REVIEW by F L Mastaglia

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DRUG INDUCED MYOPATHIES

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Iatrogenic disorders are an important cause of morbidity, mortality, and admission to hospital. Although drug induced myopathies may be individually uncommon, they are nevertheless an important group of disorders that must be considered when evaluating any patient presenting with muscular symptoms. Their importance lies in the fact that unlike many other neuromuscular disorders they are potentially reversible once the offending agent is withdrawn, whereas failure to recognise their iatrogenic nature will result in unnecessary morbidity and, in some instances, even a fatal outcome.

A variety of drugs used in different branches of medicine are potentially myotoxic (table 1), or can cause muscle weakness and fatigue through an effect on neuromuscular transmission or peripheral nerve function.[1,2] Some drugs such as the glucocorticoids have a predictable dose related effect and will induce myopathic weakness in any individual treated with sufficiently large doses for long enough. On the other hand, in the case of drugs such as the statins, myopathy only develops in a relatively small proportion of individuals suggesting that there is an idiosyncratic vulnerability, the nature of which is poorly understood. While the potential for glucocorticoids, statins, and a number of other therapeutic agents to cause myopathy is well established, in the case of some of the other drugs that have been implicated in case reports the evidence is more tenuous and an aetiological link remains unproven.

WHEN TO THINK OF A DRUG INDUCED MYOPATHY

Drugs can induce various pathological types of myopathy and the resulting clinical manifestations are equally variable, ranging from mild myalgia or muscle cramps to profound generalised muscle weakness which may be accompanied by myoglobinuria and acute renal failure in patients with severe rhabdomyolysis (table 2). Any drug is a potential suspect. A detailed drug history should therefore be obtained in all patients with such symptoms and the list of drugs should be scrutinised, not only for the usual suspects such as the statins and glucocorticoids (table 1), but also for new therapeutic agents whose full adverse effect profile may not yet be known, and for combinations of potentially myotoxic agents. As statins are now so widely prescribed it is not uncommon to find that some patients are taking both a statin and another myotoxic drug such as colchicine for the treatment of gout, or also have a high alcohol consumption which independently predisposes to myopathy. This situation has been referred to as 'synergistic myotoxicity'.[3] It is particularly important not to forget the possibility of a drug induced myopathy in patients who already have another pre-existing myopathy (for example, muscular dystrophy or inflammatory myopathy), or another neuromuscular disorder, especially when there is an unexpected deterioration or acceleration of their condition.

TABLE 1 Drugs that may cause myopathy

Lipid lowering agents
- Statins
- Fibrates
- Nicotinic acid
- Ezetimibe

Glucocorticoids
- Prednisone and prednisolone
- Methylprednisolone
- Dexamethasone
- Inhaled steroids

Anti-rheumatic drugs
- Colchicine
- Chloroquine
- Hydroxychloroquine

Cardiovascular drugs
- Amiodarone
- Perhexiline

Other drugs
- Emetine
- ∑-aminocaproic acid
- Etretinate
- Zidovudine
- Interferon-α
- D-penicillamine
- Streptokinase

TABLE 2 The clinical spectrum of the drug induced myopathies

- Asymptomatic hyperCKaemia
- Myalgia and muscle cramps
- Myotonia
- Acute rhabdomyolysis
- Acute quadriplegic myopathy
- Chronic proximal myopathy
- Mitochondrial myopathy
- Inflammatory myopathy
- Dyskalaemic myopathy
- Focal myopathies

LIPID LOWERING AGENT MYOPATHY

Myopathy is an important adverse effect of the statin and fibrate groups of lipid lowering drugs that interfere with the biosynthesis of cholesterol. A myopathy may also develop in patients

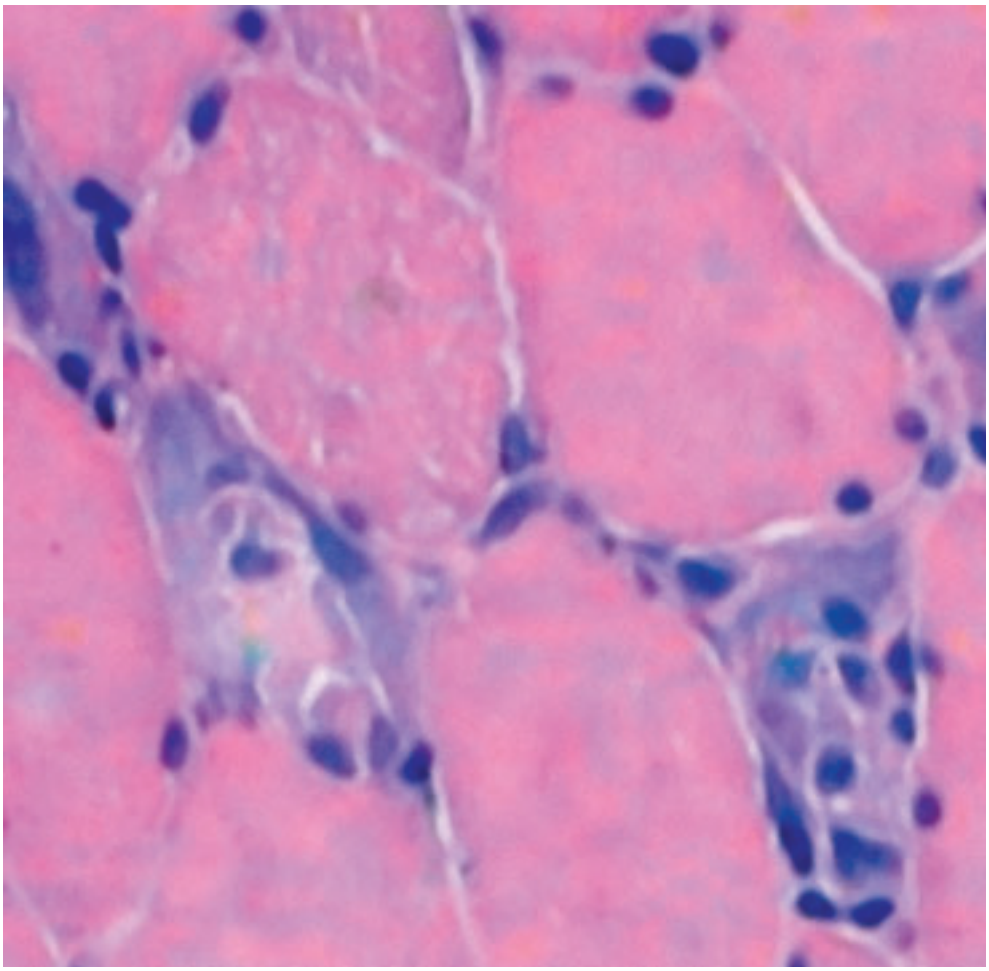

Figure 1
Necrotising myopathy in a patient on atorvastatin. Haematoxylin and eosin stained necrotic fibres (blue staining) undergoing myophagia and regeneration (courtesy of Professor P Serdaroglu).

treated with high doses of nicotinic acid.[4] A case control study in the United Kingdom showed that the risk of myopathy was increased eightfold in patients taking a statin and 42-fold in patients on a fibrate.[5] Although the absolute risk is still small, in view of the fact that millions of individuals are now taking statins and that these agents are being increasingly prescribed, the number of patients developing muscle symptoms and seeking medical attention is significant and likely to grow. The lower risk of myopathy found in a number of the pre-marketing statin trials in which differences in the frequency of muscular symptoms in the placebo and statin groups were not statistically significant may reflect the exclusion of higher risk patients (see below) and adherence to a more fixed protocol than is likely in real life post-marketing clinical practice.[6]

The statins inhibit the function of the enzyme 3-hydroxy 3-methyl glutaryl coenzyme A (HMG-CoA) reductase, leading to a reduction in the formation of mevalonate which is an important intermediary metabolite in the synthesis of cholesterol, and of ubiquinone (coenzyme Q_{10}) which is an important intermediary in the respiratory enzyme chain.[7] Inhibition of ubiquinone synthesis is thought to be a major factor contributing to the development of the myopathy, and to the exercise intolerance and myalgia experienced by some patients on statins.

Spectrum of the statin myopathies

The spectrum of severity of the statin myopathies is very broad (table 3). The most frequent manifestation is asymptomatic hyperCKaemia, which is generally mild, and which usually reverts to normal following withdrawal of the statin. In a subgroup of patients there is an exaggerated increase in the serum CK level following exercise.[8] The

TABLE 3 Statin associated myopathies

Asymptomatic hyperCKaemia
Acute necrotising myopathy (rhabdomyolysis)
Inflammatory myopathy (polymyositis; dermatomyositis)
Mitochondrial myopathy
Unmasking metabolic myopathy

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most common symptomatic presentation is with myalgia and muscle cramps, usually associated with a raised CK level. In those patients with a more severe necrotising myopathy (fig 1) these symptoms may be accompanied by proximal muscle weakness of variable severity, and more marked increases in CK level. Symptoms usually resolve within a few weeks of withdrawing the drug, but in some patients myalgia and hyperCKaemia may persist for several months or even longer. Acute rhabdomyolysis is the most severe form of statin myopathy. Although rare, it is potentially life threatening, with an estimated mortality of 0.15 per 1 million prescriptions.[9]

Which drugs are the most risky and which patients are at increased risk?

The risk of myopathy is greater with the lipophilic statins (for example, simvastatin, atorvastatin, and lovastatin) than with the hydrophilic compounds (for example, pravastatin). Cerivastatin, the most hazardous drug in the first group, was withdrawn from the market in 2001 after the occurrence of more than 100 cases of fatal rhabdomyolysis. In a recent retrospective survey in the United States, the risk of severe rhabdomyolysis resulting in hospitalisation was found to be 12 times greater in patients treated with cerivastatin than with simvastatin, atorvastatin, or pravastatin, and seven times greater in patients taking one of the latter three drugs in combination with a fibrate.[10] The newly marketed statin rosuvastatin has also been associated with a higher risk of myopathy and other adverse effects such as renal failure and hepatotoxicity when used in high doses.[11]

Certain groups of patients are at greater risk of developing statin myopathy and rhabdomyolysis. These include the elderly, those on high doses of statins, and patients with diabetes, hypothyroidism, chronic renal failure, or hepatobiliary disease. Patients taking multiple medications, in particular gemfibrozil, and drugs which are substrates for or which inhibit the CYP3A4 enzyme system which metabolises most of the statins, also have a higher risk of developing myopathy: these include cyclosporine, macrolide antibiotics (for example, erythromycin and clarithromycin), azole antifungal agents (for example, itraconazole and ketoconazole), calcium channel blockers (for example, mibefradil, diltiazem, and verapamil), the SSRI antidepressants, as well as a number of others.[12] Co-administration of a statin and another agent metabolised by the same CYP450 enzyme pathway will result in increased levels of the statin and so myotoxicity may only develop when one of these drugs or another potentially myotoxic agent is started.[3] Statins should therefore be administered with caution, using the lowest possible dose, in the above groups of patients and in patients taking other medications that may affect the pharmacokinetics of the drug. Regular consumption of grapefruit juice, which contains the CYP3A4 inhibitor furano-coumarin, can also affect the pharmacokinetics of statins and may trigger rhabdomyolysis.[13] It is therefore recommended that grapefruit and grapefruit juice should be avoided or kept at a low level during statin therapy. Genetic polymorphisms in the CYP450 system may account for individual variation in susceptibility to myotoxicity.[14]

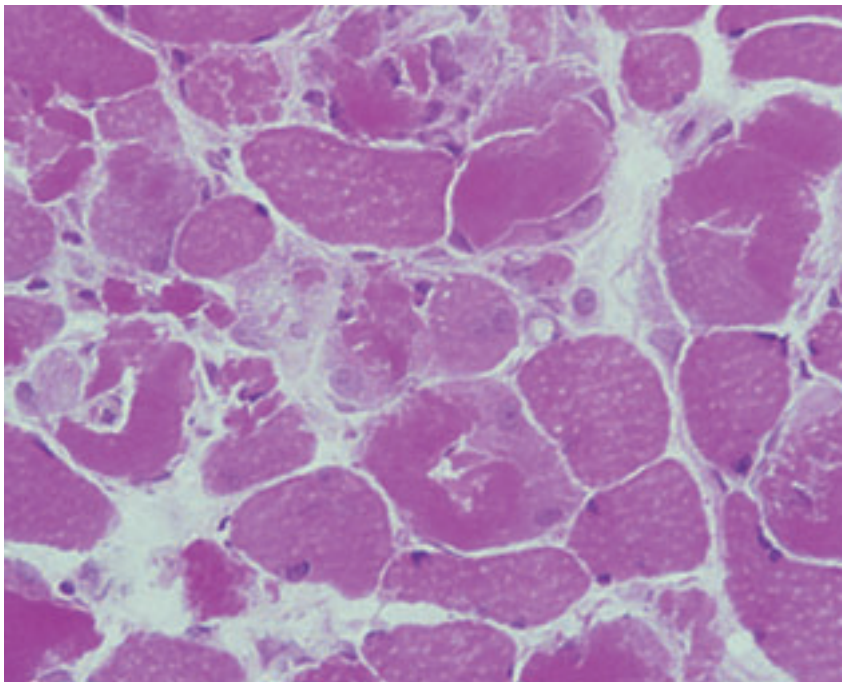

Figure 2
Severe rhabdomyolysis due to ∑-aminocaproic acid. Haematoxylin and eosin stained section showing phagocytic breakdown of muscle fibres and associated regenerative changes.

What to do?

It is not known whether persisting elevation of the serum CK level in patients without symptoms will eventually lead to the development of a symptomatic myopathy. In practice it has been considered safe to continue treatment unless the CK level exceeds 3–5 times the upper limit of normal.[15] My personal approach in this situation is to repeat the CK level and review the patient and, if the CK level

TABLE 4 Drug induced inflammatory myopathies

Polymyositis
Dermatomyositis
Interstitial myositis
Eosinophilic fasciitis
Macrophagic myofasciitis

continues to rise, or if muscular symptoms develop, stop the medication.

In patients who have definite symptoms of a myopathy and a raised CK level, the statin should be stopped. Mild symptoms such as myalgia and cramping usually resolve over a period of a few weeks but recovery is slower in patients with a more severe necrotising myopathy and may take several months, during which there is a gradual improvement in muscle weakness and normalisation of the serum CK level. When the symptoms have fully resolved and the CK level is normal, the usual practice is to switch to a potentially less myotoxic statin such as pravastatin, alone or in combination with ezetimibe, which reduces the intestinal absorption of cholesterol. However, continued monitoring is necessary as there have recently been reports of myalgia and myopathy occurring in patients taking ezetimibe.[16]

In some patients myalgia, reduced exercise tolerance, and a raised CK may persist for longer periods and they are often referred to a neuromuscular clinic. My own approach, if the patient is seen within the first few months after stopping the statin, is to prescribe co-enzyme Q_{10} supplements and, if the symptoms persist after a period of about six months, or even earlier if there is continued deterioration and rise in the CK level, to perform a muscle biopsy. A number of such patients turn out to have an inflammatory or mitochondrial myopathy which has been induced or unmasked by the statin.[17]

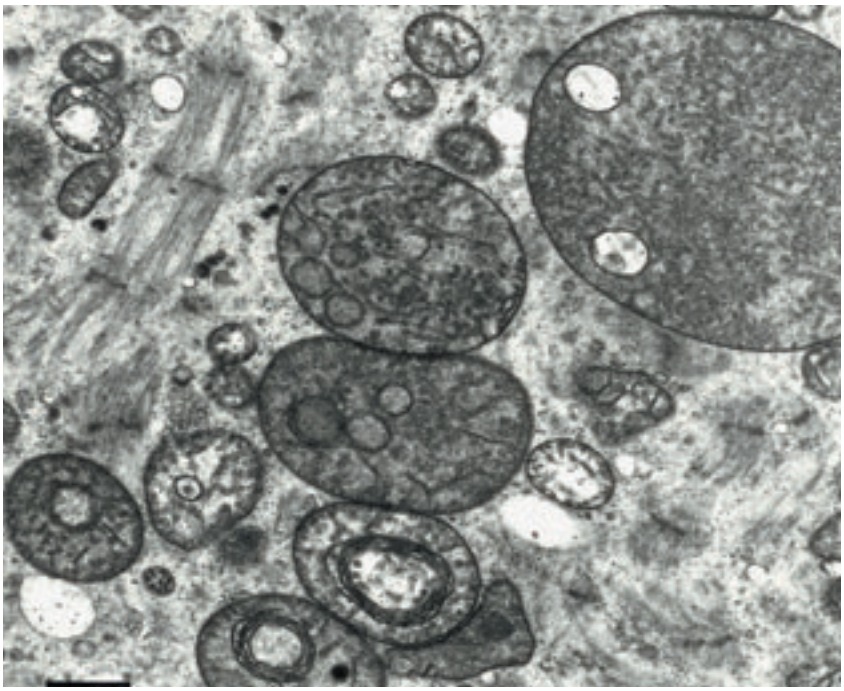

Figure 3
Mitochondrial myopathy due to zidovudine. Electron micrograph of portion of a muscle fibre showing greatly enlarged and pleomorphic mitochondria with abnormal cristae mitochondriales (bar=1 mm) (courtesy of Dr P Panegyres).

ACUTE RHABDOMYOLYSIS

This is the most serious form of drug induced myopathy. In addition to statins and other drugs that cause a necrotising myopathy (for example, ∑-aminocaproic acid), it may occur following self-administration of heroin, cocaine, and other narcotic drugs, or intoxication with alcohol, and in patients with prolonged drug induced coma, seizures, dyskinesias, or the neuroleptic malignant syndrome.[18] Although a variety of other drugs have also been implicated in causing acute rhabdomyolysis, few of these have been proven to be myotoxic and in many cases other factors such as muscle compression due to prolonged immobility, hypoxia, and hypotension are likely to have played a major role.

Severe muscle pain, tenderness, and weakness usually develop over a period of 24–48 hours and may be associated with marked swelling, particularly of the lower limb muscles, that may lead to the development of a secondary compartment syndrome. The serum CK level is markedly raised and electromyography reveals florid myopathic motor unit changes and spontaneous potentials in multiple muscles. Myoglobinuria is an early feature and may lead to acute oliguric renal failure. Muscle biopsy shows widespread muscle fibre necrosis, and mild reactive inflammatory changes (fig 2). The prognosis for recovery is generally good, but some patients die as a result of multiple organ failure.

The management of patients with acute rhabdomyolysis is primarily supportive and symptomatic with careful monitoring of renal function and fluid and electrolyte balance along with early treatment of any metabolic derangements. It is important that such patients are managed jointly with a renal physician or in an intensive care unit. Measurement of intracompartment pressures is important in patients with severe muscle swelling and pain. Fasciotomy and muscle decompression may be required if the pressure falls below mean arterial pressure

MITOCHONDRIAL MYOPATHY

A myopathy characterised by myalgia, exercise intolerance, proximal or generalised muscle weakness, and raised CK levels may occur in patients with the acquired immunodeficiency syndrome following long term treatment with zidovudine, which inhibits mtDNA replication.[19, 20] Muscle biopsies in such cases have shown ragged red and COX negative fibres with pleomorphic mitochondria (fig 3). A muscle

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biopsy is the only reliable way of distinguishing zidovudine myopathy from an HIV associated inflammatory myopathy.

A mitochondrial myopathy with similar symptoms has also been reported in patients taking statins.[21] These cases differ from the more usual form of statin myopathy in having normal serum CK levels. Mitochondrial abnormalities are a prominent feature of the myopathy induced by germanium which is a constituent of a number of dietary supplements and elixirs.[22]

INFLAMMATORY MYOPATHIES

Polymyositis/dermatomyositis

Drugs may occasionally initiate an immune mediated inflammatory myopathy (table 4). The best known examples are D-penicillamine and interferon-α, both of which have been associated with the development of polymyositis or dermatomyositis as well as other autoimmune disorders such as myasthenia gravis.[23, 24] In the case of D-penicillamine the occurrence of myositis has been associated with the HLA-B18, B35, DR4 haplotype.[23] In most of the reported cases the myositis has improved promptly on withdrawal of the medication but in some a course of corticosteroids has been required. An immune mediated inflammatory myopathy has also been reported as a complication of streptokinase administration.[25]

Eosinophilia-myalgia syndrome

The eosinophilia-myalgia syndrome is an interstitial form of eosinophilic myositis and fasciitis which was first reported in the early 1990s in patients using preparations containing L-tryptophan as a hypnotic. Over 1500 cases were reported to have occurred in the United States.[26] The condition was characterised by severe myalgia, muscle tenderness and hyperaesthesia with oedema and induration of the skin of the extremities, and a marked eosinophilia. In some cases a peripheral neuropathy and other systemic features were also present.[26] The bulk source of the tryptophan preparation in the American cases was traced to a single manufacturer and the syndrome is now thought to have been caused by a chemical contaminant.[27]

Macrophagic myofasciitis

This condition was first recognised in the 1990s in France where over 130 cases were documented,[28] but it has also occurred in other parts of the world. It is characterised by diffuse myalgia, arthralgia, and fatigue, with a good response to corticosteroid therapy, and is now thought to be caused by intramuscularly injected vaccines containing aluminium hydroxide.[28] Biopsies from the deltoid muscle show inflammatory cell infiltrates around the muscle tissue in most patients. The inflammatory cells are mainly lymphocytes and macrophages, the latter containing inclusions that have been shown to be composed of aluminium hydroxide. All 50 patients in one report had been vaccinated for either hepatitis or tetanus.[28] Symptoms may develop immediately after vaccination or be delayed for as long as a few months to a few years.

TABLE 5 Glucocorticoid induced myopathies

Chronic proximal myopathy
Acute quadriplegic myopathy (critical care myopathy; acute steroid myopathy)
Laryngeal myopathy (inhaled steroids)
Diaphragmatic myopathy (in asthmatics)

CORTICOSTEROID MYOPATHY

Myopathy is a common complication of prolonged treatment with glucocorticoids because these agents interfere with the synthesis of muscle proteins (table 5).[29] It is most likely to occur in individuals treated with the 9-α-fluorinated steroids dexamethasone, betamethasone and triamcinolone,[30] but may also occur with prolonged administration of prednisone or prednisolone. The risk of myopathy is greatest in patients treated with daily doses of prednisone over 40 mg, but a myopathy may develop even with doses as low as 10 mg per day in some patients if they

BULBO-SKELETAL MYOPATHY[42]

A 32 year old female with anorexia nervosa and depression developed myalgia and increasing generalised weakness over a period of several weeks leading to inability to walk. She also had dysphagia and nasal regurgitation of liquids. She was not taking any regular medications. Sensation and reflexes were normal. The serum CK level was raised (x15) and EMG confirmed a myopathic process. Muscle biopsy showed a myopathy with cores and cytoplasmic bodies in muscle fibres. Emetine myopathy was diagnosed and a urine screen for emetine was positive. The patient subsequently admitted to purging with ipecac, which contains emetine. Her condition improved progressively once she stopped doing this.

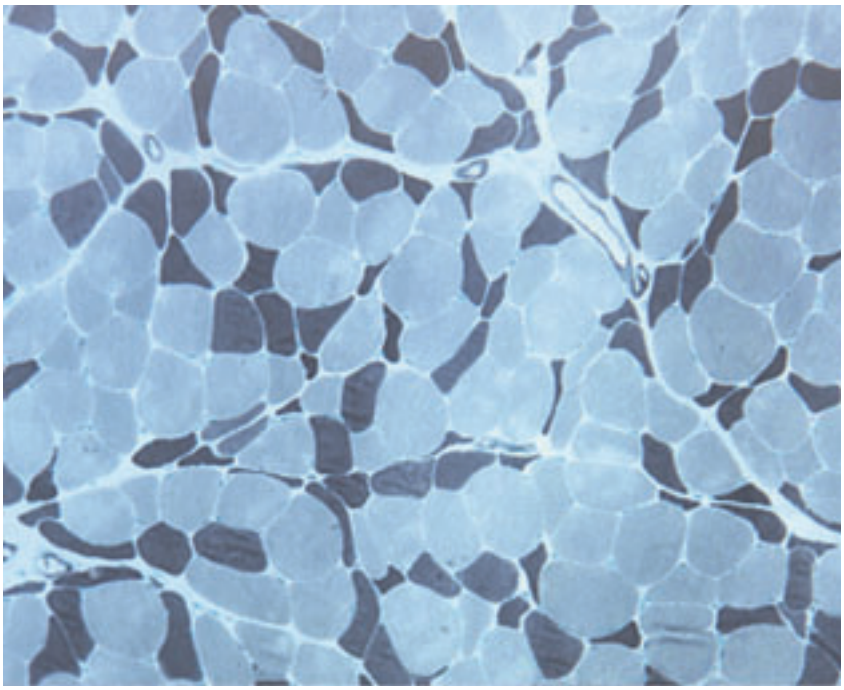


Figure 4
Corticosteroid myopathy. Myosin ATPase (pH 9.4) preparation showing selective atrophy of type II (darkly stained) muscle fibres.

are continued for prolonged periods.[31]

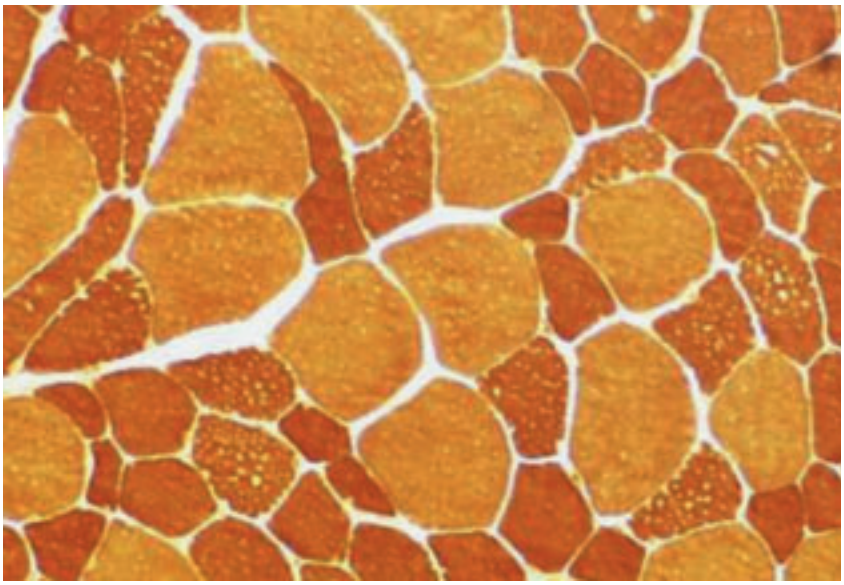
Weakness and atrophy of proximal limb muscles, particularly of the quadriceps femoris, develop insidiously and may become profound and disabling if allowed to progress. The muscles innervated by the cranial nerves are usually spared, but a localised myopathy of the laryngeal muscles resulting in dysphonia has been reported in patients using long term inhaled corticosteroids.[32] It is important to be aware that weakness of the diaphragm may develop in asthmatics on prolonged corticosteroid therapy which may further compromise respiratory function.

The serum CK level is usually normal or reduced and, if raised, should suggest other diagnostic possibilities such as a necrotising or inflammatory myopathy, or other causes for hyperCKaemia (table 6).[33]

Patients with an inflammatory myopathy such as dermatomyositis, polymyositis, or inclusion body myositis may develop a secondary corticosteroid myopathy if high doses of prednisolone are continued for too long, with a resulting increase in the degree of weakness and disability. The finding of a persistently raised serum CK level and of florid myopathic changes with spontaneous discharges on electromyography in this group of patients favours continued activity of the myositic process rather than a steroid myopathy. However, the two conditions may coexist and in some cases it may be necessary to repeat the muscle biopsy to determine whether or not the myositis is still active. In corticosteroid myopathy the pathological changes are a selective atrophy of type II muscle fibres, and particularly of the type IIB subgroup (fig 4). However, in most cases a muscle biopsy is not necessary unless there is concern about the possibility of an alternative type of myopathy.

The myopathy is usually reversible if the steroid is withdrawn, or if the dose is gradually reduced, or to some extent if an alternate day regimen is implemented. There is some evidence that physical inactivity may render muscles more susceptible to the effects of glucocorticoids and that a regular programme of physical training may help to prevent or reduce the severity of the myopathy.[34]

Figure 5
Chloroquine neuromyopathy. Myosin ATPase (pH 7.2) preparation showing widespread vacuolation which is most prominent in the darker staining type II fibres.



ACUTE QUADRIPLEGIC MYOPATHY

A more severe acute form of myopathy may develop in patients treated with high parenteral doses of corticosteroids, particularly if administered in combination with non-depolarising neuromuscular blocking agents. This condition has been variably referred to as 'acute quadriplegic myopathy', 'critical care myopathy', or 'acute steroid myopathy', and has been encountered particularly in severe asthmatics treated with high doses of intravenous hydrocortisone,[35] and in liver or heart transplant patients.[36, 37] It is characterised clinically by profound generalised muscle weakness, hypotonia, and depression of the tendon reflexes. The respiratory muscles are often severely affected leading to difficulties in weaning off the ventilator. The CK level is usually moderately raised, but may be normal

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in some cases. Histological changes in muscle biopsies are non-specific, including atrophy, necrosis, and central loss of ATPase activity in muscle fibres. However, electron microscopy shows a selective loss of thick (myosin) filaments in sarcomeres, with preservation of Z-bands and thin filaments, which is characteristic of the condition.

The electrophysiological hallmark of acute quadriplegic myopathy is markedly reduced excitability to direct muscle stimulation. However, the electromyographic findings are non-specific and nerve conduction studies are normal, apart from a reduction in amplitude of the compound muscle action potentials in some cases. Nerve conduction studies should, however, always be performed to exclude a 'critical care neuropathy' or other acute form of peripheral neuropathy such as the Guillain-Barré syndrome, which may be clinically indistinguishable from acute quadriplegic myopathy. Repetitive nerve stimulation studies should also be performed to exclude myasthenia gravis or other disorder of neuromuscular transmission such as botulism.

The prognosis for recovery is generally good, and better than that in critical care neuropathy in patients who survive the intensive care unit treatment period. Gradual recovery usually occurs over a period of several months with the help of an intensive programme of physiotherapy and physical activity.

DYSKALAEMIC MYOPATHY

Diffuse muscle weakness can develop in individuals who become severely hypokalaemic during treatment with thiazide diuretics, amphotericin B, carbenoxolone, lithium, or fluoroprednisolone-containing nasal sprays, or as a result of laxative abuse.[18] Hypokalaemic myopathy may also develop as a result of consuming large quantities of liquorice, or liquorice extracts which are constituents of certain traditional Chinese drugs, or of snuff or chewing tobacco, all of which contain the powerful mineralocorticoid analogue glycyrrhizinic acid. Profound muscle weakness may also develop due to hyperkalaemia in patients treated with potassium-retaining diuretics.

The weakness in such cases is usually generalised and may be profound, with hypotonia and depression of the tendon reflexes, and so may resemble the Guillain-Barré syndrome. In some cases weakness is episodic, resembling familial hypokalaemic periodic paralysis. The serum CK level is usually markedly raised and myoglobinuria and acute renal failure may develop. Histological changes in affected muscles consist of swelling and vacuolation of muscle fibres, and in more severe cases, necrosis and regeneration.[38] However, muscle biopsy is not necessary to make the diagnosis. Complete recovery is the rule after correction of the hypokalaemia or hyperkalaemia.

TABLE 6 Causes of sustained elevation of serum creatine kinase activity

- Physical exercise
- Muscle trauma (pressure, injections)
- Dyskinesias
- Psychosis/delirium
- Drugs (alcohol, others)
- Hypothyroidism
- Hypokalaemia
- Myopathies
  - Muscular dystrophies
  - Malignant hyperthermia
  - Metabolic
  - Inflammatory
- Idiopathic hyperCKaemia

MYOTONIA

A number of drugs including colchicine, chloroquine, dichlorophenoxyacetate, clofibric acid, 20,25-diazacholesterol, and the statins may induce electrical myotonia by altering the excitability of the plasmalemma, but myotonia is rarely apparent clinically.[39] In addition, certain drugs may unmask previously undetected myotonia or exacerbate hereditary forms of myotonia. These include the depolarising muscle relaxants, such as suxamethonium, which can markedly exacerbate myotonia during general anaesthesia; non-depolarising

NEUROMYOPATHY

A 55 year old female with systemic lupus erythematosus presented with a one month history of progressive limb weakness (more severe proximally than distally), quadriceps atrophy, and absent ankle reflexes. She had been treated with prednisone 10 mg/day for 18 months and chloroquine phosphate for the last five months. The serum CK level was 170 IU/l (normal <200). Electromyography showed myopathic units with fibrillations and positive waves in multiple limb muscles. Nerve conduction studies indicated a sensorimotor peripheral neuropathy. A quadriceps muscle biopsy showed a vacuolar myopathy with numerous autophagic vacuoles in muscle fibres on electron microscopy (fig 5). The biopsy findings were typical of chloroquine myopathy[43] and are not found in glucocorticoid myopathy. She improved progressively over a period of several months after stopping chloroquine. Hydroxychloroquine can cause a similar neuromyopathy,[44] as can amiodarone, perhexiline, colchicine (fig 6), and vincristine.[18]

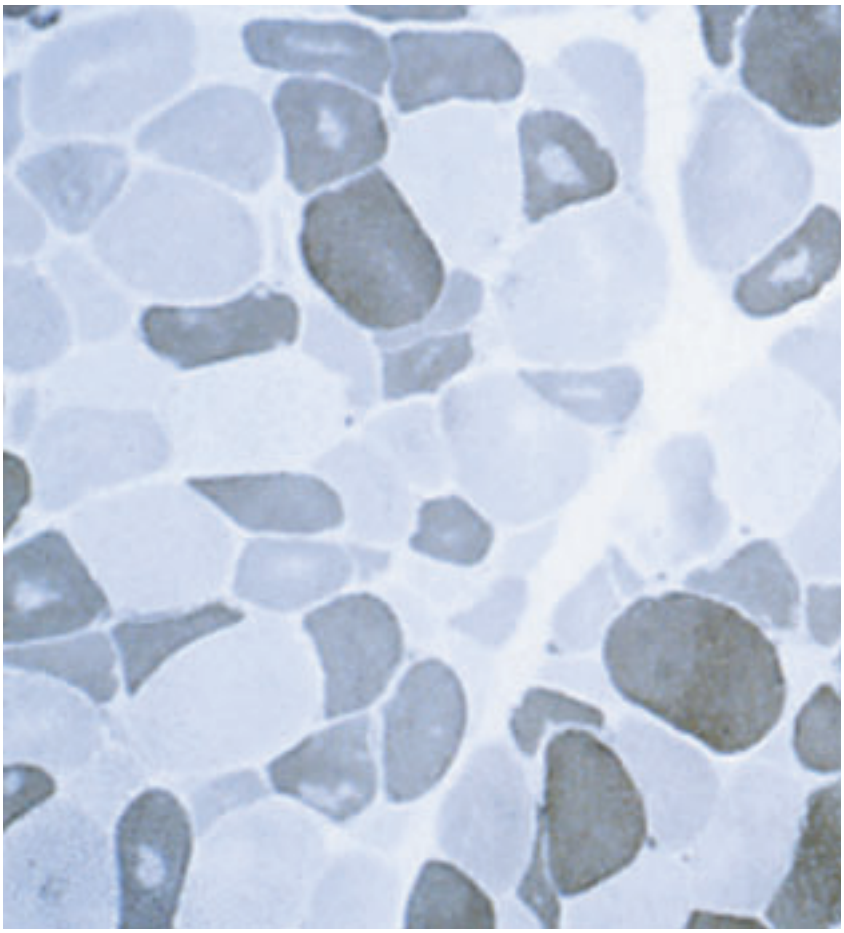

Figure 6
Colchicine neuromyopathy. Myosin ATPase (pH 4.6) preparation showing central cores devoid of enzyme activity which are most apparent in the darker staining type II fibres.

relaxants which do not have this action should therefore be used. The β2-adrenergic blockers propranolol and pindolol and the β2-agonists fenoterol and ritrodrine, can also aggravate myotonia.[40] A number of diuretics, including frusemide, ethacrynic acid, mersalyl, and acetazolamide can induce myotonia experimentally and should be used with caution in individuals with hereditary forms of myotonia.[41]

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CONCLUSIONS

- Always consider a drug induced disorder first when confronted with a patient with myalgia, muscle cramps, or weakness. Take a detailed history of drug intake, including use of self-administered preparations such as laxatives, health products, emetics, and drugs of addiction.
- It is particularly important to consider a drug induced myopathy in patients with a pre-existing myopathy or neuromuscular disorder if there is an unexpected deterioration in their condition; bear in mind potential myotoxic adverse effects of medications when prescribing for such patients.
- Patients on a combination of more than one potentially myotoxic drug, or with a high alcohol intake, are at greater risk of developing a myopathy.
- Drugs may cause various types of myopathy including necrotising, inflammatory, mitochondrial, lysosomal, and core myopathies, as well as selective type II fibre atrophy.
- The clinical spectrum of drug induced myopathies includes asymptomatic hyper CKaemia, myalgia and muscle cramping, subacute or chronic proximal myopathy, and profound generalised muscle weakness.
- The statins are the most important cause in current clinical practice of drug induced myopathy and acute rhabdomyolysis.
- Remember that drug induced disorders can mimic most other types of myopathy and neuromuscular disorder, but are readily treatable, and are reversible if the drug association is recognised and the drug in question stopped.

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