterized by the relative preservation of articular cartilage and the maintenance of joint space, but with hypertrophic osteophyte formation and capsular contracture. At the elbow, OA is characterized by pain, stiffness, mechanical symptoms, and weakness. OA has an idiopathic etiology, but is associated with heavy use of the arm. It is most commonly seen in men with a history of heavy use of the extremity, such as manual laborers, weight lifters, and throwing athletes.

Loss of terminal elbow extension and impingement-type pain at terminal extension and flexion are common in the earlier stages of the disease process. In the later stages, the elbow progresses to a greater degree of motion loss and pain in the mid-arc of motion. Usually, patients will report that it is painful to carry heavy objects at the side of the body with the elbow in extension. Treatment of OA of the elbow initially consists of NSAIDs and activity limitation. Operative interventions include open or arthroscopic debridement, open ulnohumeral arthroplasty, interposition arthroplasty, or total elbow arthroplasty.

Loose Bodies

Loose bodies are a common cause of elbow pain and locking types of symptoms. A loose body is often produced by a traumatic event, repetitive injury, or arthritic process. Pain and locking occur most commonly in the anterior or posterior aspects of the elbow joint. Loose bodies can be seen on plain X-ray or MRI. Arthroscopic or open removal is the treatment of choice.

Elbow Contracture

Elbow contractures typically occur after a traumatic event. The most common location for a soft tissue contracture is from the anterior capsule. Treatment consists of static and dynamic splinting, as well as pain management. Early ROM following an injury is critical to prevent stiffness. Operative intervention, with either open or arthroscopic anterior capsular release, is required when patients fail to progress with physical therapy.

Heterotopic bone formation can also occur in the posttraumatic patient. It most commonly requires open resection of the heterotopic bone when functional limitations are significant.

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Overview of Neuromuscular Disorders Causing Upper Extremity Pain

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INTRODUCTION

Daily experience in the electrodiagnostic (EDX) medicine laboratory underscores the importance of familiarity with musculoskeletal causes of neck, shoulder, arm, and hand pain. Conditions in this group of disorders must always be considered in the differential diagnosis of patients sent to the electromyography (EMG) laboratory.

This manuscript reviews neurogenic disorders that cause shoulder and upper extremity pain, with an emphasis on cervical radiculopathy and brachial plexopathy. Suspected plexopathy can be an intimidating diagnostic call for inexperienced clinicians and EDX physicians. It requires a firm grasp of peripheral nerve and muscle anatomy, and knowledge of the typical clinical presentations and patterns of EDX abnormality in radicular and peripheral nerve lesions. EDX studies are also very important for defining the severity of the lesion and establishing the prognosis.

EDX EVALUATION

General Principles

Cervical radiculopathies produce abnormalities characteristic of lesions of the ventral and dorsal nerve roots proximal to the level of the sensory ganglion cell.6,10,11 Plexopathies demonstrate the pattern of a lesion arising at or distal to the sensory ganglion cell-spinal nerve level. The sensory ganglion cell bodies are located along the dorsal roots at the level of the spinal forams.

Lesions of the dorsal roots proximal to the level of the sensory ganglion cells, such as radiculopathies or nerve root avulsions, do not produce aberrations of the sensory nerve action potentials (SNAPs) because the sensory cell bodies and peripherally directed axons remain intact. Lesions at or peripheral to the cell bodies can cause Wallerian degeneration in the sensory axons supplying the limbs. Nerve conduction studies in patients with plexopathies should show irregularities in SNAPs in clinically involved territories. The response amplitude tends to be more abnormal than latency or velocity.

Motor conduction studies may also be abnormal if the site of the lesion is the nerve root or plexus component of the affected peripheral nerve. As long as sufficient axons remain to produce a detectable response, results will show an “axonal” pattern of reduced compound muscle action potential (CMAP) amplitude, but only mild slowing of velocity. F waves may deviate from the norm in involved territories, but many of the plexus type lesions affect nerves that do not lend themselves to standard F-wave study. Involvement of the C8 nerve root or the lower plexus may produce ulnar or median F-wave deviations. F waves from C5 to C7, or upper and middle plexus pathways, cannot be recorded by standard techniques.

Other conduction techniques for evaluation of very proximal segments are available. These include stimulation at the nerve root and Erb’s point, and magnetic stimulation. This author is not convinced that these advanced techniques add any significant information to the evaluation of patients with radiculopathy or plexopathy.
Technical challenges are associated with all of them, and unless the physician is very familiar with the testing methods, the results should be interpreted with caution.

Needle examination is very important in differentiating radiculopathy from plexopathy, or lesions of the nerve trunks. Needle examination results help define the territory of involvement and also establish severity, chronology, and prognosis. Acute radiculopathy tends to produce both limb and paraspinal deviations because the lesion is located proximal to the bifurcation of the ventral and dorsal rami. However, irregularities in fibrillation and positive waves in paraspinal muscles are not always demonstrable. Showing abnormalities in at least two different muscles that are in the same myotome, but supplied by different nerves is a reasonable goal.

Proper timing of the needle examination in relation to the start of the lesion is important to assure the best yield from the evaluation. At least 3 to 4 weeks need to pass from onset before acute abnormalities like positive sharp waves and fibrillation potentials can be seen. Nerve root lesions more often affect a single spinal level, while those in the plexus tend to show aberrations spanning more than one radicular or peripheral nerve territory. When plexopathy is suspected, the most abnormal muscles should also be evaluated in the contralateral limb. Even if there is no obvious clinical deficit, irregularities may be present bilaterally in some of the plexus lesions.

The needle examination can also be very valuable for detecting recovery before it may be evident on clinical examination. Low amplitude, highly polyphasic, unstable motor unit action potentials (MUAPs) in clinically abnormal muscles indicate that reinnervation is occurring. At times, these might be seen even when no visible contraction is present. Waning abundance of fibrillation potentials or positive sharp waves can also be a sign of nascent improvement. Long duration, high amplitude, stable configuration MUAPs indicate that reinnervation is complete. If there are myokymic discharges in limb muscles, postradiation plexopathy or neuropathy is the likely cause of dysfunction.

**RADICULOPATHY**

Cervical radiculopathy is an important cause of neck, shoulder and arm pain, and neurological dysfunction of the limb. Patients are often referred to the EMG laboratory for evaluation when this condition is being considered. Cervical radiculopathy is about one-tenth as common as lumbar nerve root involvement. The cervical nerve roots can be compressed by disk herniations, or in more chronic situations, by osteophytes.1,6,7,11

In the cervical region, the nerve root exits above the vertebral body with the same number, except C8. For example, a disc herniation between the C5 and C6 vertebrae compresses the C6 nerve root. C8 is the exception to this rule because there are 8 cervical nerve roots but only 7 cervical vertebrae. A herniated disc between C7 and T1 compresses the eighth nerve root. Caudal to C8, the nerve roots exit below the vertebral body of the same number.

C7 is the most commonly involved root and accounts for 70% of cases of cervical radiculopathy. C6 is affected in about 20% of cases. C8 is the symptomatic nerve root in approximately 6% of patients, while C5 is affected in an estimated 2% of patients. Familiarity with the dermatome and myotome patterns of these nerve roots is very important. To some degree, these are reviewed below, in the brachial plexopathy section.

An experienced clinician can be reasonably confident about the affected spinal level based on the distribution of pain. Pain is perceived in the spinal segment’s sclerotome or sensory territory of the deep soft tissue and joint components. It may result from compression of the nerve roots and the spinal nerve, or be generated by nociceptive nerve endings in the disrupted disk, i.e., “diskogenic pain.” C6 tends to produce pain at the top of the trapezius, tip of the shoulder, anterior upper arm, and the radial forearm. The pain of C7 lesions tends to be perceived in the spine of the scapular, posteroaxial upper arm, elbow, and dorsal forearm.

With C8 involvement, pain is experienced in the medial forearm. Medial scapular pain is a feature of all of these levels. Neck motion tends to be limited by pain, and neck motion, particularly extension, makes it worse. Coughing and sneezing also tend to increase the pain of cervical radiculopathy. Disc herniations located very laterally may produce paresthesias and weakness, but little pain.

**BRACHIAL PLEXUS**

**Anatomy and Function**

The brachial plexus is formed from axons arising from the ventral rami of cervical 5 down through thoracic 1. The sensory innervation follows a logical sequence in the form of the dermatomes, and translates logically into the trunks and cords of the plexus. C5 supplies the radial side of the forearm, and C6, the thumb and index finger. These are upper trunk plexus territories. C7 is represented in the middle and ring fingers and passes by the middle trunk. C8 supplies the fifth finger and ulnar side of the hand. T1 innervates the ulnar side of the forearm. Both of these roots merge into the lower trunk and medial cord.

At first encounter, the organization of the motor supply seems less logical, but it conforms to an understandable pattern once the scheme is grasped. C5 and C6 control shoulder motions and elbow flexion. The suprascapular, axillary, and musculocutaneous nerves mediate those functions and are derivatives of the upper trunk of the plexus. The C6 and C7 levels mediate wrist extension and flexion via axons that enter the upper and middle trunks then pass into the lateral and posterior cords before terminating in the median and radial nerves. C7 is the major root level for elbow extension.

Those axons enter the posterior cord and then the radial nerve. Finger flexion and extension are mediated by the C7 and C8 spinal levels. The middle and lower trunks and then the posterior and medial cords are the conduits for these axons, which are destined for the radial and median nerves. The intrinsic hand muscles of
both the median and ulnar territories are supplied by the C8 and T1 spinal levels. The lower trunk and then medial cord is the pathway for those axons. The median and ulnar nerves are the target.

**LESIONS**

Etiologies of brachial plexus lesions include trauma, autoimmune inflammation, neoplastic infiltration, previous therapeutic radiation, as well as an inherited predisposition. The principles of EDX evaluation for differentiating these types of lesions are discussed above.

**Trauma**

Trauma acts through traction on both neural and supportive tissues. Lesions occur at the myelin sheath, axonal, vascular, and supportive tissue levels. Gunshot and knife wounds disrupt these tissues. Forces acting downward on the shoulder tend to damage the upper portion of the plexus. Abducting forces tend to involve the lower portion of the plexus. The effects of birth trauma are easy to appreciate in this type of paradigm. A fetus whose shoulder impacts on the mother’s pelvis while the head is being delivered experiences caudally directed forces on the shoulder and plexus. An upper plexus-type pattern of involvement is seen with deficits in shoulder abduction, external rotation, and elbow flexion. This is the classic pattern of Erb’s palsy. Posterior and anterior displacing forces on the shoulder, such as during falls, can affect all portions of the plexus.

Downward traction on the shoulders and plexus from improperly fitting backpacks can cause injury. Incorrect positioning or use of retractors during surgery can also result in plexus trauma. Lower trunk abnormality after median sternotomy and deficits after shoulder joint replacement are other examples of traumatic plexopathy. An important issue in traumatic conditions is whether the lesion is in the plexus or actually at the nerve root level, such as in nerve root avulsion. Depending on the site, the prognosis may be markedly different. The principles of EDX evaluation for differentiating these types of lesions are discussed above.

**Inflammatory and Idiopathic**

Plexopathy can be due to presumed inflammatory lesions that occur after systemic infections and vaccinations. This type of plexopathy can also be idiopathic. It is not clear whether the target of the inflammation is the vascular supply of the plexus or the neural structures. These lesions tend to affect the upper portion of the plexus, but individual nerves from this area may be involved in apparent isolation. The condition tends to begin with spontaneous onset of pain in the neck, shoulder, and upper arm area.

The pain often builds to an excruciating level over days to a few weeks, and is perceived as being deep in the tissues. Weakness and sensory symptoms appear a week or more after the pain begins. The weakness is most often found in shoulder abduction and external rotation, as well as elbow flexion. Scapular winging due to long thoracic nerve involvement may be seen in combination with the other types of deficits mentioned above, or in isolation. Sensory loss occurs along the radial side of the forearm, in the first two digits, and at times, over the area of the insertion of the deltoid to the humerus. Most patients improve after the attack, although some are left with neurological deficits.

The eponyms Parsonnage-Turner syndrome or neuralgic amyotrophy are applied to inflammatory and idiopathic lesions. It is not understood why the predominant effect is in the upper trunk territory. Motor nerve conductions tend to yield little information in the EDX evaluation of these patients. However, sensory studies can help define the lesion as being postganglionic by showing abnormality in clinically involved territories. The lateral antebrachial cutaneous, superficial radial, and median sensory nerves are more commonly involved. By demonstrating the distribution of abnormality, the needle examination is the more informative portion of the EDX study.

Although this type of plexopathy may occasionally spread to the opposite side during the original attack, this condition does not tend to recur; doing so suggests the inherited form of brachial plexopathy.

**Neoplasms**

Neoplastic plexopathy can be caused by direct spread from adjacent structures, such as the apex of the lung, via lymphatic drainage, or by metastatic spread to vertebral bodies. The inferior portion of the plexus tends to be involved. Sensory symptoms occur in the fourth and fifth fingers as well as the medial forearm. Pain in the neck, shoulder, axilla, or medial arm is an early manifestation. Weakness is present in the intrinsic hand muscles and finger-motion-associated forearm muscles. Horner’s syndrome may be present, caused by destruction of the upper sympathetic ganglia by the same infiltrative process. The plexopathy may be the initial manifestation of the neoplasm, part of the known diagnosis, or appear years later as a recurrence.

Distinguishing this type plexopathy from C8 or T1 radiculopathy may be clinically difficult. However, it should be electrodagnostically clear. The plexus lesion should cause the ulnar and medial antebrachial SNAPs to have abnormally low amplitudes. An ulnar nerve lesion could also be considered, but does not explain weakness of the median innervated hand functions, like thumb abduction, or the radial functions, like thumb extension. These are expected in a lower trunk plexus lesion.

**Radiation**

Plexopathy following therapeutic radiation has several distinctive features. One is a long latency between the treatments and the appearance of the lesion. A 5- to 10-year delay, if not longer, is common. Patients note an insidious onset of weakness, muscle atrophy, and fasciculation. The upper trunk territory tends to be involved, so weakness is more often found in the shoulder and
elbow flexor muscle groups. Sensory loss occurs in the lateral antebrachial cutaneous, superficial radial, and median sensory areas. Pain tends to be relatively low grade. All of these manifestations slowly worsen.

Another characteristic feature of this type of plexopathy is myokymic discharges on needle examination of clinically abnormal muscles. These are spontaneous, time-locked groups of MUAP-like discharges with an auditory pattern reminiscent of galloping horses. The pathogenesis of postradiation plexopathy is thought to be a vasculopathy affecting the vasa nervorum of the nerves in the radiation portals. It is not understood why the upper trunk type of plexus involvement happens. This type of lesion does not imply excessive doses of radiation were used. A similar process can involve the lumbosacral plexus. There is no effective treatment for this entity.

Inherited Lesions

Inherited brachial plexopathies demonstrate a dominant genetic pattern. Patients experience attacks that are very clinically similar to the inflammatory, autoimmune lesions described above.\textsuperscript{3,12} The upper trunk pattern of involvement is most common. Significant pain is present, and is usually the initial manifestation of an attack. The attacks may come on after vigorous physical exertion. Females may have them shortly after parturition. The prognosis for recovery is good, but this type of brachial plexopathy can recur months to years later. Some families show the facial feature of hypotelorism.

This is not the same entity as a hereditary predisposition to pressure palsy. The gene which codes for the SEPT9 has been implicated in some patients with this condition.\textsuperscript{3} Septins are proteins involved in cellular trafficking, but how abnormalities in this protein cause brachial plexopathy is still not understood.

THORACIC OUTLET SYNDROME

Thoracic outlet syndrome is a nebulous entity invoked to account for neck, shoulder, and arm symptoms for which no other cause can be found. It’s marked by a rare lesion termed the “true neurogenic thoracic outlet syndrome.” The typical patient is a female with a long history of mild, often unilateral arm pain. Weakness of hand grip and atrophy of intrinsic hand muscles are present. The median innervated thenar muscles are predominantly affected. At first glance, the pattern of atrophy suggests severe median neuropathy at the wrist. Many of these patients have undergone carpal tunnel surgery without benefit.

They present with weakness and atrophy of ulnar supplied hand muscles as well as sensory loss in the ulnar aspect of the hand and the medial forearm. EDX tests show abnormalities in the ulnar and medial antebrachial SNAPs, and axonal type abnormalities in median and ulnar motor conduction. In contrast to median neuropathy at the wrist, the median SNAP is normal. Needle examination shows chronic neurogenic type abnormalities in lower trunk innervated muscles.

Radiographic findings show either a cervical rib or an elongated transverse process of the seventh cervical vertebra. The cervical rib, or the fibrous band from the transverse process, impinges on the lower portion of the plexus. Surgery to remove the abnormal structure tends to produce little clinical improvement because the condition tends to be very chronic by the time it’s diagnosed.\textsuperscript{2,10}

SUMMARY

Understanding peripheral nerve and muscle anatomy, as well as typical clinical presentations and patterns of EDX abnormality in radicular and peripheral nerve lesions is important for making an accurate diagnosis in patients sent to the EMG laboratory for neck, shoulder, arm, and hand pain.

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