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Toxic Myopathies

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Abstract

Muscle tissue is highly sensitive to many substances. Early recognition of toxic myopathies is important, as they potentially are reversible on removal of the offending drug or toxin, with greater likelihood of complete resolution the sooner this is achieved. Clinical features range from mild muscle pain and cramps to severe weakness with rhabdomyolysis, renal failure, and even death. The pathogenic bases can be multifactorial. This article reviews some of the common toxic myopathies and their clinical presentation, histopathologic features and possible underlying cellular mechanisms.

Introduction

Many substances including commonly prescribed medications can produce adverse effects on muscle.(1,2,3,4) Alcohol, one of the oldest substance known, has an ability to cause muscle weakness that has been recognized since the middle of 19th century(5). Adverse effects of pharmaceuticals on muscles have been described mostly within the last 50 years. Cholesterol lowering medications, particularly the statins (6,3,7,8,9) have been the most commonly prescribed drugs that have been described to cause a myopathy in recent years and autoimmune mechanisms are discussed in the idiopathic inflammatory myopathy chapter. Medications can have a direct or indirect adverse effect on the muscle. Direct effect can be focal as might occur secondary to drug being injected into tissue, or generalized. Indirect toxic effects may result from the agent creating an electrolyte imbalance or inducing an immunological reaction. Clinical manifestations of toxic myopathies range from muscle pain to more serious muscle damage leading to rhabdomyolysis (1,11) Although some categories of drugs are associated with specific forms of myopathies, a drug can cause more

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than one type of myopathy. History of drug use is important in the evaluation of patients presenting with various muscle disorders, and an understanding of the pathophysiology of drug-induced myopathy is useful in the management of these patients.

Clinical Presentation

Clinical manifestations of drug-induced myopathy are often indistinguishable from those of myopathies due to other causes, as well as from idiopathic forms. Clinical manifestations can be varied and with combination of various symptoms including diffuse myalgia (muscle pain and stiffness) without any other neurologic signs, painless proximal myopathy (weakness), painful myopathies, focal myopathy with focal area of damage due to injections, myokymia or rhythmic rippling of muscles, mitochondrial myopathy associated with inhibition of mitochondrial DNA and characterized by ragged red fibers, rhabdomyolysis with myoglobinuria, malignant hyperthermia and secondary effects of myopathies.

Pathophysiology/Pathogenesis

Based on pathogenic mechanisms 7 main categories of toxic myopathies are recognized (4,3): (1) necrotizing myopathy; (2) amphiphilic Myopathies (3) antimicrotubular myopathy; (4) mitochondrial myopathy; (5) inflammatory myopathy; (6) hypokalemic myopathy and (7) steroid myopathy/critical illness myopathy (Table 1).

Necrotizing Myopathy

Introduction

A number of drugs can cause a generalized necrotizing myopathy with cholesterol-lowering drugs being the major cause of this type of myopathy (12,10). Other agents include the immunophilins (cyclosporine and tacrolimus), rarely the antihypertensive agent labetalol and propofol. With statins, besides toxic necrotizing myopathy which stops with discontinuation of the medication, recent evidence suggests that statins also trigger an autoimmune myopathy that progresses for months after statin discontinuation which we referred to as statin-associated necrotizing autoimmune myopathy (SANAM) (see Idiopathic Inflammatory Myopathy chapter).

Statins

Clinical presentation: While myalgias, weakness or asymptomatic elevation of creatine kinase (CK) levels (6) do occur with statin exposure, severe necrotizing myopathy may be complicated by myoglobinuria and renal failure. The degree of serum CK elevation is proportionate to the amount of muscle damage. Proximal weakness develops after periods of statin exposure ranging from weeks to years in SANAM.

The weakness usually progresses beyond 2 months following statin cessation in the autoimmune variant whereas patients with toxic necrotizing myopathy patients stabilize in strength and markedly improve within a 2 to 3 months of statin cessation. The CK levels are markedly elevated. A retrospective chart review performed at The University of Kansas Medical Center showed 11/18 (61%) patients on statins having SANAM and 7/18 (39%)

with toxic necrotizing myopathy (Table 2). Mean age of onset was 55, with more females than males, and disease duration upon presentation was 2-12 months (Table 2). Proximal leg weakness was the most common presentation with SANAM, few had proximal arm weakness and neck flexor weakness. Respiratory or bulbar dysfunction was not seen in our patients (13).

Laboratory features and Electrophysiology: Myositis autoantibody panel is usually negative in these patients but a novel antibody is present in most cases (see below). In our SANM group, one patient had antinuclear antigen (ANA) positive and rheumatoid factor positive. One patient also had Jo-1 positive without any evidence for interstitial lung disease. Erythrocyte sedimentation rate (ESR) is usually normal. Electromyography (EMG) showed myopathic units in all SANAM cases with fibrillation potentials seen in 9 patients, myotonia seen in 5.

Histopathology: Muscle biopsies reveal muscle fiber necrosis with prominent phagocytosis and small basophilic regenerating fibers in patients with elevated serum CK and weakness or myalgias. Lipid-filled vacuoles within myofibers and cytochrome oxidase-negative myofibers may be rarely appreciated, but these are not consistent findings (14). scattered myofiber necrosis, myophagocytosis, with at times mild perivascular inflammation, some regenerating myofibers are seen in SANAM.

Pathogenesis: Needham in 2007 reported an up-regulation of MHC-I expression even in non-necrotic fibres of patients presenting with progressive necrotizing myopathy after statin use(15). Later, Mammem in 2011 showed that statins induce antibody to 200 and 100 kD autoantigen Statins also upregulate expression of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) which is the main auto antibody target in SANAM (16). NCAM positive regenerating muscle cells express high levels of HMGCR. This may sustain the immune response even after statin discontinuation (17,18,16,19,14).

Treatment: Multiple long-term immunosuppressive agents are required in most SANAM cases as described in the Idiopathic Inflammatory Myopathies Chapter.

Cholesterol-Lowering Drugs (excluding statins)—Niacin, ezetimibe (Zetia), colescam (Welchol), fibric acid derivatives such as fenofibrate and gemfibrozil are other cholesterol-lowering agents. Although monotherapy with each of these has been reported to cause myopathy in few case reports and review articles (20), the link between these drugs exposure and development of myopathy is best established for gemfibrozil. With each agent, the risk of myopathy appears to increase with concomitant statin therapy. Gemfibrozil interferes with statin metabolism, increases statin plasma concentrations and is associated with increased risk of rhabdomyolysis compared to fenofibrate when coadministered with a statin (21).

Clinical presentation: Patients may present with myalgias, CK elevations or weakness that may start few weeks after starting the medications and sometimes may develop several years after drug initiation.

Immunophilins—The immunophilins (i.e. cyclosporine and tacrolimus are commonly used as immunosuppressive agents, especially in patients requiring transplantation and rarely in some autoimmune diseases

Clinical features: These cause generalized myalgias and proximal muscle weakness develops within months after starting these medications (22). Myoglobinuria can also occur. Tacrolimus has also been associated with hypertrophic cardiomyopathy and congestive heart failure (23). In a comprehensive review including 34 patients who developed myopathy on cyclosporine, only 2 received cyclosporine monotherapy (24). In remaining cases, cyclosporine was administered along with other potential myotoxins such as a statin or colchicine, making it difficult to determine whether cyclosporine alone can cause myopathy.

Laboratory features and electrophysiology: Serum CK is usually elevated, Nerve conduction studies (NCS) are usually normal. EMG is remarkable for evidence of increased muscle membrane instability with fibrillation potentials, positive sharp waves, and occasional myotonic potentials. Early recruitment of small amplitude, short duration MUAP's may be demonstrated in weak muscle groups.

Histopathology: Muscle biopsies demonstrate necrosis and non-specific type 2 muscle fiber atrophy. Sometimes there is evidence of mitochondrial damage including ragged red fibers and lipid vacuoles.

Pathogenesis: Pathogenic basis is not known. Perhaps, these agents destabilize the lipophilic muscle membrane leading to muscle fiber degeneration, due to their 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) (24).

Treatment: Myalgias, muscle strength and cardiac function improve with reduction or discontinuation of the offending cyclophillin.

Labetolol (25,26)

Clinical features: this results rarely in myotoxocity manifesting as acute or insidious onset proximal weakness or myalgias.

Laboratory features and electrophysiology: Serum CK can be markedly elevated. EMG demonstrates increased insertional and spontaneous activity with short duration, small amplitude, polyphasic MUAP's, which recruit early, are evident

Histopathology: Routine light microscopy can be normal or can reveal necrotic and regenerating fibers. Electron microscopy revealed subsarcolemmal vacuoles in one case (25).

Pathogenesis: Etiology of the muscle necrosis is not known

Propofol

Clinical features: Propofol is an anesthetic agent that is frequently used for sedation in mechanically ventilated patients and sometimes used for treatment of status epilepticus. Propofol infusion syndrome is associated with myoglobinuria, metabolic acidosis, acute cardiomyopathy and skeletal myopathy. This is usually seen with infusion rates of 5mg/kg/hour and greater for more than 48 hours (27). Acute quadriplegic myopathy (AQM) in the intensive care unit (ICU) has also developed in patients treated with propofol in combination with high-dose intravenous corticosteroids (Hansen, 2003). However, it remains to be determined if propofol is an independent risk factor for the development of AQM (29).

Laboratory features: Serum CK levels are markedly elevated. Electrophysiological findings are not known in children. However in adults, AQM patients have low amplitude compound muscle action potentials (CMAPs), profuse fibrillation potentials, positive sharp waves, and early recruitment of short-duration, small amplitude polyphasic MUAP's (Hansen 2003)

Histopathology: Muscle biopsies reveal necrosis of skeletal and cardiac muscle (30). Patients with AQM, may have prominent necrosis and loss of thick filaments (Hansen 2003)

Pathogenesis: Mechanism is unknown. However, the propofol infusion syndrome is thought to be a failure of free fatty acid metabolism due to inhibition of free fatty acid entry into the mitochondria and to specific sites in the mitochondrial respiratory chain (27).

Treatment: Propofol should be discontinued and supportive therapy instituted for myoglobinuria, metabolic acidosis, hyperkalemia and renal failure.

Snake Venom

Clinical features: Some of the snake venoms contain potent myotoxins. For example, venom from the South American rattlesnake (*Crotalus durissus*) causes severe weakness. Snake-venom poisoning often involves multiple organ systems.

Histopathology and Pathogenesis: The mechanism depends on the snake venom. The South American rattlesnake venom contains crotoxin and other peptides that interact with sodium channels in the sarcolemma and T tubules. This results in increased sodium influx and resulting myofiber necrosis. Some snake venom, such as cobra and viperidae venom contain peptides with phospholipase A2 activity, which can cause rapid muscle –fiber necrosis within a few hours (31).

Treatment: Snake bite is usually a medical emergency requiring consultation with expert who can be contacted at a regional poison control center (32).

Amphiphilic Drug Myopathy (Drug-induced autophagic lysosomal myopathy)

Amphiphilic drugs contain separate hydrophobic and hydrophilic domains, which allow the drugs to interact with the anionic phospholipids of cell membranes and organelles.

Chloroquine

Clinical features—Chloroquine, a quinolone derivative, is used for treatment and prevention of malaria due to their ability to disrupt the metabolism of heme. Chloroquine and hydroxychloroquine are also used to treat dermatomyositis, sarcoidosis, systemic lupus erythematosus, and other connective tissue diseases due to their immunomodulatory effect. Some patients develop slowly progressive, painless, proximal weakness and atrophy, which are worse in the legs than in the arms (33). A cardiomyopathy can also occur (34). Sensation is often reduced as are muscle stretch reflexes, particularly at the ankle, secondary to a concomitant neuropathy (33). This “neuromyopathy” usually occurs in patients who take 500mg/d for a year or more but has been reported with doses as low as 200mg/d. The neuromyopathy improves after chloroquine discontinuation. In a 3-year longitudinal study of patients with rheumatic diseases taking antimalarials, the prevalence of myopathy was 9.2% and the annual incidence of myopathy was 1.2% (35).

Laboratory features and neurophysiology—Serum CK levels are usually elevated. Motor and sensory NCS reveal mild to moderate reduction in the amplitudes with slightly reduced velocities in patients with superimposed neuropathy (36). Individuals with only the myopathy usually have normal motor and sensory studies. Fibrillation potentials and myotonic discharges are seen primarily, but not exclusively, in the proximal limb muscles. Early recruitment of small amplitude, short duration polyphasic MUAP's are appreciated in weak proximal muscles. Neurogenic appearing units and reduced recruitment may be seen in distal muscles that are more affected by toxic neuropathy.

Histopathology—Autophagic vacuoles are evident in as many as 50% of skeletal and cardiac muscle fibers (36,33,37). Type 1 fibers appear to be preferentially affected. The vacuoles stain positive for acid phosphatase, suggesting lysosomal origin. On EM, the vacuoles are noted to contain typical concentric lamellar myeloid debris and curvilinear structures. Autophagic vacuoles are also evident in nerve biopsies.

Pathogenesis—Chloroquine is believed to interact with 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 (33,38). The myopathy is usually not as severe as seen in chloroquine and Vacuoles are less prominent on routine light microscopy, but EM still usually demonstrates abnormal accumulation of myeloid and curvilinear bodies.

Amiodarone

Clinical features—Amiodarone is an antiarrhythmic medication that may cause a tremor or ataxia and neuromyopathy (39,40). The neuromyopathy is characterized by severe proximal and distal weakness along with distal sensory loss and reduced muscle stretch reflexes. The legs are more affected than the arms. The myotoxic effects may be exacerbated in patients who also develop amiodarone-induced hypothyroidism. Patients with renal insufficiency are predisposed to developing the toxic neuromyopathy. Concurrent use of amiodarone and statin increases the risk of statin myopathy (41).

Laboratory features—Serum CK levels are elevated. Motor and sensory NCS reveal reduced amplitudes and slowed conduction velocities particularly in the lower extremities. EMG demonstrates fibrillation potentials and positive sharp waves in proximal and distal muscles. In proximal muscles, MUAP's are typically polyphasic, short in duration, and 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 (eg, chloroquine)

Treatment—Muscle strength gradually improves following discontinuation of amiodarone and may take up to 6 months.

Antimicrotubular Drug Myopathies

Colchicine

Clinical features: This is commonly prescribed for gout and also used for management of familial Mediterranean fever. Colchicine can cause a generalized toxic neuromyopathy (42). It is weakly amphiphilic, but the toxic effect is believed to arise secondary to its binding with tubulin and prevention of tubulin's polymerization into microtubular structures. The neuromyopathy usually develops after chronic administration but it can also develop secondary to acute intoxication (42,43,44). Chronic renal failure, concomitant statin use and age over 50 years are risk factors for the development of neuromyopathy (45). Patients usually manifest with progressive proximal muscle weakness over several months. Clinical myotonia has been described (46,47). A superimposed toxic neuropathy leads to distal sensory loss as well as diminished reflexes.

Laboratory features—Serum CK level is elevated up to 50-fold in symptomatic patients. Serum CK may also be mildly elevated in asymptomatic patients taking colchicine.

Electrophysiologic findings: Nerve conduction studies reveal reduced amplitudes, slightly prolonged latencies, and mildly slow conduction velocities of motor and sensory nerves in the arms and legs (42,43). Needle EMG demonstrates positive sharp waves, fibrillation potentials, and complex repetitive discharges, which are detected with ease in all muscle regions. Myotonic discharges may also be seen (47). The myopathic MUAP abnormalities can be masked in the distal limb muscles secondary to the superimposed peripheral neuropathy.

Histopathology: Muscle biopsies revealed vacuolar changes characterized by acid phosphatase-positive vacuoles and myofibrillar disarray foci. Ultrastructural study demonstrates autophagic vacuoles. Most of the vacuoles express dystrophin but not merosin. One study by Fernandez showed several fibers reacted with anti-MHC class I antibody and granular deposits of membrane attack complex were observed on the surface of numerous myofibers. Anti-alphaB-crystallin antibody strongly reacted with vacuolar content (48). In addition, nerve biopsies can reveal evidence suggestive of a mild axonal neuropathy.

Pathogenesis: The abnormal assembly of microtubules most likely disrupts intracellular movement of localization of lysosomes, leading to accumulation of autophagic vacuoles. The selective type I involvement is probably due to the higher tubulin amount in type I fibers. AlphaB-crystallin overexpression is related to its microtubule protection properties. Fernandez suggested that vacuoles randomly floating in sarcoplasm might occasionally meet the plasma membrane and open in the extracellular space, leading to complement activation (48).

Treatment: weakness typically resolves within 3-4 weeks after discontinuing the colchicine.

Vincristine

Clinical features: Vincristine is a chemotherapeutic agent, which disrupts gene transcription and also promotes the polymerization of tubulin into microtubules. More common side effect of vincristine is a toxic axonal sensorimotor polyneuropathy that is associated with distal muscle weakness and sensory loss. Proximal muscle weakness and myalgias are less common (49).

Laboratory features: Serum CK levels have not been reported in patients suspected of having a superimposed myopathy. NCS demonstrate markedly reduced amplitudes of SNAPs and CMAPs, while the distal latencies are slightly prolonged and conduction velocities are mildly slow (49). Needle EMG demonstrates positive sharp waves, fibrillation potentials, and neurogenic appearing MUAPS in the distally located muscles of the upper and lower extremities.

Histopathology: Biopsies of distal muscles demonstrate evidence of neurogenic atrophy and occasionally, the accumulation of lipofuscin granules. Proximal muscle biopsies reveal scattered necrotic fibers (49). On EM, there is prominent myofibrillar disarray and subsarcolemmal 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 Myopathies

Zidovudine (Azidothymidine)

Clinical features—Azidothymidine(AZT), an analog of thymidine, is the nucleoside reverse-transcriptase inhibitor (NRTI) that is commonly associated with myopathy (50). Patients usually present with an insidious onset of progressive proximal muscle weakness and myalgias (51, Dalakas 1995). However, these clinical features do not help to distinguish AZT myopathy from other HIV –related myopathies such as polymyositis and inclusion body myositis. Such myopathies related to HIV infection are heterogenous and include inflammatory myopathy, microvasculitis, noninflammatory necrotizing myopathy, type 2 muscle fiber atrophy secondary to disuse or wasting due to chronic debility and a toxic myopathy secondary to AZT (51,52). Regardless of the etiology of the myopathy, patients manifest with progressive proximal muscle weakness and myalgias. In addition, muscle weakness may be multifactorial. Given the advent of modern antiretroviral therapies, AZT myopathy is rarely seen.

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 (eg, greater than five times the upper limit of normal) is more suggestive of an HIV associated polymyositis. Motor and sensory NCS are normal unless there is a concomitant peripheral neuropathy. Needle EMG may demonstrate positive sharp waves and fibrillation potentials and early recruitment of short duration, small amplitude polyphasic MUAPs (53,54,55).

Histopathology—An HIV positive individual patient may have one or more of HIV associated myositis, nemaline rod myopathy, AZT induced mitochondrial myopathy, and type 2 muscle fiber atrophy. Thus, muscle biopsy may be helpful to differentiate these. Muscle biopsies are remarkable for the presence of ragged red fibers, suggesting mitochondrial abnormalities in AZT myopathy. The number of ragged red fibers correlates with the cumulative dose of AZT (56). Necrotic fibers, cytoplasmic bodies, nemaline rods and fibers with microvacuolization may be seen in addition to ragged red fibers (57,51). In contrast to HIV associated inflammatory myopathy significant endomysial inflammation with or without invasion of non-necrotic fibers should not be present in cases of pure AZT myopathy (58) EM reveals abnormalities of the mitochondria and myofilaments.

Pathogenesis—AZT acts as a false substitute for the viral reverse transcriptase, thereby limiting its enzymatic activity and replication of the HIV virus. However, AZT also inhibits the activity of mitochondrial DNA polymerase, which probably accounts for the mitochondrial abnormalities. When treated with AZT, patients with HIV have a decrease in quantity of mitochondrial DNA and decline in respiratory chain enzymatic activity,

compared to untreated infected patients (59,60). Although, AZT is responsible for at least some of the mitochondrial abnormalities evident on muscle biopsy, the contribution of these mitochondrial abnormalities to the muscle weakness remains controversial.

Treatment—Patients with AZT myopathy usually improve following discontinuation of the medication (51, 55). The histological and molecular abnormalities on repeat muscle biopsies resolve coinciding with clinical improvement following discontinuation of AZT (61). The major drawback of discontinuing AZT is the possible increase in HIV replication. In patients with normal or only mildly elevated serum CK and normal or only slightly increased spontaneous activity on EMG, it is impossible to distinguish AZT myopathy from other HIV-associated myopathies. One approach is starting a nonsteroidal anti-inflammatory drug with or without decreasing the dose of AZT (51). If there is still no objective improvement in strength, one should consider discontinuation of AZT. If there is still no objective improvement, patient should undergo a muscle biopsy and be considered for immunomodulating therapy (eg intravenous immunoglobulin (IVIG) or corticosteroid treatment), if there is histological evidence of an inflammatory myopathy. Patients can be rechallenged with AZT, particularly if there are no ragged red fibers on biopsy. Newer therapies have reduced significantly reliance on AZT in HIV treatment.

Other antirviral agents

The risk of mitochondrial myopathy with other nucleoside reverse transcriptase inhibitors (eg lamivudine, zalcitabine, didanosine) is probably less than that of AZT (62,63). However, these agents are clearly associated with mitochondrial toxicity, and patients may develop associated hyperlactemia and hepatic steatosis on these medications (64). In patients with HIV infection it is unclear if the myopathy was felt to be due to mitochondrial toxicity, myositis, or wasting syndrome.

Drug Induced Inflammatory Myopathies

Cholesterol Lowering agents—discussed in the section on necrotizing myopathies.

L-tryptophan/eosinophilia myalgia syndrome

Clinical features—Eosinophilia-myalgia syndrome was described in the late 1980s and 1990s and was found to be caused by a contaminant used in the production of L-tryptophan (65,66,67,68,69). The clinical, laboratory, electrophysiologic and histopathological features were similar to that seen in diffuse fasciitis with eosinophilia (Shulman syndrome, 70). Patients developed a subacute onset of generalized muscle pain and tenderness with variable degrees of weakness. Onset could have been within a few weeks or several years after starting tryptophan. Numbness, paresthesias, arthralgias, lymphadenopathy, dyspnea, abdominal pain, mucocutaneous ulcers, and an erythematous rash were also common. Some patients developed a severe generalized sensorimotor polyneuropathy mimicking Guillain-Barre syndrome (71,72) or multiple mononeuropathies suggestive of a vasculitis (73).

Laboratory features—The serum CK levels were normal or elevated. Autoantibodies were absent and ESR was usually normal. The absolute eosinophil count was elevated.

Decreased amplitudes of compound muscle and sensory nerve action potentials with normal or mildly reduced conduction velocities were evident in patients with a polyneuropathy (72,73). A few patients with severe Guillain-Barre syndrome had electrophysiologic studies showing multifocal conduction block and slowing of conduction velocities (74). Needle EMG revealed fibrillation potentials, complex repetitive discharges (72,73,74) and small and large polyphasic MUAPs (72). The electrophysiological abnormalities improve with discontinuation of tryptophan.

Histopathology—Muscle biopsies demonstrated diffuse or perivascular inflammatory infiltrate in the fascia, perimysium, and to a lesser extent, in the endomysium (72). The majority of inflammatory cells were CD8+ T cells and macrophages, while eosinophils and B cells comprised <3% of the infiltrating cells. There was no deposition of membrane attack complex on small blood vessels. Nerve biopsies showed predominantly perivascular inflammatory infiltrate, mainly mononuclear, with occasional eosinophils in the epineurium, endoneurium, and/or perineurium with axonal degeneration (72,73).

Pathogenesis—The disorder was caused by a contaminant(s) in the manufacture of tryptophan. Two trace adulterants have been identified as the possible toxins: 3-phenylaminoalanine and 1,1'-ethylidenebis tryptophan. The mechanism by which this contaminant resulted in the disorder is unknown, but the eosinophilia and eosinophilic infiltrate in tissues suggest some form of allergic reaction.

Treatment—Discontinuation of L-tryptophan and treatment with high-dose corticosteroids were usually effective in resolution of most of the symptoms (71).

Toxic oil Syndrome—The toxic oil syndrome was quite similar to the eosinophilia-myalgia syndrome associated with tryptophan (75). This condition was restricted to a single epidemic in Spain and has not recurred since 1981-1982. The disorder was found to be significantly associated with consumption of contaminated rapeseed oil produced by a particular refinery. Two compounds, 1,2-di-oleyl ester (DEPAP) and oleic anilide are considered to be biologically relevant contaminants that may contribute to disease development.

D- Penicillamine

This is rarely used nowadays to treat Wilson disease, rheumatoid arthritis, and other connective tissue disorders. Besides autoimmune myasthenia gravis, approximately 0.2-1.4% of patients treated with D-penicillamine developed an inflammatory myopathy reminiscent of polymyositis or dermatomyositis (76,77). Discontinuation of the drug results in resolution of the symptoms. The medication may be restarted at a lower dosage without recurrence of the inflammatory myopathy.

Cimetidine

Rare cases of inflammatory myopathy have been reported with cimetidine, a histamine H2 receptor antagonist. Patients develop generalized weakness and myalgias associated with CK elevations up to 40,000 U/L and interstitial nephritis (78,79). Muscle biopsy shows

perivascular inflammation, predominantly consisting of CD8 + lymphocytes. There is no deposition of immunoglobulin or complement on small blood vessels, nor did the patients have a cutaneous rash to suggest dermatomyositis. However, cases of cutaneous vasculitis have been described with cimetidine use (80).

Procainamide

Proximal muscle weakness and myalgias rarely occur with procainamide usage (81). Serum CK levels are elevated, and EMG have been reported as being consistent with a patchy myopathy. Muscle biopsies demonstrate non-specific perivascular inflammation and rare necrotic muscle fibers. The pathogenesis may be related to lupus-like vasculitis, which can occur in patients treated with procainamide. In one study Antirapsyn antibodies were reported in chronic procainamide-associated myopathy (82). The myopathy resolves following withdrawal of procainamide.

Phenytoin

Myalgias and weakness may develop in patients treated with phenytoin due to hypersensitivity reactions (83). Serum CK levels can be significantly elevated, and muscle biopsies show scattered necrotic, regenerating muscle fibers without evidence of inflammation (84). EMG can reveal increased spontaneous activity with fibrillation potentials and positive sharp waves. Small amplitude, short-duration, polyphasic MUAP's which recruit early may be observed. The myopathy improves with discontinuation of the phenytoin and a short course of corticosteroids.

Lamotrigine

A case of severe myoglobinuria and renal failure associated with a generalized rash, anemia, leukopenia, and thrombocytopenia shortly after the patient was started on antiepileptic medication lamotrigine was reported (4). Clinical and laboratory features resemble thrombocytic thrombocytopenic purpura. Patient was treated with plasmapheresis and discontinuation of lamotrigine.

Alpha-interferon

Alpha-interferon is used in the treatment of viral hepatitis and certain malignancies (e.g, chronic myelogenous leukemia[CML] and melanoma). A rare side effect of alpha-interferon is the occurrence of autoimmune disorders including myasthenia gravis and myositis (85,86). Overproduction of type 1 interferons, such as alpha-interferon, have been implicated in the pathogenesis of dermatomyositis in some studies (87,88).

Imatinib Mesylate (Gleevec)

Imatinib mesylate is a tyrosine kinase inhibitor use to treat patients with CML and other solid tumors. Myalgias occur in 21-52% of patients (89) and CK elevations in 45%. One patient with CML developed polymyositis while taking imatinib (90). CML28 antibodies were detected in the patient's serum. CML28 is identical to hRrp46p, a component of the human exosome, a multiprotein complex involved in processing of RNA. Antibodies directed against hRrp46p and other components of the human exome (eg. PM-Scl 100 and

PMScl 75) have been noted in patients with polymyositis. The patient's strength and serum CK normalized with discontinuation of the imatinib and a course of corticosteroids.

Myopathies Due to Impaired Protein Synthesis or Increased Catabolism

Steroid myopathy

Clinical features—Chronic exposure to high dose oral steroids causes greatest risk of developing steroid myopathy. Prednisone at doses of 30mg/d or more (or equivalent doses of other corticosteroids) is associated with an increased risk of myopathy (91). However, steroid myopathy may occur after just a few weeks of treatment. Steroid myopathy manifests as proximal muscle weakness and atrophy affecting the legs more than the arms (91,92,93). The distal extremities, oculobulbar, facial muscles, sensation and muscle stretch reflexes are normal. Most patients exhibit a Cushingoid appearance with facial edema and increased truncal adipose tissue (94). Any synthetic glucocorticoid can cause the myopathy, but those that are fluorinated are more likely to result in muscle weakness than the nonfluorinated compounds (95). Women appear to be more at risk than men (approximately 2:1) of developing a steroid myopathy. Alternate day dosing may reduce the risk of corticosteroid-induced weakness. Acute onset of severe generalized weakness can occur in patients receiving high dosages of intravenous corticosteroids with or without concomitant administration of neuromuscular blocking agents or sepsis.

Laboratory and electrophysiological features—Serum CK is normal. Serum potassium can be low as a result of glucocorticoid excess and cause some degree of weakness. Motor and sensory nerve conductions are normal in steroid myopathy (96,97). Repetitive stimulation studies should not demonstrate a significant decrement or increment. Needle EMG is normal as well or with subtle myopathic changes without any fibrillation potentials. 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, there is little in the way of electrophysiologic pathology to observe.

Histopathology—Muscle biopsies reveal atrophy of type 2 fibers, especially the fast-twitch, glycolytic type 2B fibers (94). 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. Exact pathogenesis of corticosteroid myopathy is not known, but could be the result of decreased protein synthesis, increased protein degradation, alterations in carbohydrate metabolism, mitochondrial alterations, or reduced sarcolemmal excitability (94).

Treatment—Reduction in the dose, tapering to an alternate-day regimen, or switching to a nonfluorinated steroid along with a low carbohydrate diet and exercise to prevent concomitant disuse atrophy are major modes of therapy (94, 95).

It is important to distinguish steroid myopathy from an exacerbation of underlying immune mediated neuromuscular disorder (eg inflammatory myopathy, myasthenia gravis and chronic inflammatory demyelinating polyneuropathy) in a patient being treated with corticosteroids (98). If the weakness developed while the patient was on chronic 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.

Finasteride

Clinical features—Finasteride is used to treat benign prostatic hypertrophy. It is a 4-azasteroid that inhibits 5 α -reductase, and thus 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 (5mg qd) (99), another patient being treated for baldness reported severe myalgias and had elevated CK. Sensation and muscle stretch reflexes were normal.

Laboratory features—Serum CK levels were normal or elevated.

Electrophysiological findings—Nerve conduction studies were normal, while the EMG demonstrated showed small polyphasic MUAP's

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-Azosteroids and has structural similarity to corticosteroids. Thus, the pathogenic mechanism may be similar to that seen of steroid myopathy.

Treatment—Discontinuation of finasteride was associated with normalization of strength and improvement in CK level and EMG abnormalities.

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 (500-600 mg/d for over 10 days) (100,101,102). Patients also complain of muscle pain, tenderness and stiffness. Muscle stretch reflexes are usually diminished, but the sensory examination is completely normal.

Laboratory features—The serum CK levels may be mildly to moderately elevated. Needle EMG examination can be normal although, positive sharpwaves and fibrillation potentials are usually apparent. There is early recruitment of small amplitude, short duration MUAPs.

Histopathology—Muscle biopsies reveal scattered necrotic fibers, small atrophic and regenerating fibers as well as many fibers containing 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 electron microscopy is similar to myofibrillar myopathy (103)

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.

Treatment—The myopathy resolves following discontinued use of emetine.

Toxic Myopathies with Unknown Pathogenic Mechanism

Acute quadriplegic myopathy/critical illness myopathy

Clinical features—High-dose corticosteroids may trigger critical illness myopathy, in particular, among patients with prolonged intensive care unit (ICU) stay, mechanical ventilation, or persistent systemic inflammation (104,105). Especially in those who also received nondepolarizing, neuromuscular blocking agents (106). The first patient reported with this acute form of steroid myopathy was a 24-year-old woman placed on large doses of intravenous hydrocortisone (up to 3 g a day) for status asthmaticus (107). After 8 days, her airway obstruction resolved, but she was unable to resist gravity in both proximal and distal muscles. She gradually improved and could walk unassisted after 3 weeks but continued to have distal leg weakness after 2 months. Since this initial description, many additional patients have been reported in the literature (106,108,109;). However, most prospective studies could not identify corticosteroids as an independent risk factor for critical illness myopathy, summarized in a recent Cochrane review (110). Similarly, ICU-acquired neuromyopathy was common (34%) among 128 survivors of persistent acute respiratory distress syndrome but was not significantly associated with methylprednisolone treatment (111). Diffuse weakness develops as early as 4 days to 7 days after initiation of corticosteroids (111,112);. Complete flaccid quadriplegia develops in some patients, especially those receiving more than 80 mg total of vecuronium (109). In a series, distal limb and facial weakness were present in most patients (109). Extraocular muscles were involved in 1 of 14 patients.

Laboratory features and electrophysiological findings—In most patients, creatine kinase is normal or mildly elevated. EMG findings in this myopathy are variable. Insertional activity may be normal or show fibrillation potentials (113). Myopathic motor units may be recorded on voluntary contraction (93), but in severe cases, patients may not be able to recruit any motor units.

Histopathology—Muscle biopsy reveals type II atrophy, necrotic muscle fibers, and/or loss of myosin thick filaments as visualized on the adenosine triphosphatase (ATPase) stain.

Pathogenesis—The mechanism of muscle injury is poorly understood.

Treatment—Supportive care and treating underlying systemic abnormalities. Mortality is high due to the sepsis and organ failure. Corticosteroids and neuromuscular blockers should

be discontinued if possible. Physical therapy and occupational therapy to prevent contractures and help regain muscle strength and functional abilities.

Omeprazole

Inhibits H⁺/K⁺ ATPase enzyme system (proton pump) and is used for treatment of gastric and duodenal ulcers and reflux. Rare cases of neuromyopathy have been reported with this. Patients develop proximal weakness and myalgias along with paresthesias and stocking distribution of sensory loss. Muscle reflexes are diminished or absent. Serum CK levels are usually normal or mildly elevated. NCS may be normal or reveal an axonal sensorimotor polyneuropathy. EMG can be normal or show small polyphasic MUAP's. Muscle biopsies showed type 2 muscle fiber atrophy. Symptoms improve with discontinuation of omeprazole (114,115,116).

Isoretinion

Isoretinion (Accutane) is used for treatment of severe acne. Exercise induced myalgias are common, rarely can develop proximal weakness. Serum CK can be normal or elevated. Rhabdomyolysis has also been reported in few cases. Decreased serum carnitine levels may be seen. EMG shows myopathic MUAP's. Muscle biopsy shows atrophy of muscle fibers. Pathogenic mechanism is not clear. Symptoms improve with discontinuation of medication (117,118).

Myopathies Associated with Anesthetic Agents and Centrally Acting Medications

Malignant Hyperthermia

Clinical features—Malignant hyperthermia is a rare, genetically heterogenous group of disorders and is characterized by severe muscle rigidity, myoglobinuria, fever, tachycardia, cyanosis and cardiac arrhythmias precipitated by depolarizing muscle relaxants (eg succinylcholine) and inhalational anesthetic agents (eg halothane)(119) 203. The incidence of malignant hyperthermia ranges from 0.5% to 0.0005%. At least 50% of patients had previous anesthesia without any problems. The signs of malignant hyperthermia usually appear during surgery but can develop in the postoperative period and time for first signs could differ among anesthetic drugs (120). Rarely, attacks of malignant hyperthermia have been triggered by exercise, ingestion of caffeine, and stress. The halothane contracture test or caffeine contracture test can be used to screen for susceptibility to malignant hyperthermia (121), besides the genetic testing. However, these tests are usually available at specialized centers only. Minimally invasive, intramuscular halothane and caffeine test also has been described recently (122)

Laboratory features and electrophysiological studies—Serum CK can be normal or high in between the attacks. During the attacks, serum CK levels are markedly elevated and myoglobinuria can be seen. Hyperkalemia, hypoxia and hypercarbia can also be seen during an attack (123). NCS and EMG are usually normal in the interictal periods. However, EMG performed immediately after an attack of malignant hyperthermia may demonstrate increased spontaneous activity and perhaps, small polyphasic MUAP's recruiting early.

Histopathology—Muscle biopsies demonstrate nonspecific myopathic features and necrotic fibers after an attack.

Pathogenesis and Molecular Genetics—Numerous susceptibility loci have been identified (Table 3) and are associated with mutations of the ryanodine receptor (MHS1), sodium channels (MHS2), calcium channels (MHS3 and MHS 5), and other proteins (including MHS4, MHS5) and CPT2.

Treatment—Depolarizing muscle relaxants and inhalational anesthetic agents should be avoided in subjects with known susceptibility factors. In those who develop malignant hyperthermia, the anesthetic agent must be stopped and aggressive cooling measures must be instituted. In addition to supportive measures, Dantrolene 2mg/kg to 3mg/kg rapid IV every 5 minutes for a total cumulative dose of 10mg/kg should be given.

Myopathies Secondary to Drugs of Abuse

Alcoholic myopathy

Chronic alcohol abuse more commonly causes neuropathy. However, several forms of toxic myopathy due to alcohol have been described: acute necrotizing myopathy, acute hypokalemic myopathy, chronic alcoholic myopathy, asymptomatic alcoholic myopathy and alcoholic cardiomyopathy (124,125). Acute necrotizing myopathy patients present with myalgias, muscle cramping, swelling and weakness following an intense binge drinking. Symptoms are usually associated with elevated CK levels and irritability on EMG, and in severe cases, acute renal failure. Muscle biopsies reveal widespread muscle fiber necrosis. CK levels and muscle symptoms may resolve over several weeks, however may recur with repeated exposure to alcohol in those who are susceptible to this form of toxic myopathy. Some patients develop acute hypokalemia with weakness evolving over a period of 1-2 days, low potassium < 2meq/L and elevated CK levels. Muscle biopsy may reveal vacuoles. This myopathy resolves with potassium supplementation.

Some alcoholics develop primarily proximal limb-girdle weakness, especially in lower limbs attributed to chronic alcoholic myopathy. Asymptomatic alcoholic myopathy has been suggested in patients with elevated serum CK levels without any weakness. The pathogenic basis for the various forms of alcoholic myopathies is not known and may involve direct toxic effects or malnutrition. The metabolism of alcohol may lead to accumulation of toxic metabolites or free radicals that may be damaging to lipid membranes.

Other drugs

Illicit drugs and controlled narcotics (eg heroin, meperidine, cocaine, pentazocine, pramipexole, amphetamine, etc) may be myotoxic. Inhalation of volatile agent (eg toluene) can also cause generalized weakness.

Conclusion

Many drugs have potential to cause muscle damage including commonly prescribed medications such as statins. A good medical history including current and previous

medication history should be obtained, as stopping the offending agent usually leads to improvement of myopathy as muscle cells have the capacity to regenerate. However, continued use and immune mediated myopathies can be associated with significant morbidity and mortality. SANAM required chronic immunosuppression.

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- Many drugs have potential to cause muscle damage including commonly prescribed medications such as statins.
- A good medical history including current and previous medication history should be obtained, as stopping the offending agent usually leads to improvement of myopathy as muscle cells have the capacity to regenerate.
- However, continued use and immune mediated myopathies can be associated with significant morbidity and mortality.

Table 1**Toxic Myopathies**

Pathogenic Classification	Drugs
Necrotizing Myopathy	Cholesterol-lowering agents Cyclosporine Labetolol Propofol Alcohol
Amphiphillic	Chloroquine Hydroxychloroquine Amiodarone
Antimicrotubular	Cochicine Vincristine
Mitochondrial myopathy	Zidovudine Other HIV-related antiretrovirals
Inflammatory myopathy	L-tryptophan D-Penicillamine Cimetidine Phenytoin Lamotrigine Alpha-interferon Hydroxyurea Imatinib
Hypokalemic myopathy	Diuretics Laxatives Amphotericin Toluene abuse Licorice Corticosteroids Alcohol abuse
Critical illness myopathy	Corticosteroids Nondepolarizing neuromuscular blocking agents
Others	Omeprazole Isotretinoin Finasteride Emetine

Table 2
Comparison of KU SANM group with prior literature

	Grable-Esposito et al. 2010	KU
Cases	25	11
Mean age of onset(yrs)	64.7	55
Female/male ratio	1.1/1	2.6/1
Phenotype	Proximal arm and leg	Proximal leg mainly
Bulbar symptoms	3	2
Post-statin D/C weakness for	> 1month	>2 month
Mean CK	8203	5700
Autoimmune d/o & Abnormal labs	Hashimoto thyroiditis ANA (2)	- Jo1 (1), ANA (1) and RF
# RX with immunosuppressants	22	10

Table 3**Malignant Hyperthermia**

Susceptibility Genes	Inheritance Patterns
Ryanodine receptor	Autosomal dominant
SCN4A Sodium channel	Autosomal dominant
CACNL2A calcium channel	Autosomal dominant
CACNA1S calcium Channel	Autosomal dominant
Carnitine palmitoyltransferase II	Autosomal dominant
Dystrophin	X linked recessive
Myotonin protein kinase	Autosomal dominant
Myotonin protein kinase	Autosomal dominant
CLCN1 chloride channel	Autosomal dominant
Perclan	Autosomal recessive

Table 3 Adapted from Mammen AL Toxic myopathies. Continuum (Minneapolis, Minn). 2013 Dec;19(6 Muscle Disease):1634-49; with permission.