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TOXIC AND DRUG INDUCED MYOPATHIES

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INTRODUCTION

Although the “*do no harm*” dogma of Hippocrates is faithfully followed by all practitioners, drugs used for therapeutic interventions either alone or in combination, may sometimes cause unexpected toxicity to the muscles, resulting in a varying degree of symptomatology, from mild discomfort and inconvenience to permanent damage and disability. The clinician should suspect a toxic myopathy when a patient without a pre-existing muscle disease develops myalgia, fatigue, weakness, or myoglobinuria, temporally connected to the administration of a drug or exposure to a myotoxic substance. Myotoxic agents can cause a myopathy by: a) directly affecting a muscle organelle, such as mitochondria, lysosomes, myofibrillar proteins; b) altering muscle antigens, thereby inducing an immunologic or inflammatory reaction; and c) inducing systemic effects, such as electrolyte disturbances, nutritional deprivation or malabsorption, which secondarily affect the muscle function.

The review provides an update on the drugs with well documented myocytotoxicity and cautions the clinicians to be alert for the potential toxicity of newly marketed drugs; highlights the clinical features and pathomechanisms of the induced muscle disease; and offers guidance on how best to treat and distinguish toxic myopathies from other acquired or hereditary muscle disorders. Myotoxicity resulting from direct insertion of transgenes to the muscle, an exciting new tool currently tested for treatment of muscular dystrophies, will be also discussed.

PRINCIPLES OF DRUG-RELATED MYOCYTOTOXICITY

Although FDA encourages physicians to file a report via MedWatch when a drug reaction is suspected, only the serious drug-related myocytotoxicities, such as myoglobinuria, are usually reported. Mild symptoms, such as myalgia or fatigue, are rarely reported during the post-marketing period. As a result, the true incidence or the frequency of drug-induced myocytotoxicities remains unclear. Furthermore, the data available prior to marketing are limited to monotherapies in a small patient population without taking into account the interactions with other drugs, as seen in practice.

A drug-induced myopathy is defined as the subacute, and rarely acute, manifestation of myopathic symptoms, such as muscle weakness, fatigue, myalgia, CK elevation or myoglobinuria, that occur in patients without muscle disease when exposed to therapeutic doses of certain drugs. After discontinuation of the suspected agent, the clinical or biochemical signs of muscle involvement usually improve supporting the causative effect of the offending myotoxic drug. Sometimes however, the toxicity is irreversible, as we have witnessed with the drug Fialuridine, a nucleoside analogue that caused irreversible myocytotoxicity by incorporating into the mitDNA chain, as discussed later. The muscle biopsy is essential to document myotoxicity, but at times it may be uninformative, as occurs in some patients with myoglobinuria or mild muscle weakness caused by statins or nucleoside analogues.

The type of histological abnormalities seen in toxic myopathies varies from non-specific alterations to a distinctive necrotizing, inflammatory or vacuolar myopathy. Because toxic myopathies are potentially reversible, prompt diagnosis and pharmacovigilance are needed to institute early therapy, prevent irreversible changes and protect other patients from similar toxicity.

CLINICAL AND HISTOLOGICAL SPECTRUM OF TOXIC MYOPATHIES

The clinical manifestations are variable and include myalgia, hyperCKemia, muscle weakness or myoglobinuria. According to the type of injury induced to the muscle fiber or specific organelle, the toxic myopathies can be classified as follows [1-5] (Table1):

a) *Necrotizing myopathy*. This is histologically defined by the presence of scattered necrotic fibers invaded by macrophages. There is absence of widespread MHC-I upregulation or a large number of lymphocytic infiltrates invading non-necrotic fibers, as seen in inflammatory myopathies. Generically, it is the most typical toxic effect to the muscle;

b) *Inflammatory myopathy*. It has the features similar to those seen in polymyositis, including CD8+ T cells invading non-necrotic, MHC-I - expressing fibers. It can be caused by statins, D-penicillamine, or intramuscular injections of genes.

c) *Thick filament loss myopathy*. This is the prototypic cause of muscle weakness seen in ICU. It is also caused by steroids in a setting of acute denervation or in combination with neuromuscular blocking agents;

d) *Type II muscle fiber atrophy*. It is caused by many conditions but the primary cause is long-term steroid use combined with inactivity;

e) *Mitochondrial myopathy*. This is histologically characterised by the presence of “ragged red” or “ragged blue” fibers, COX-negative fibers and increased lipid accumulation. It is typically seen with nucleoside analogues;

f) *Lysosomal storage myopathy*. This is typically caused by amphiphilic drugs, which contain a hydrophobic region that interacts with acidic phospholipids of membranes, generating the storage of myeloid structures within the lysosomes in the form of autophagic vacuoles [1-3]. Chloroquine is the main drug in this group;

g) *Anti-microtubule myopathy*. The classic example in this group is colchicine, which inhibits the polymerization of microtubules resulting in disruption of cytoskeletal network with swollen lysosomes and autophagic vacuoles [6];

h) *Myofibrillar myopathy*. The representative drug in this group is emetin which causes disruption of the Z discs followed by breakdown of myofilaments and accumulation of myofibrillar proteins [1-5, 7]; and

i) *Fasciitis*. This is histologically characterized by inflammation and thickening of the myofascia. Clinically, it causes muscle pain and induration. Toxic oil syndrome and contaminated L-tryptophan have been the main causative agents.

The drugs clearly implicated in causing a toxic myopathy are listed in Table 2. As new drugs become available, it is very likely that the list will increase, necessitating the need for pharmacovigilance. It should be noted that a number of drugs such as statins, colchicine, L-tryptophan, can cause both, a myopathy and a neuropathy which enhances further the toxicity to the neuromuscular system. Drugs that cause only neuropathy, but rarely a myopathy as monotherapy, such as ddC, ddl, d4T, perhexiline, amiodarone, vincristine, gold sodium thiomalate, and TNF- α inhibitors, will not be discussed as being beyond the scope of this review.

COMMON DRUGS INDUCING MUSCLE TOXICITY

1. ANTI-CHOLESTEROL: STATIN-INDUCED MYOPATHIES

Statins is a group of fungus-derived drugs that inhibit the 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, an enzyme that catalyzes the conversion of HMG-CoA to mevalonic acid, the precursor of cholesterol [8-10]. The statins, according to the degree of myotoxicity they induce, include sequentially the following: cerivastatin (now withdrawn), simvastatin, lovostatin, pravastatin, atorvastatin and fluvastatin [10-11]. These drugs are multipotent, “wonder drugs”, because in addition to lowering the cholesterol, they have immunomodulating properties and neuroprotective actions. Experimentally, statins affect the mitochondria and the sarcoplasmic reticulum especially in the type II fibers which contain 30% less fat than the type I fibers, rendering them more vulnerable to damage caused by a reduction in

cholesterol available for membrane biosynthesis [12]. Dysfunction of mitochondria has been shown in muscle biopsies of patients with statin-induced myopathic symptoms. Further, after treatment with statins and low fat diet, there is an up to 54% reduction of serum ubiquinone, a co-enzyme Q10 that participates in electron transport during oxidative phosphorylation [13]. About 50% of the body's ubiquinone is obtained through fat ingestion, while the other 50% from endogenous synthesis [10, 13]. Reduction of LDL is probably a contributing factor since ubiquinone is transported in the LDL particles. As a result, two trials have been already conducted using ubiquinone to treat statin-induced myopathy, as discussed later.

Apart from participating in mitochondrial toxicity, statins induce shifting of Th₁ to Th₂ responses, leading to changes in regulatory T cells, B cell reactivity and production of autoantibodies [14]. Further, they may inhibit LFA-1 function on endothelial cell wall inhibiting T cell transmigration [15].

Based on our experience with patients referred to us for statin-related myopathies and review of the literature, the following types of myopathic symptoms and signs can be distinguished after treatment with statins:

a. HyperCKemia in asymptomatic patients

In some patients, on routine testing there may be elevation of CK that does not exceed 5-6 times the ULN, rarely reaching up to 10 times the ULN. These patients have normal strength and no complaints of fatigue or muscle pain. Because CK elevation is always associated with elevation of SGOT, SGPT or γ -GT, the erroneous impression of liver toxicity is suspected. The CK usually fluctuates, reaching the highest levels after exercise. We usually manage these patients by follow-up clinical and biochemical examinations. In our experience, the CK stabilizes to a lower level, up to 3 times, above the ULN. In a few patients that we have biopsied because the CK remained high, we have noted either no abnormalities or mild, non-specific, changes including an occasional "ragged-red", or necrotic fiber.

It is unclear how common is such asymptomatic hyperCKemia, but some estimates suggest up to 5% of all treated patients [10]. Whether it is prudent to discontinue statins in such patients, especially before excessive physical tasks, such as marathon running or weight lifting, remains a matter of debate. In our experience, such elevations are inconsequential if the patients are asymptomatic and their CK elevation is less than 10 times the ULN.

b. Myalgia with or without hyperCKemia

Myalgia has been reported to occur in up to 9-25% of statin-treated patients [10, 11]. Most times, the CK is normal but at times there is hyperCKemia up to the levels reported above. The strength is normal. In these patients, myalgia usually improves after discontinuation of the drug. If the muscle strength is normal and the myalgia is tolerable, we observe the patients for 2-3 months before performing a diagnostic biopsy or changing the statin to another one. In a few muscle specimens we have examined, the changes are minimal and non-specific with an occasional necrotic or "ragged-red" fiber.

c. Muscle weakness with CK elevation

These patients are the least common but represent the largest group in our practice because clinically they have a myopathy and need diagnostic

work-up. In some of our patients the myopathy is mild, subacute and temporally related to the initiation of statin therapy; in some others however, the myopathy is more chronic without a clear cause-and effect relationship, raising the suspicion that the statin might not have been the culprit in inducing it, but rather in unravelling a pre-existing muscle condition. Muscle biopsies may show a few necrotic fibers without inflammation. At times, however, there may be scattered inflammatory autoinvasive T cells and upregulation of MHC-I, suggestive of an immune-related inflammatory process similar to polymyositis. Such patients require immunotherapy. We have been 3 such patients and have followed up one who responded to steroids or IVIg. Cases of statin-induced PM and DM have been reported by others [16].

On the other hand, in patients who present with a more indolent and severe chronic myopathic process, statins might have been coincidental to the cause of the myopathy. We have seen patients with IBM who thought to have good strength prior to statins and sought medical advice because of CK elevation. These patients continued to worsen even after stopping the statin and, retrospectively, admit that their weakness had probably preceded statin administration. Whether statins can worsen a pre-existing myopathic condition and facilitate the unravelling of a full-blown immune-mediated or toxic myopathy remains an undocumented possibility. We have seen a large number of IBM or ALS patients who take statins without any overt signs of added muscle toxicity. In patients with pre-existing myopathy who have discontinued statin fearing worsening of their condition, we recommend resumption of therapy if it is essential for their cardiovascular health.

d. Rhabdomyolysis

This is a potentially serious but rare event. It is defined as an acute elevation of CK (>15.000 ULN) often accompanied by myalgia, weakness and myoglobinuria. Its reported incidence varies, from 0 for fluvastatin, 0,04 for pravastatin and atorvastatin, 0,19 for lovastatin and as high as 3,16 for cervistatin (which has been now removed from the market) [10]. FDA data estimate the incidence of rhabdomyolysis similar for all statins (except of the cervistatin) when used as monotherapy, and much lower than 1 per 100.000 prescriptions [17]. The incidence of rhabdomyolysis is increased however when statins are combined with other drugs. Most notable among them is simvastatin when combined with amiodarone (FDA warning posted 8/8/2008), gemfibrozil or cyclosporine [5, 10, 11, 18]. The risk is also dose-related occurring when simvastatin is given at doses greater than 20 mg per day. Overall, of the 601 cases submitted to the FDA between Nov 1997- March 2000, 55% of the incidents were due to combinations with gemfibrozil (16%), fibrates (13%), cyclosporine (8%), macrolide antibiotics (7%), warfarin (5%), digoxin (4%) and azole antifungus (2%) [10, 18].

The mechanism of muscle injury through these drug interactions is probably the affect on cytochrome P-450 (CYP) 3A4 system. Statins are metabolized to a varying degree by CYP 3A4, except probably of pravastatin which is cleared by the kidneys [10]. The concomitant medications mentioned above inhibit CYP3A4, increasing thereby the concentration of statins. Other mechanisms may be also implicated [10]. The risk of rhabdomyolysis can be exacerbated by several other factors including compromised hepatic and liver function, hypothyroidism and diabetes [10]. The possibility that statins have

unmasked a presymptomatic metabolic myopathy, which was responsible for the rhabdomyolysis, or the event was coincidental, should be always kept in mind. There are reports of acid maltase deficiency or genetic risk factors for metabolic muscle defects in some of the reported cases of rhabdomyolysis, including heterozygosity for disease-causing mutations, such as myodenylate, CPT deficiency and McArdle disease [5, 19]. There is strong evidence of a genetic predisposition to statin myopathy tightly linked to SLCO1B gene that encodes an organic anion transporter [20].

Rhabdomyolysis is a medical emergency that requires immediate discontinuation of drugs and admission to ICU for hydration and electrolyte control. Because these drugs need to be combined with others in several settings (for example statins with fibrates or niacin in patients with very high level of LDL-C, statins with cyclosporine in transplant recipients, statins with antiretrovirals in HIV-positive patients) [10], the doctors should be aware of the increased risks and monitor the patients very closely. Atorvastatin and pravastatin appear to be the most preferable statin in these circumstances because of the lower incidence of rhabdomyolysis [10].

e. *Peripheral Neuropathy*

Symptoms of small-fiber sensory neuropathy develop in a small number of patients, about 2-3 months after starting therapy [21]. Neuropathy is rare, with figures quoting an incidence of 12 per 100.000 person-years and prevalence of 60 per 100.000 persons. We have seen four cases of neuropathy induced by statins. The patients reported a “coasting affect” (temporary worsening after stopping the drug), with subsequent improvement, but not complete resolution of painful dysesthesias. We manage the patients symptomatically (Neurontin, Lyrika) and in some we have cautiously tried to re-introduce another statin.

Treatment of statin-induced myopathic symptoms

The relationship with reduced CoQ10 described above, makes it reasonable to use this coenzyme for the treatment of myopathic symptoms. In one controlled trial, CoQ10 (100 mg /day) showed significant improvement of pain and daily activities, but not of the CK elevation, compared to controls who received Vit E [22]. Another study however, showed no benefit of 200 mg daily [5]. Both of these studies were under-dosed and underpowered. In patients with hyperCKemia or features of necrotizing myopathy we usually prescribe, empirically, high doses of CoQ10, up to 600-800 mg daily. In patients with statin-induced inflammatory myositis, we administer steroids or IVIg.

Prevention of statin myopathy may be accomplished when one anticipates drug interactions. At the more global level however, pharmacogenomics may become useful in the future, if practical issues of routine testing for SLCO1B1 variants are overcome. Since 60% of the patients with simvastatin myopathy were attributed to variant SLCO1B1 [20], it is very likely that checking for homozygosity for the risk allele, could significantly reduce the incidence of myocytotoxicity.

Reports questioning the safe use of statins in myasthenia gravis are of interest [23]. In one report, 6 of 54 patients (11%) experienced worsening of MG symptoms during the first 8 weeks after starting therapy, with higher level of AChR antibodies in two of them; three of these patients improved after discontinuation of statin. In rare cases, initiation of statin therapy has either

unmasked pre-existing MG or worsened it. The neurologist should be aware of such a possibility but the evidence of toxicity remains still weak. This author has not witnessed such a worsening in more than 20 MG patients who take statins for increased cholesterol after steroid use. Whether the concomitant use of steroids prevented such a theoretical worsening, remains unclear.

2. ANTI-RHEUMATIC, ANTI-INFLAMMATORY AND IMMUNOSUPPRESSIVE DRUG-INDUCED MYOPATHY

a) *D-penicillamine*

This is the best known drug responsible for immune-mediated neuromuscular complications including polymyositis and myasthenia. The incidence of PM and DM induced by D-penicillamine is about 0.6% [1-5]. Myositis improves after the drug is discontinued but some times immunosuppressants are required. It is very likely that patients with alleles predisposing to the development of PM and DM are more susceptible to developing these rare complications.

b) *Chloroquine and Hydroxychloroquine*

The antimalarial drugs chloroquine and hydroxychloroquine, often used by rheumatologists can cause macular and corneal degeneration, peripheral neuropathy, and myopathy. The myopathy is seen with long-term administration of high doses of chloroquine (500 mg daily) [14]. At times, it may be associated with sensory neuropathy. Clinically and histologically, this myopathy resembles acid maltase deficiency. It is characterised by muscle weakness with often normal CK level, an observation that should be kept in mind by the clinicians. Respiratory muscles may be also affected. The histological features resemble those occurring with acid maltase deficiency namely, multiple vacuoles with acid phosphatase-positive material, myeloid bodies within the vacuoles, and enlarged lysosomes with increased lysosomal enzyme activity [7]. The myopathy is slowly reversible upon drug discontinuation.

c) *Colchicine Myopathy*

Colchicine interferes with the growth of microtubules, thereby affecting mitosis by interacting with tubulin and inhibiting the polymerization of microtubules [1, 3, 6]. After long-term use, colchicine causes a vacuolar myopathy with accumulation of lysosomes and autophagic vacuoles, as well as an axonal neuropathy [6]. Patients who are between 50 and 70 years of age and who have gout and a mild, chronic, renal insufficiency or take nephrotoxic drugs, such as cyclosporine, are predominately affected. Symptoms include proximal muscle weakness, elevation of the serum CK level, distal sensory involvement, and areflexia. Symptoms resolve 4 to 6 weeks after discontinuance of the drug.

d) *Interferon- α*

The drug used for chronic active hepatitis can cause autoimmune phenomena after long term use, including polymyositis and myasthenia. In our experience most patients have a chronic-fatigue-like symptomatology that may improve with low-dose prednisone. Cases with documented myositis however, have been reported [1]. Symptoms improve after discontinuation of the drug.

e) *Cyclosporine and Tacrolimus*

In our experience, these drugs rarely cause myopathy by themselves but they are implicated in myotoxicity when used concurrently with statins or colchicine.

f) Corticosteroids

Patients with hyperadrenocorticism (i.e., Cushing syndrome) can develop weakness. Similar phenomena can occur during chronic administration of prednisone (usually at dosages greater than 20 mg daily) or dexamethasone [2]. The latter, may cause weakness within 15 days when administered to cancer patients at high cumulative doses between 186-1896 mg [1]. The steroid-induced myopathic weakness is generally mild, spares the neck flexor muscles, and may theoretically aggravate the weakness caused by the underlying immune disease or malignancy. Lowering the steroid dose reverses the myopathic weakness. The serum CK level is normal, and EMG is not informative.

Steroids do not actually cause a true myopathy, hence the normal CK and EMG, but only atrophy of type II fibers “steroid-atrophy” (Figure). The term “steroid-myopathy” is therefore a misnomer. Dexamethasone in cancer patients is more likely to cause weakness probably due to a compounding effect on type II fiber by steroids and the remote effects of cancer.

Acute quadriplegic myopathy in the form of critical illness can be seen in mechanically ventilated patients receiving high doses of corticosteroids, especially for asthmatic disorders, in combination with depolarizing agents such as pancuronium [2,24]. These patients have histological features identical to critical illness, myopathy, characterized by selective loss of thick filaments [24]. Rats treated with high-dose-steroids develop the same clinicopathologic features if their muscles are acutely denervated, confirming the toxic effect of steroid in the exposed muscle membrane [25]. We have seen such acute paralysis paradoxically in rare patients with myasthenia gravis whose muscles are theoretically in a functionally state of denervation from the circulating AChR antibodies. The disease is reversible with aggressive mobilization and discontinuation of steroids.

3) ANTI-NUCLEOSIDE ANALOGUES

Patients treated with the nucleoside analogue Reverse Transcriptase Inhibitors (NRTIs), develop a varying degree of myopathy or neuropathy after long-term therapy. Zidovudine (AZT) causes myopathy [26]; zalcitabine (ddC), didanosine (ddl) and Lamivudine (3TC) cause neuropathy; stavudine (d4T) and Fialuridine (FIAU) cause neuropathy or myopathy and lactic acidosis [27, 28]. The tissue distribution of phosphorylases responsible for phosphorylation of NRTIs relates to their selective tissue toxicity [29].

The clinical features of zidovudine-myopathy are proximal muscle weakness, occurring 6-12 months after treatment onset, myalgia (predominantly in the thighs and calves), fatigue, myopathic changes on EMG, and elevated serum CK levels, which can increase with exercise [26,29]. Weight loss and elevation of the serum lactate level may herald the onset of zidovudine myopathy. Five weeks after zidovudine is discontinued, symptoms resolve, muscle histology improves and the depleted mtDNA rebounds. The above symptomatology occurred in patients taking high doses

of AZT. Currently, with the lower dose used, the most common symptom is fatigue and myalgia.

The unique histological features of zidovudine myopathy are ragged-red fibers, many cytochrome-c oxidase-negative fibers with deficiency of COX (complex IV) activity and intracellular fat accumulation, all indicative of mitochondrial dysfunction[26]. Zidovudine is a DNA-chain terminator that inhibits the γ -DNA polymerase in the mitochondrial matrix, terminates the mtDNA synthesis and results in as much as a 78% depletion of muscle mtDNA [26-28]. AZT-treated patients also demonstrate high lactate production and marked phosphocreatine depletion, as determined with in vivo MRS spectroscopy owing to impaired oxidative phosphorylation. Animals treated with AZT and cells in culture treated with NRTIs develop similar changes. There is now evidence that NRTI-related neuropathy is also due to mitochondrial toxicity with mtDNA depletion in the affected nerves and severe abnormality in the mitochondria of axons and Schwann cells[27].

The NRTIs (AZT, ddC, ddI, d4T, 4TC) contain azido groups that compete with natural thymidine triphosphate as substrates of DNA pol-gamma and terminate the mtDNA synthesis [29]. In contrast to AZT and d4T, another nucleoside analogue, the Fialuridine (FIAU), causes an irreversible mitochondrial myopathy with lactic acidosis, because FIAU contains 3'-OH groups and serves as an alternate substrate for thymidine triphosphate with DNA pol-gamma. As a result, it is incorporated within the mitochondrial DNA chain causing permanent mtDNA dysfunction [29]. A syndrome of lipodystrophy, lactic acidosis, and myopathy has been also seen with highly active antiretroviral therapy, consisting of one protease inhibitors in combination with two nucleoside analogues, especially stavudine (d4T) [28].

The NRTI-induced mitochondrial dysfunction has influenced the clinical application of these agents especially at high doses and when combined. They have produced in humans a new category of acquired mitochondrial toxins which cause clinical manifestations that resemble the genetic mitochondrial disorders.

4) DRUG CONTAMINANTS CAUSING PREDOMINATELY FASCIITIS

a) Eosinophilia–myalgia syndrome and toxic-oil syndrome

In eosinophilia–myalgia syndrome and toxic-oil syndrome there is inflammation predominantly localized to the fascia, dominated initially by eosinophils (eosinophilic fasciitis). These two syndromes are triggered by exogenous toxins and represent classic examples of myocytotoxicity due to adulterated natural products. These two forms of fasciitis are different from hyperacute necrotizing myofasciitis (“flesh-eating disease”) caused usually by b-haemolytic streptococci, presumably acting as a superantigen, that follow a variety of wounds and surgical interventions [30].

The eosinophilia–myalgia syndrome was caused by prolonged oral intake of large doses of a contaminated L-tryptophan preparation taken as a therapeutic agent, mainly for insomnia [31]. There was marked systemic eosinophilia with generalized myalgia and moderate muscle weakness. Another important feature was thickening of the skin, mimicking scleroderma. Histologically, lymphocytes (CD8+ cytotoxic cells), and eosinophilic polymorphonuclear leukocytes early in the disease process, infiltrate the perimysial region and interstitial spaces of muscle [32]. Muscle fiber necrosis was rare and serum CK activity did not rise significantly. Coexisting peripheral

neuropathy was not uncommon. In some cases, the muscle biopsy showed no abnormality, despite clinical symptoms.

The pathogenic factor appears to be a contamination of L-tryptophan with an acetaldehyde ditryptophan derivative, which seems to induce an autosensitisation [32]. The disease usually subsides after cessation of exposure but resolution may be slow. Corticosteroid therapy may help to accelerate recovery.

b) Macrophagic myofasciitis

This is a distinctive inflammatory disorder identified in several French patients who presented with myalgias, fatigue and mild muscle weakness [33]. Muscle biopsy revealed pronounced infiltration of the connective tissue around the muscle (epimysium, perimysium and perifascicular endomysium) by sheets of periodic acid–Schiff base-positive macrophages and occasional CD8+ T cells. Serum CK may at times be elevated. Most patients respond to glucocorticoid therapy, and the overall prognosis is favourable. The pathology is almost always seen at the sites of previous vaccinations, even several months later, and has been linked to a type of aluminium component used as a substrate for preparation of the vaccines. Macrophagic myofasciitis has been reported exclusively from France. The author has not seen any case in USA or Greece among a large number of patient referrals and review of biopsy specimens.

5) TOXICITY FROM DIETARY AGENTS

a) Germanium Myopathy

Germanium and its compounds have been used in elixirs or dietary supplements promoted by health-food stores. This compound causes a toxic myopathy characterized by muscle weakness with vacuolization, increased phosphatase activity and lipid accumulations. Abnormal mitochondria are typically seen [34].

b) Emetin

This is an alkaloid derived from ipecac used mainly as an emetic in acute poisoning. Syrup of ipecac is often abused by anorectics to induce vomiting. It may cause skin changes resembling dermatomyositis, as well as a myopathy with cardiotoxicity. The drug affects intermediate filaments resulting in disruption of the Z discs followed by breakdown of myofilaments and myofibrillar protein accumulations, similar to those seen in desmin myopathies [35]. Myotoxicity is seen with doses above 500 mg given over a 10 day period. The changes are reversible, but recovery is slow [5].

6) TOXICITY FROM RECREATIONAL DRUGS

These include cocaine, heroin, amphetamine, PCP and ETOH causing rhabdomyolysis and sometimes compression syndrome [36]. The illicit drugs are almost always mixed with various agents. Whether the drugs by themselves affect the muscle, or it is the combination with the adulterants that trigger the toxicity, remains unclear.

Patients with alcoholism can develop an acute or a chronic myopathy. The acute myopathy presents as rhabdomyolysis or myoglobinuria and it is preceded by muscle edema and pain. It can recur if the patient resumes drinking. Acute myopathy in patients with alcoholism may also be related to

hypokalemia when the serum K⁺ concentration is below 2.5 mEq. This myopathy is painless, is not accompanied by muscle swelling, and is quickly reversible [37]. Proximal muscle weakness in patients with long-term alcoholism is often multifactorial and is not necessarily due to a primary myopathic process [37]; for example, poor nutrition, inactivity, or neurogenic disease may be involved. Histologically, type II fiber atrophy is the most common abnormality. Some long-term drinkers may experience an asymptomatic elevation of the serum CK level—as much as 20 times higher than normal levels—that is aggravated by physical activity.

Although the exogenous causes of myoglobinuria may be multifactorial, illicit drugs and alcohol account for the majority of the patients. In one of the largest series of 475 patients with myoglobinuria reported from John Hopkins, the cause was illicit drugs/alcoholism in 163 patients, followed by medical drugs (statins, colchicine, AZT, lithium) in 54 [38]. Less frequent causes were muscle diseases in 49, trauma in 42, neuroleptic malignant syndromes in 38, idiopathic in 34, seizures in 32, immobility in 21 and various medical conditions in the rest 40[38].

7) OTHER

Procainamide, Amiodarone, epsilon-aminocaproic acid (EACA) and antipsychotics can rarely cause myopathic symptoms. Of interest among them are the antipsychotics, which, even in the absence of neuroleptic malignant syndrome, can cause hyperCKemia. Up to 10% of the patients receiving clozapine, risperidone, melperone, olanzapine, loxapine, or haloperidol may develop CK elevation [39]. Sometimes the CK may be above 1,000. Muscle biopsy is usually uninformative. Because these drugs are potent serotonin 5-HT₂α inhibitors and 5HT receptors are present in the sarcolemma, the toxic effect may be related to blockade of these receptors [1,3].

EACA, after prolonged administration, can cause a necrotizing myopathy. The drug is not used anymore. Amiodarone causes a neuropathy but when combined with simvastatin can cause rhabdomyolysis, as mentioned earlier.

8) MYOPATHY CAUSED BY INTRAMUSCULAR INJECTIONS

a) Needle myopathy

Although intramuscular injections of various drugs can cause swelling, local pain or haemorrhage, it is unclear if some of the injected material can also cause necrotizing myopathy. Needle insertions by themselves however, can cause mild muscle injury and elicit an inflammatory response that might persist for up to a month (needle myopathy). The clinical importance of this effect relates to insertion of EMG needles and the subsequent performance of a diagnostic muscle biopsy. Muscle biopsies should not be performed at the injection sites at least one month after the needle insertion.

b) Localized indurations and fibrosis

Fibrosis of the overlying connective tissue, fascia and skin due to formation of granulation tissue can occur after chronic intramuscular administration of certain antibiotics, opiates, pentazocine and other drugs. This condition results in a fibrous contracture of segments of affected muscle causing a fixed posture of a limb [1,3,5]. Whether this is due to repeated needle trauma or due to a combination with the offending drug is unclear. The acidity or

alkalinity of the injected material or repeated infections, as seen in drug addicts, may be additional contributing factors [5].

c) Immunity to intramuscularly injected, recombinant Adeno-Associated Virus (rAAV)-mediated gene transfer

rAAV, carrying different promoter-transgene cassettes, when injected into muscle for delivery of muscular dystrophy genes, can elicit a robust cellular immune response with CD8+ T cells invading MHC-I antigen expressing muscle fibers, similar to the changes seen in polymyositis [40]. This is due to a transgene-related effect because intramuscular injections of rAAV expressing no transgene do not elicit such an immune response [40]. The induction of cellular immunity to AAV vectors in humans appears to be a limiting factor of intramuscular gene delivery and requires immunosuppression. At present, the development of cell-mediated cytotoxicity responses to AAV capsid peptides appears to limit the transgene expression in the injected muscle, necessitating safer vectors for direct gene delivery to the muscle.

FIGURE

Severe atrophy of type II fibers “steroid-atrophy” , in a patient with inflammatory myopathy (ATP-ase stain). Note the inflammatory infiltrate,s indicating that steroid atrophy co-exists with inflammation

Table 1. Types of myopathies induced by drugs

1. Necrotizing myopathy
a) Statins, b) fibrates, c) epsilon Aminocaproic Acid (EACA)
2. Inflammatory myopathy
a) Statins, b) D-penicillamine, c) α -interferon, d) intramuscular gene therapy
3. Thick-filament loss myopathy
Critical illness neuromyopathy
4. Type II fiber atrophy
Steroids, systemic effects of cancer
5. Mitochondrial Myopathies
AZT, fialuridine, germanium
6. Lysosomal storage myopathies
Chloroquine, (? Perhexiline)
7. Anti-microtubular myopathies
Colchicine
8. Myofibrillar myopathies
Emetin/ ipecac poisoning
9. Fasciitis (toxic oil syndrome, EMS, Macrophagic fasciitis)

Table 2. Most common drugs and toxic conditions causing myopathy or hyperCKemia

- 1) Anti-cholesterol
 - a) Statins (cerivastatin >simvastatin> atorvastatin> lovostatin> pravastatin> fluvastatin)
 - b) Concomitant drugs increasing the risk of statin-associated myopathic symptoms [Fibrates (especially gemfibrozil) but also clofibrate or Niacin; cyclosporine; Azole antifungals; macrolide antibiotics; HIV-protease inhibitors; Nefazodone; verapamil; amiodarone.
- 2) Anti-Rheumatic/Inflammatory/Immunosuppressive
D-penicillamine, Colchicine, Chloroquine, α -interferon, Cyclosporine, Tacrolimus, Steroids
- 3) Antinucleoside analogues
Zidovudine, Fialuridine
- 4) Contaminated products
L-tryptophan contaminants; Aluminium-containing vaccines; Toxic oil
- 5) Dietary agents
Germanium, Emetin
- 6) Recreational
Cocaine, Heroin, Amphetamines, PCP, Alcohol
- 7) Other
Anti-psychotics, Epsilon aminocaproic Acid and (EACA), Procainamide, Amiodarone (when combined with statins)
- 8) Intramuscular injections
Needle Myopathy, Fibrotic agents (Meperidine Pentazocine), Gene therapy

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