ALCOHOLIC MYOPATHY

A. Chaudhuri[*]

P.O. Behan[†]

INTRODUCTION

Alcohol has been an integral part of man's social history since antiquity. After the art of distillation was rediscovered in the Middle Ages, alchemists found, in ethanol, a cure for every illness, a tradition that still continues in this age with the Gaelic name for whisky (*usquebaugh*, meaning 'water of life'). In more recent times researchers have wondered why the enzyme alcohol dehydrogenase, which converts ethanol to its major metabolite, acetaldehyde, exists in the body if alcohol has no physiological role.

Though 'alcohol' is a generic name, in practice it usually means 'ethyl alcohol' or 'ethanol' (C_2H_5OH). Other aliphatic alcohols include methyl alcohol (methanol) and isopropyl alcohol, both of which are used as industrial solvents, are occasionally implicated in accidental human poisoning and have no reported direct effect on skeletal muscles. Skeletal muscle rigidity secondary to basal ganglia injury that is partially levodopa-responsive is, however, known to occur following methanol poisoning.[1]

CLINICAL FEATURES OF ALCOHOLIC MYOPATHY

There are two distinct types of alcoholic myopathy: an acute, painful condition with swelling of affected muscles both in the arms and the legs and a chronic, painless myopathy affecting the proximal limb girdle muscles with wasting.[2-4] Both forms of alcoholic myopathy are due to the direct toxic effects of ethanol and its principal metabolite, acetaldehyde, on skeletal muscles. Indeed, ethanol is the most commonly encountered neurotoxin and is incriminated as the commonest cause of acute myoglobinuria in medical practice.[3]

Acute alcoholic myopathy

Attacks of acute alcoholic myopathy usually occur after binge drinking[3] and a previous period of fasting or caloric deprivation is considered to be a predisposing factor. This acute form develops over hours to days and affected patients are typically men. Proximal muscles are most severely involved but the distribution of weakness may be asymmetrical or multifocal; muscle enzymes, including serum creatine kinase (CK), are invariably raised. Most patients will also have myoglobinuria or other evidence of acute rhabdomyolysis, hence this form of myopathy is also known as 'alcoholic rhabdomyolytic myopathy' (ARM). This acute disorder is always painful; the patient experiences conspicuous muscle cramps and there is tenderness and swelling of the affected

[*]*Clinical Lecturer in Neurology, University of Glasgow*
[†]*Professor of Neurology,*
University Department of Neurology,
Institute of Neurological Sciences,
Southern General Hospital, Glasgow

muscles. The clinical picture may be confused with venous thrombophlebitis when muscle involvement is asymmetric[5] and, rarely, dysphagia can also occur. ARM may be associated with signs of acute liver injury (acute alcoholic hepatitis) and congestive cardiac failure. Electromyography (EMG) shows profuse fibrillations and myopathic changes similar to acute polymyositis. Attacks of ARM may recur on a number of occasions following alcoholic binges.

Following its original description by Hed *et al.* in 1962,[5] acute alcoholic myopathy is now known to present with variable severity, ranging from transient asymptomatic rises in serum CK and myoglobin levels to a more fulminant rhabdomyolysis, myoglobinuria and renal failure.[6,7] It has been recently suggested that magnetic resonance (MR) imaging of thigh and leg muscles may be useful in the evaluation of alcoholic myopathy, mainly in predicting the onset of rhabdomyolysis.[8] Alcoholic patients with a recent history of rhabdomyolysis have been shown, by ^{31}P nuclear spectroscopic MR, to have evidence of a metabolic myopathy during aerobic exercise, with a greater utilisation of muscle phosphocreatinine and reduced adenosine triphosphate (ATP) turnover.[9]

Acute alcohol intoxication can also lead to secondary skeletal muscle injury as a result of focal trauma (crush injury), seizures (from rhabdomyolysis), delirium tremens and electrolyte or metabolic dysfunction. Another type of secondary acute alcoholic myopathy is an *ischaemic myopathy* which develops as a result of focal compression of buttock, leg or shoulder muscles. This occurs in an inebriated alcoholic lying for a prolonged period on the affected muscles, immobile and insensate.

Rarely, acute painless myopathy has also been seen after alcohol intake where the cause of myopathy was hypokalemia provoked by alcohol;[10,11] severe degrees of hypokalemia (<2 mmol/L) may also develop in an alcoholic due to vomiting and/or diarrhoea in the course of a prolonged drinking bout, giving rise to an acute, painless proximal myopathy. Hypomagnesemia precipitating subacute myopathy and hypocalcemia in alcoholic patients is also reported.[12]

Chronic alcoholic myopathy

Ekbom *et al.,* in 1964, first drew attention to the syndrome of painless progressive wasting of pelvic and shoulder girdle muscles in chronic alcoholic myopathy.[13] It is a more common disorder than the acute form of alcoholic myopathy, and is an under-recognised complication of ethanol abuse which evolves over weeks to months.[3] Clinically, symptomatic chronic alcoholic myopathy usually presents with proximal limb girdle weakness, wasting, normal or minimally raised muscle enzymes and EMG evidence of a chronic muscle disease. Patients also usually have other stigmata of chronic alcoholism, i.e. polyneuropathy, cardiomyopathy or liver cirrhosis. The myopathy of a chronic alcoholic is typically painless though some patients may complain of muscle

cramps. In some cases, an elevation of serum aldolase may be a more sensitive marker than serum CK. In one study of 100 male alcoholic patients,[14] 44 had alcoholic myopathy and 24 (55%) of these patients in the same study had clinical symptoms of myopathy, 15 (35%) had proximal muscle atrophy, 27 (60%) had increased serum muscle enzymes and 37 (80%) had significantly decreased muscle strength by myometric measurement. Most patients with chronic alcoholism show evidence of a skeletal myopathy often associated with a similar disease affecting heart muscle as well (alcoholic cardiomyopathy).[14,15] A polyneuropathy coexists in many patients which is responsible for any distal, and also some proximal, muscle weakness. Extraocular, facial or bulbar muscles are not involved.

There is failure of normal lactic acid generation by skeletal muscle during ischaemic exercise tests in chronic alcoholics.[16] Typically, needle EMG in alcoholic myopathy shows few positive sharp waves, myopathic changes in motor units (small, short duration, polyphasic potentials are measured) and rapid recruitment of motor units with a complete interference pattern of reduced amplitude on minimal effort. Often, a combination of mixed myopathic and neuropathic changes is present in the proximal muscles with additional evidence of a sensorimotor neuropathy distally which is predominantly of the demyelinative type.[17] One third of patients may present with a more subacute syndrome of proximal muscle weakness, minimal pain, modestly elevated serum CK levels and mild myoglobinuria.[18] These patients probably represent an overlap of the acute variety of alcoholic myopathy (*subacute alcoholic myopathy*).

EPIDEMIOLOGY OF ALCOHOLIC MYOPATHY

All patients with alcoholic myopathy invariably have a long history of alcohol consumption and it is estimated that 50-60% of all chronic alcoholics will have some evidence of skeletal and cardiomyopathy.[7,18,19] Ethanol is toxic to striated muscles (skeletal and cardiac) in a dose-dependent manner. In one study, a direct correlation was shown between the severity of the myopathy and estimated lifetime doses of ethanol that exceeded 13 kg (13,000 g)/kg of body weight.[18] This is equivalent to a 70 kg man drinking more than 12 oz of whisky (120 g ethanol) every day for 20 years.[20] Myopathy did not develop in patients who drank less.[18] There is also a greater risk of chronic alcoholic myopathy and cardiomyopathy developing in women when compared with men. In one study, myopathy and cardiomyopathy were as common in female alcoholics as in male despite the fact that the mean lifetime dose of alcohol in these women was only 60% of that of the male alcoholics.[21]

It is generally accepted that diseases of skeletal and cardiac muscle in patients with chronic alcoholism are clinically and histologically related.[14,15] Indeed, presence of muscle weakness in an alcoholic person indicates the likelihood of an associated cardiomyopathy. It has also been suggested that it is probably not just purely alcohol that contributes to myopathy; associated nutritional deficiency may play a synergistic role. The presence of B-complex vitamin deficiency, malabsorption due to chronic pancreatitis and associated chronic liver disease (hepatitis or cirrhosis) have been postulated to contribute towards the development of symptomatic muscle disease during the lifetime of a chronic alcoholic. However, most patients with alcoholic myopathy are not evidently malnourished,[7,18] and, in one study, muscle atrophy in alcoholics was not associated with vitamin B_{12}, folate, pyridoxine, riboflavin or thiamine deficiencies.[22] However, in another study, triceps skinfold and midarm muscle mass were under the fifth percentile in 39% and 34% of hospitalised alcoholic patients respectively.[23]

PATHOGENESIS OF ALCOHOLIC MYOPATHY
Experimental and animal models
Skeletal muscle has been shown to be damaged by administration of ethanol to well-nourished volunteers.[24] Experimental alcoholic myopathy can be induced in rats by a combination of prolonged alcohol intake (mean 15.3 g ethanol/kg/day for up to ten weeks) and a short fast,[25] the predominant histological finding being type IIB fibre atrophy. Biochemically the activity of glycolytic enzymes was depressed and mean mitochondrial respiratory rates were lower.[25] In another acute study, rats were given single boluses of ethanol and rates of protein synthesis were examined 2.5 hours later.[26] The results suggested defective synthesis of skeletal muscle protein. In another experimental model in rats,[27] ethanol caused acute elevation in serum CK of muscle origin. *In vitro* studies on isolated actomyosin preparations obtained from skeletal muscles of alcohol-fed baboons and volunteers have shown reduced ATPase activity, reduced sarcolemmal calcium uptake and diminished contractility of actomyosin.[28]

Mechanism of muscle injury by ethanol
The precise mechanism of acute muscle injury caused by alcohol intoxication is unknown but present evidence favours a direct toxic effect of alcohol on muscle cells. It is possible that ethanol dissolves into the plasma membrane of skeletal muscle cells,[29] altering their sarcolemmal transport mechanism, transmembrane ion-fluxes,[30-32] receptor-effector coupling,[33] calcium sequestration and actin-myosin interaction.[28] The biochemical pathways of chronic alcohol-induced muscle damage are equally unclear, despite data to show that malnourishment,[23] hypokalemia[34] or hypophosphatemia[35] are primary events in its pathogenesis. Long-term exposure to ethanol produces lasting changes in cellular membranes[32,36] leading to alterations in sarcolemmal fluidity, configuration and membrane pump (Na^+/K^+-ATPase) activity.[3] A number of other mechanisms for muscle cell injury due to ethanol have been proposed, including alteration of sarcolemmal permeability leading to disturbances of sodium-potassium transport and reduced uptake of intracellular calcium by the sarcoplasmic reticulum,[3] glycogen depletion,[37] accumulation of lipids within the muscle,[38,39] oxidation induced by free radicals,[40] sustained decrease in muscle mRNA content,[41] reduced fractional rate of skeletal muscle protein synthesis[42] and intramuscular neuropathy[43] as a part of chronic alcoholic polyneuropathy.

Acetaldehyde, the product of alcohol dehydrogenase activity, reacts with many cellular proteins to form acetyldehyde-protein derivatives (adducts) that are themselves cytotoxic and which may also provoke immune response.[44] Despite having relatively high circulating cortisol concentrations, myopathy in chronic alcoholics is not thought to be due to hypercortisolemia (pseudo-Cushing's syndrome).[45] Though data from animal experiments suggest that acute rhabdomyolysis may arise from a superimposed

mitochondrial failure,[25] studies in human alcoholics indicate that chronic myopathy is not associated with a deficiency of mitochondrial energy supply.[46]

The precise mechanism that transforms a reversible type of muscle injury caused by alcohol into an irreversible, permanent muscle damage caused by alcohol has never been understood. Changes in the sarcolemmal membrane and intracellular calcium transport both in the skeletal and cardiac muscles may act as the primary events for developing chronic atrophic myopathy. It has been shown experimentally that, following long-term exposure to alcohol, cells adapt by increasing the concentration and activity of voltage-dependent calcium channels. The calcium channel-blocker verapamil prevented the development of ethanol-induced muscle abnormalities in an experimental model of alcoholic cardiomyopathy.[47] The cellular signal transduction system responsible for regulating intracellular second messenger system (cyclic adenosine monophosphate or cAMP) is another major target of ethanol, both in the short and long term. In the short term, ethanol increases the production of receptor-dependent cAMP, but long-term exposure reduces its level.[20] This is called *heterologous desensitisation of cAMP production*[48] and has been confirmed by measuring lymphocytic cAMP concentrations in chronic alcoholics.[49] Heterologous desensitisation induces changes in the secondary messenger system function and could be expected to lead to inappropriate cell signalling in response to various circulating hormones and chemical messengers.

MUSCLE PATHOLOGY IN ALCOHOLIC MYOPATHY
Acute alcoholic myopathy
Muscle biopsy usually shows polyfocal areas of sterile necrosis with selective vulnerability of type I muscle fibres (defined by their low myosin adenosine triphosphatase activity). (Figure 1.) Mild mononuclear infiltration may be present and there may be areas of regenerating muscle fibres.[50,51]

Chronic alcoholic myopathy

TABLE 1		
Histological criteria for alcoholic myopathy.		
Mild myopathy:	Scattered myocytolysis **or** *at least four* of the following criteria:	
	Fibre atrophy	
	Inflammation	
	Fibre regeneration	
	Fibre size variability	
	Internal nuclei> 10% of fibres	
	Moth eaten fibres>10% of fibres	
	Subsarcolemmal deposition of 10% of fibres	
	Type 1 fibre predominance	
	Fat deposition in endomysia	
	Tubular aggregates	
Moderate myopathy:	Scattered myocytolysis **and** *at least three* of the previous criteria.	
Severe myopathy:	Myocytolyis in up to 5% of fibres.	

Selective type II fibre atrophy (defined by their high myosin adenosine triphosphatase activity) is characteristic of chronic alcoholic myopathy. This is, however, non-specific since type II fibre atrophy has been associated with a variety of unrelated muscle diseases such as inactivity, caloric malnutrition, systemic diseases, cirrhosis, steroid therapy, denervation and metabolic myopathies (e.g. hypothyroidism and osteomalacia). Approximately 30-50% of patients with chronic alcoholic myopathy have a reduction of type II fibre size, often selective for fibre type IIB, whereas type I fibres are relatively unaffected.[19,52,53] The selective injury to type IIB muscle fibres may be reversible.[52] Table 1 shows the current histological criteria used to classify alcoholic myopathy in the absence of other causes.[54] (Figure 2.)

Other features which may be seen in the muscle biopsy
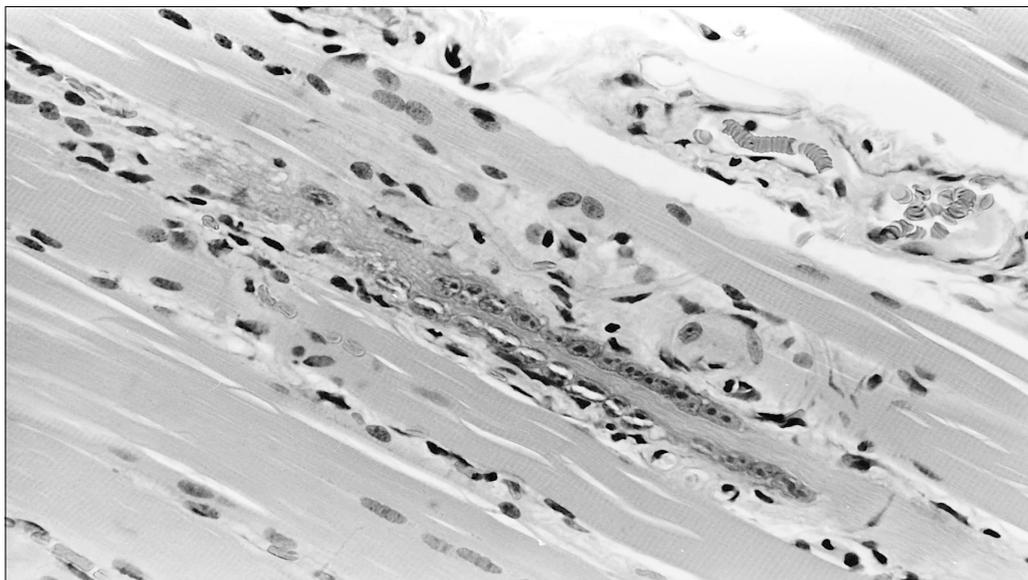

FIGURE 1
A central regenerating fibre with large nuclei and prominent nuclei is seen. Longditudinal section of muscle.
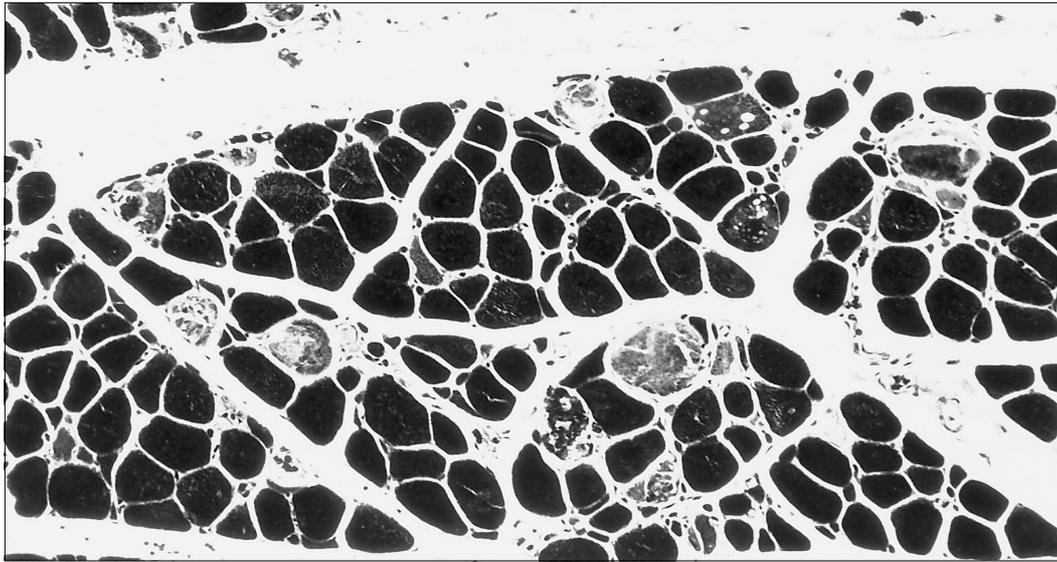Haematoxylin and eosin x 260.

FIGURE 2

Several fascicles with acutely necrotic fibres are seen. There is considerable variation in fibre size also, suggesting chronic damage. PTAH x 160. Reproduced, by kind permission of the publisher, from Mastaglia RA, Lord Walton of Detchant (eds). *Skeletal Muscle Pathology, 2nd Edition* Edinburgh: Churchill Livingstone, 1992.

include dilatation of the sarcoplasmic reticulum, enlarged and distorted mitochondria and increased fat.[28,55] In a study of 48 human muscle biopsies from patients with alcoholic myopathy, increased glycogen and reduced pyruvate kinase activity were noted before the first histological signs of myopathy appeared; when histological evidence of myopathy was present, glycogen levels fell.[56] Additional abnormalities occasionally found in the muscle biopsy are the presence of tubular aggregates[55,57] and evidence of hypokalemic vacuolar myopathy.[34] Histological changes of neurogenic features (fibre type grouping) may be present in biopsies from proximal muscles (quadriceps muscle) indicating denervation due to possible intramuscular neuropathy contributing to muscle atrophy and weakness.[43]

Correlation between clinical and pathological evidence of myopathy
There is no consistent correlation between clinical symptoms, nutritional status and histological evidence of myopathy in chronic alcoholics. Type II fibre atrophy is frequently seen in the skeletal muscle biopsies of chronic alcoholics without any evidence of symptomatic myopathy.[58] In their study of 151 inpatients with a history of chronic heavy alcohol intake (>100 g per day for at least three years) and not selected for muscle symptoms,[7] Martin *et al.* found no clear relationship between musculoskeletal symptoms and muscle biopsy histology. Twenty three patients had raised serum CK, 92 (60%) patients had histological evidence of chronic myopathy with type II fibre atrophy and five patients (7%) had evidence of acute myopathy. In a recent study of muscle biopsy in 100 chronic alcoholics,[53] type II fibre atrophy was found in only one-third of patients (selective for type II B in 23 cases) even-though 61 of these 100 patients had evidence of skeletal myopathy, 26 cases had alcoholic cardiomyopathy, 23 patients were found to have peripheral neuropathy and 12 had cirrhosis. Thus the presence of type II fibre atrophy in the skeletal muscle histology of chronic alcoholics appeared to be entirely non-specific, although patients who had both symptomatic myopathy and type II fibre atrophy in muscle

biopsies had a significantly higher total lifetime dose of ethanol (31.7±17 kg/kg body weight), showed a higher incidence of peripheral neuropathy and had evidence of significantly lower anthropometric parameters of caloric nutrition (% of ideal weight, perimeter of non-dominant arm and lean body mass).[53]

INVESTIGATIONS FOR ALCOHOLIC MYOPATHY
There is a good enough correlation between clinical symptoms, the presence of atrophic limb girdle myopathy and decreased muscle strength to allow a clinical diagnosis of chronic alcoholic myopathy to be made in most patients with an appropriate history of alcohol consumption and without a family history of muscle disease. Since peripheral neuropathy, cardiomyopathy and liver cirrhosis commonly co-exist in patients with chronic alcoholic myopathy, patients should be screened for evidence of other alcohol-induced organ-specific injuries. Based on current evidence, we do not recommend muscle biopsy as a diagnostic tool in the evaluation of alcoholic myopathy unless metabolic or inflammatory myopathy is a differential diagnosis (Table 2**)**. The recommended investigations for suspected alcoholic myopathy are given in Table 3.

ALCOHOL AND FATIGUE
In small doses, alcohol lessens the appreciation of fatigue and increases the ability for muscular work, probably because it acts as a CNS stimulant. At large doses, however, alcohol causes CNS depression and diminishes the amount of muscular work that may be accomplished.

In acute alcohol intoxications, the severity of central nervous system (CNS) symptoms is typically greater when the blood alcohol concentration is rising rather than falling (*Mellanby effect*)[29] and is presumably caused by alterations in specific neurotransmitters and neuronal function.[59] Alcoholic blackouts typically tend to occur during short-term consumption of large amounts of alcohol in otherwise healthy individuals.[59] It has been proposed that alcoholic blackouts result from a disorder of central serotoninergic

Acute/subacute onset:

Necrotising polymyopathy with rhabdomyolysis:
    muscle compression (ischaemic myopathy)
    drug induced myopathy(e.g. 'statin' group of drugs,
       zidovudine)
    toxic myopathy (e.g. alcohol)
    malignant hyperthermia
    muscle infarction
    crush injury

Metabolic myopathy:
    hypokalemia
    hypophosphatemia
    hereditary disorders of muscle glycolysis (e.g.
      McArdle's)

Paroxysmal myoglobinuria (Meyer-Betz and related
    diseases)
Acute polymyositis
Atypical presentation of Guillain-Barre syndrome
Eosinophilia-myalgia syndrome

Chronic:

Metabolic (hypocalcemia, hypophosphatemia)
Endocrine (hypothyroid)
Drug/toxin induced
Myasthenic syndromes (e.g. Lambert-Eaton)
Peripheral neuropathy (e.g. diabetes, CIDP)

neurotransmission, since plasma levels of the serotonin precursor, tryptophan, are decreased in patients with history of blackouts due to ethanol intoxication,[60] and a trial of the serotonin reuptake inhibitor zimelidine has shown improvement in memory function in moderately intoxicated subjects.[61]

Most patients with well-defined chronic fatigue syndrome (CFS) are unable to tolerate even the smallest amount of alcohol, and experience blackouts and conspicuous deterioration of their fatigue symptoms.[62] Alcohol intolerance is so characteristic of CFS that most patients are forced to stop drinking socially. Alcohol intolerance in CFS patients is probably a marker of a serotonin supersensitivity that has been well documented in neuroendocrine tests (e.g. buspirone-stimulated prolactin release).[60] In a comparative study of dynamic muscle function tests and histomorphometry, basal lactate levels were found to be higher in patients with chronic alcohol abuse in comparison to the CFS patients.[63] Muscle biopsy in CFS patients usually do not show type II fibre atrophy.[63,64]

TREATMENT OF ALCOHOLIC MYOPATHY
There is no specific treatment for alcohol-induced muscle disease. As a general rule, abstinence from alcohol is associated with gradual improvement of myopathy in most, but not all, patients with chronic alcoholic myopathy whereas continued ethanol abuse will result in clinical deterioration; supplementation of protein, B-complex vitamins (especially folate) and minerals is advisable. The outcome is more favourable in acute alcoholic myopathy

although full recovery may take several months.

Early treatment should be instituted for acute renal failure complicating ARM. Specific treatment will be required in patients for any associated cardiomyopathy, cirrhosis or chronic pancreatitis. Changing the drinking habit and lifestyle are priorities that need to be strongly emphasised and patients should be referred to the local alcohol rehabilitation unit for counselling.

CONCLUSION
Alcoholic myopathy is probably more under-recognised than uncommon in clinical practice,[3] and most patients with chronic alcoholic myopathy will also have evidence of associated peripheral neuropathy and cardiomyopathy. The definitive mechanism of alcoholic myopathy is unknown, however it is clear that altered cellular permeability and intracellular signalling may lead to a number of changes within the muscle cells in the presence of alcohol that could effectively reduce the substrates for cellular energy[65] and suppress muscle protein synthesis.[41,42] Alcohol abstinence is the only proven way to recover from muscle weakness though, in some cases, abstinence may only prevent further progression of alcoholic myopathy.

All cases:	Full blood count and MCV
	ESR and CRP
	U & Es, glucose
	Serum CK, aldolase, LDH
	Liver function tests (total protein,
	albumin, AlT, AsT, gGT)
	Calcium profile (Ca, P, alkaline
	phosphatase)
	Thyroid function test (TSH)
	Urine for myoglobin
	Stool for occult blood
	ECG
	Chest X-ray
	EMG & nerve conduction studies
Acute cases:	As above, plus:
	Serum myoglobin
	Plasma bicarbonate and H^+
	Blood gases
	Periodic serum U &Es, creatinine
	Prothrombin time
	Urine Na^+
	Monitor: blood pressure, heart rate,
	temperature and 24-hour urine
	output
Optional:	Serum folate, Vitamins B_1 and B_{12}
	Serum ferritin
	Serum magnesium and 1,25 Vit D
	Echocardiography
	Abdominal ultrasound
	CT scan of head
	Muscle biopsy
	Psychiatric assessment

REFERENCES

1 Guggenhein MA, Couch JR, Weinberg W. Motor dysfunction as a permanent complication of methanol ingestion. Presentation of a case with a beneficial response to levodopa treatment. *Arch Neurol (Chic.)* 1971; **24:**550-4.

2 Perkoff GT, Dioso MM, Bleisch V, Klinkerfuss G. A spectrum of myopathy associated with alcoholism: clinical and laboratory features. *Ann Int Med* 1967; **67:**481-92.

3 Haller RG, Knochel JP. Skeletal muscle disease in alcoholism. *Med Clin North Am* 1984; **68:**91-103.

4 Mastaglia FL. Toxic myopathies. In: Rowland LP, DiMauro S (eds). *Handbook of clinical neurology* Amsterdam: Elsevier Science Publishers BV, 1992; **18**(62):595-622.

5 Hed RC, Lundmark C, Fahlgren H, Orell S. Acute muscular syndrome in chronic alcoholism. *Acta Med Scand* 1962; **171:**585-99.

6 Kahn LB, Meyer JS. Acute myopathy in chronic alcoholism. *Am J Clin Pathol* 1970; **53:**516-30.

7 Martin F, Ward K, Slavin G *et al*. Alcoholic skeletal myopathy, a clinical and pathological study. *Q J Med* 1985; **55:**233-51.

8 Kishi T, Kitani M, Uegaki J, Naganuma R. Alcoholic myopathy: evaluation with magnetic resonance imaging - a case study. *Alcoholism, Clinical and Experimental Research* 1997; **21:**1730-1.

9 Bollaret PE, Robin-Lherbier B, Escanye JM *et al*. Phosphorus nuclear magnetic resonance evidence of abnormal skeletal muscle metabolism in chronic alcoholics. *Neurology* 1989; **39:**821-4.

10 Rubenstein AE, Wainapel SF. Acute hypokalemic myopathy in alcoholism. A clinical entity. *Arch Neurol* 1977; **34:**553-5.

11 Sharief MK, Robinson SF, Swash M. Hypokalemic myopathy in alcoholism. *Neuromuscular Disorders* 1997; **7:**533-5.

12 Pall HS, Williams AC, Heath DA, Sheppard M, Wilson R. Hypomagnesaemia causing myopathy and hypocalcemia in an alcoholic. *Postgrad Med J* 1987; **63:**665-7.

13 Ekbom K, Hed R, Kirstein L, Astrom KE. Muscular affection in chronic alcoholism. *Arch Neurol* 1964; **10:**449-58.

14 Sacanella E, Fernandez-Sola J, Cofan M *et al*. Chronic alcoholic myopathy: diagnostic clues and relationship with other ethanol related diseases. *Q J Med* 1995; **88:**811-17.

15 Fernandez Sola J, Estruch R, Garu JM *et al*. The relation of alcoholic myopathy to cardiomyopathy. *Ann Intern Med* 1994; **120:**529-36.

16 Perkoff GT, Hardy P, Velez-Garcia E. Reversible acute muscular syndrome in chronic alcoholism. *N Engl J Med* 1966; **274:**1277-85.

17 Victor M, Adams RD, Collins GH. *The Wernicke-Korsakoff syndrome and related neurological disorders due to alcoholism and malnutrition* Contemporary Neurology series (Vol 3), Philadelphia: FA Davis, 1989.

18 Urbano-Marquez A, Estruch R, Novarno-Lopez F *et al*. The effects of alcoholism on skeletal and cardiac muscle. *N Engl J Med* 1989; **320:**409-15.

19 Hudson P. Alcohol myopathy. *BMJ* 1984; **288:**584-5.

20 Diamond I. Alcoholic myopathy and cardiomyopathy. *N Engl J Med* 1989; **320:**458-60.

21 Urbano-Marquez A, Estruch R, Fernandez-Sola J *et al*. The greater risk of alcoholic cardiomyopathy and myopathy in women compared with men. *JAMA* 1995; **274**(2):149-54.

22 Peters TJ, Martin F, Ward K. Chronic alcoholic skeletal myopathy - common and reversible. *Alcohol* 1985; **2:**485-9.

23 Romero JC, Santolaria F, Gonzalez-Reimers E *et al*. Chronic alcoholic myopathy and nutritional status. *Alcohol* 1994; **11:**549-55.

24 Song SK, Rubin E. Ethanol produces muscle damage in human volunteers. *Science* 1972; **175:**327-8.

25 Trounce I, Byrne E, Dennett X. Biochemical and morphological studies of skeletal muscle in experimental chronic alcoholic myopathy. *Acta Neurol Scand* 1990; **82:**386-91.

26 Preedy VR, Salisbury JR, Peters TJ. Alcoholic muscle disease: features and mechanisms. *J Pathol* 1994; **173:**309-15.

27 Haller RG, Drachman DB. Alcoholic rhadomyolysis: an experimental model in the rat. *Science* 1980; **208:**412-5.

28 Rubin E, Katz AM, Lieber CS, Stein EP, Puszkin S. Muscle damage produced by chronic alcohol consumption. *Am J Pathol* 1976; **83:**499-515.

29 Goldstein DB. *Pharmacology of alcohol* New York: Oxford University Press, 1983.

30 Leslie SW, Barr E, Chandler J, Farrar RP. Inhibition of fast- and slow-phase depolarisation dependent synaptosomal calcium uptake by ethanol. *J Pharmacol Exp Ther* 1983; **225:**571-5.

31 Messing RO, Carpenter CL, Diamond I, Greenberg DA. Ethanol regulates calcium channels in clonal neuronal cells. *Proc Natl Acad Sci USA* 1986; **83:**6213-5.

32 Durand D, Carlen PL. Decreased neuronal inhibition *in vitro* after long term administration of ethanol. *Science* 1984; **224:**1359-61.

33 Luthin GR, Tabakoff B. Activation of adenylate cyclase by alcohol requires the nucleotide-binding protein. *J Pharmacol Exp Ther* 1984; **228:**579-87.

34 Khurana R, Kalyanaraman K. Hypokalemic vacuolar myopathy of chronic alcoholism. A histological and histochemical study. *Diseases of the Nervous System* 1977; **38:**287-9.

35 Knochel JP, Bilbrey GL, Fuller TJ, Carter NW. The muscle cell in chronic alcoholism: the possible role of phosphate depletion in alcoholic myopathy. *Ann NY Acad Sci* 1975; **252:**274-86.

36 Taraschi TF, Rubin E. Effects of ethanol on the chemical and structural properties of biological membranes. *Lab Invest* 1985; **52:**120-31.

37 Vernet M, Cadefau JA, Balague A *et al*. Effect of chronic alcoholism on human muscle glycogen and glucose metabolism. *Alcohol Clin Exp Res* 1995; **19:**1295-9.

38 Laposata EA, Lange LG. Presence of nonoxidative ethanol metabolism in human organs commonly damaged by ethanol abuse. *Science* 1986; **231:**497-9.

39 Sunnasy D, Cairns SR, Martin F *et al*. Chronic alcoholic myopathy: a clinical, histological and biochemical assessment of muscle lipid. *J Clin Pathol* 1983; **36:**778-84.

40 Ward RJ, Peters TJ. The antioxidant status of patients with either alcohol-induced liver damage or myopathy. *Alcohol Alcohol* 1992; **27:**359-65.

41 Wassif W, Preedy VR, Summers B *et al*. The relation between muscle fibre atrophy factor, plasma carnosinase activities, muscle RNA and protein concentration in chronic alcoholic myopathy. *Alcohol Alcohol* 1993; **28:**325–31.

42 Pacy PJ, Preedy VR, Peters TJ *et al*. The effect of alcohol ingestion on whole body and muscle protein synthesis - a stable isotope study. *Alcohol Alcohol* 1991; **26:**505-13.

43 Urbano-Marquez A, Estruch R, Graw JM *et al*. On alcoholic myopathy. *Ann Neurol* 1985; **17:**418.

44 Israel Y, Hurwitz E, Niemella O, Arnon R. Monoclonal and polyclonal antibodies against acetaldehyde-containing epitopes in acetaldehyde-protein adducts. *Proc Natl Acad Sci USA* 1986; **83:**7923-7.

45 Duane P, Peters TJ. Glucocorticoid status in chronic alcoholics with and without skeletal muscle myopathy. *Clin Sci* 1987; **73:**601-3.

46 Cardellach F, Galofre J, Grau JM *et al*. Oxidative metabolism in muscle mitochondria from patients with chronic alcoholism. *Ann Neurol* 1992; **31:**515-8.

47 Garrett JS, Wikman-Coffelt J, Sievers R *et al*. Verapamil prevents the development of alcoholic dysfunction in hamster myocardium. *Am J Coll Cardiol* 1987; **9:**1326-31.

48 Mochly-Rosen D, Chang F-H, Cheever L *et al*. Chronic ethanol causes heterologous desensitization of receptors by reducing a_5

messenger RNA. *Nature* 1988; **84:**1413-16.

[49] Diamond I, Wrubel B, Estrin W, Gordon A. Basal and adenosine receptor-stimulated levels of cAMP are reduced in lymphocytes from alcoholic patients. *Proc Natl Acad Sci USA* 1987; **84:**1413-16.

[50] Martinez AJ, Hooshmand H, Faris AA. Acute alcoholic myopathy. Enzyme histochemistry and electron microscopic findings. *J Neurol Sci* 1973; **20:**245-52.

[51] Kahn LB, Meyer JS. Acute myopathy in chronic alcoholism. A study of 22 autopsy cases with ultrastructural observation. *Am J Pathol* 1970; **53:**516-30.

[52] Slavin G, Martin F, Ward P *et al.* Chronic alcohol excess is associated with selective but reversible injury to type 2B muscle fibres. *J Clin Pathol* 1983; **36:**772-7.

[53] Fernandez-Sola J, Sacanella E, Estruch R *et al.* Significance of type II fibre atrophy in chronic alcoholic myopathy. *J Neurol Sci* 1995; **130:**69-76.

[54] Mastaglia FL, Walton J. *Skeletal muscle pathology.* First edition, New York: Churchill Livingstone, 1982.

[55] Del Villar Negro A, Merino Angelo J, Rivera-Pomar JM. Skeletal muscle changes in chronic alcoholic patients. A conventional, histochemical, ultrastructural and morphometric study. *Acta Neurol Scand* 1984; **70:**185-96.

[56] Vernet M, Cadefau JA, Balague A *et al.* Effect of alcohol on human muscle glycogen and glucose metabolism. *Alcohol Clin Exp Res* 1995; **19:**1295-9.

[57] Chui LA, Neustein H, Munsat TL. Tubular aggregates in subclinical alcoholic myopathy. *Neurology* 1975; **25:**405-12.

[58] Martin FC, Slavin G, Levi AJ. Alcoholic muscle disease. *Br Med Bull* 1982; **38:**53-6.

[59] Charness ME, Simon RP, Greenberg DA. Ethanol and the nervous system. *N Engl J Med* 1989; **321:**442-54.

[60] Branchey L, Branchey M, Zucker D *et al.* Association between low plasma tryptophan and blackouts in male alcoholic patients. *Alcoholism (NY)* 1985; **9:**393-5.

[61] Weingartner H, Buchsbaum MS, Linnoila M. Zimelidine effects on memory impairments produced by ethanol. *Life Sci* 1983; **33:**2159-63.

[62] Chaudhuri A, Behan WMH, Behan PO. Chronic fatigue syndrome. *Proc R Coll Physicians Edinb* 1998; **28:**150-63.

[63] Wassif WS, Sherman D, Salsbury JR, Peters TJ. Use of dynamic tests of muscle function and histomorphometry of quadriceps biopsies in the investigations of patients with chronic alcohol misuse and chronic fatigue syndrome. *Ann Clin Biochem* 1994; **31:**462-8.

[64] Lane R, Barrett MC, Woodraw D *et al.* Muscle fibre characteristics and lactate responses to exercise in chronic fatigue syndrome. *J Neurol Neurosurg Psychiat* 1998; **64:**362-7.

[65] Anderson TL, Torrance CA. Metabolic mechanisms of acute alcoholic myopathy. *Neurology* 1984; **34:**81.