Steroid myopathy complicating McArdle's disease

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McArdle (1951) first described a syndrome characterized by muscle cramps and stiffness after exercise and suggested that this may have been due to defective breakdown of glycogen in skeletal muscle. Deficiency of muscle phosphorylase was subsequently demonstrated in two patients with the same syndrome (Schmid and Mahler, 1959; Mommaerts, Illingworth, Pearson, Guillory, and Seraydarian, 1959). Patients with this condition usually first develop symptoms in childhood or adolescence but onset in adult life has also been reported (Engel, Eyerman, and Williams, 1963). Muscle phosphorylase deficiency is believed to be an inherited disorder and several sibships have now been described. The condition appears to be inherited as an autosomal recessive trait (Pearson, 1968) although there is a predominance of males in some reported cases (Hsia, 1968).

The occurrence of a proximal myopathy in patients receiving long-term corticosteroid therapy is also well documented (Perkoff, Silber, Tyler, Cartwright, and Wintrobe, 1959; Golding, Murray, Pearce, and Thompson, 1961; Braun, Coste, Delbarre, and Aurel, 1965; Afifi, Bergman, and Harvey, 1968) and a comparable condition has been produced in the experimental animal (D'Agostino and Chiga, 1966; Ritter, 1967; Tice and Engel, 1967; Afifi and Bergman, 1969).

In this paper we describe a patient with proven muscle phosphorylase deficiency in whom the course of the disease was modified by prolonged corticosteroid therapy. Electron microscopic examination of biopsy material from this patient revealed ultrastructural abnormalities reminiscent of those described in steroid-induced myopathy in man and in the experimental animal.

CASE REPORT

The patient was a 48-year-old male who first developed proximal muscle pains and weakness at the age of 35 years. He had suffered an attack of rheumatic fever at the age of 18 years but his past history was otherwise unremarkable and there was no family history of neuromuscular disease or of consanguinity. A diagnosis of polymyositis was made at the time of onset of his symptoms and he was treated in turn with cortisone, prednisolone, and subsequently betamethasone for the next seven years with slight improvement in the muscle pain but no improvement in muscle power. During this period he became hypertensive and developed diabetes mellitus which was treated with chlorpropamide. He also suffered from recurrent abscesses on the face, trunk, and limbs. In 1963 he was confined to a wheelchair because of increasing muscle weakness. At that time he was found to have severe atrophy and weakness of proximal muscle groups, the quadriceps being most severely affected. Corticotrophin (ACTH) in a dose of 40 u. daily was substituted for the steroids and he improved to the extent of being able to walk again and was able to return to work for a brief period. However, shortly afterwards he began to be troubled once again by pains in the muscles of the shoulder and pelvic girdles which severely limited muscular activity. The dose of ACTH was increased to 80 u. daily and prednisone was also commenced in a dose of 60 mg daily and reduced to 20 mg daily over the next month. He was subsequently treated with ACTH 40 u. daily and prednisone 20 mg daily for the next five years. During this period there was a steady progression in his symptoms and at the time of admission to the Newcastle General Hospital in December 1968 he was able to walk only about 20 yards at a slow pace, he could not climb a flight of stairs, and he experienced great difficulty in rising from the sitting position. He complained that any attempted exertion precipitated painful muscle cramps in the limbs which could persist for up to three hours and the muscles often remained tender for two to three days afterwards.

Examination at this time showed that he was frankly Cushingoid with moon facies, a 'buffalo hump', and truncal obesity. His blood pressure was 210/120 mm Hg. There was moderate atrophy of proximal muscle groups which was most severe in the quadriceps. Muscle power was difficult to evaluate as even slight exertion precipitated painful cramps. However, there was definite weakness of proximal muscle groups both in the upper and the lower extremities. The proximal muscles, particularly those of the thighs, were tender to palpation. There was no other neurological deficit and no abnormalities were found on general examination. Urinalysis showed a trace of glycosuria.

The following investigations were performed shortly after admission: haemoglobin 16·6 g/100 ml.; white cell count 13,000/cu mm (differential count normal); ESR (Westergren) 3 mm in first hour; blood film normal. Blood urea 42 mg/100 ml. Fasting blood sugar 84 mg/100 ml. Serum calcium 9·9 mg/100 ml. Serum alkaline
phosphatase King Armstrong u./100 ml. Serum aspartate transaminase 38 u./ml. Plasma proteins 5-9 g/100 ml; albumin 3-6 g/100 ml., globulin 2-3 g/100 ml.; electrophoresis showed decreased γ-globulin and increased α-2 globulin. Serum aldolase 4-3 u./ml.; creatine kinase 490 i.u./l. (upper limit of normal in this laboratory 60 i.u./l.). The chest radiograph showed a fracture of the left ninth rib. An electrocardiogram showed ventricular ectopic beats and the changes of left ventricular hypertrophy. Electromyography was performed by Dr. D. Barwick. No insertional activity or spontaneous potentials were present in the hypothenar muscles. On slight contraction there were excessive numbers of potentials of low voltage and short duration, some of which were polyphasic. The interference pattern was full. Repetitive supramaximal stimulation of the ulnar nerve above the wrist failed to produce a cramp in the muscle. Levels of lactate in blood taken from an antecubital vein after ischaemic forearm exercise (method of McArdle, 1951) failed to demonstrate a normal rise (Fig. 1).

On the eighth hospital day the patient suffered an episode of gastrointestinal bleeding with the passage of melaena stools and became shocked. He had two further episodes of bleeding on the 13th and 20th hospital days and on each occasion required transfusion. A barium meal failed to show any ulceration in the stomach or duodenum. The dose of ACTH and prednisone was gradually reduced and both drugs were finally stopped. On the 15th hospital day he developed paroxysmal atrial fibrillation and digoxin therapy was commenced. The serum aspartate transaminase level rose to 114 u./ml. at this time and an electrocardiogram showed changes of anterior myocardial infarction. He subsequently made a gradual recovery and muscular power improved considerably during the following two weeks.

When seen again after an interval of six weeks, his general condition had improved and the Cushingoid features and diabetes had resolved. However, his exercise tolerance was still extremely limited because of painful cramps. Moderate proximal muscular weakness was still present but was less marked than previously. The creatine kinase level on this occasion was 1,136 i.u./l. The ischaemic lactate test was repeated and once again failed to show a normal rise in lactate levels (Fig. 1). Electromyography was repeated on the deltoid and quadriceps muscles (Dr. A. McComas). No spontaneous activity was present in either muscle. The interference patterns, although dense, were reduced in amplitude. Individual motor units were of normal amplitude and duration but many were polyphasic. Treatment with oral fructose and diazepam have failed to influence the patient's symptoms.

PATHOLOGICAL STUDIES

MATERIALS AND METHODS A muscle biopsy was taken from the left quadriceps muscle under local anaesthesia. A portion of this biopsy was frozen immediately in isopentane cooled to −70°C for histochemical study and quantitative biochemical analysis. Histochemical techniques for phosphorylase, succinic dehydrogenase, and myosin ATPase (Barka and Anderson, 1963) were applied to 12 μ cryostat sections. The remainder of the biopsy specimen was divided, part being processed for electron microscopy by methods described in detail elsewhere (Hudson and Pearce, 1969), while the remainder was fixed in formol calcium or Gendre’s alcoholic picric acid fixative. This material was embedded in paraffin wax blocks from which 5 μ sections were cut and stained with haematoxylin and eosin, picro-mallory, phosphotungstic acid haematoxylin, and by the aequous periodic acid-Schiff (PAS) method. Ultra-thin sections for electron microscopy were stained with uranyl acetate and lead citrate and examined in a Zeiss EM9A or Siemens Elmiskop I electron microscope.

LIGHT MICROSCOPIC OBSERVATIONS Examination of the haematoxylin and eosin stained sections showed considerable variation in the diameters of muscle fibres with numerous internal nuclei and an occasional necrotic fibre. The subsarcolemmal vacuoles or ‘blebs’ characteristic of McArdle’s disease were seen in only a minority of fibres (Fig. 2) while in others vacuoles were scattered throughout the substance of the fibre (Fig. 3). Review of a biopsy performed seven years previously showed similar changes. The PAS stained sections showed that many of the fibres contained abnormally high concentrations of PAS-positive material when compared with a normal biopsy specimen (Fig. 4), although this was less striking.
than in other cases of McArdle's disease we have reviewed. Predigestion of serial sections with diastase before staining confirmed that the PAS-positive material was glycogen. The cryostat sections showed complete absence of phosphorylase activity in muscle fibres (Fig. 5), while succinic dehydrogenase and myosin ATPase activities and the amount and distribution of sudanophilic lipids appeared to be normal.

**ELECTRON MICROSCOPIC OBSERVATIONS** Electron microscopic examination of the biopsy sample revealed ultrastructural features which were both interesting and unexpected. In cases of McArdle's disease (Salter, Adamson, and Pearce, 1967) and skeletal muscle glycogenosis associated with acid maltase deficiency (Hudgson, Gardner, Medwin, Worsfold, Pennington, and Walton, 1968) previously studied in this laboratory, the most impressive ultrastructural abnormality has been the accumulation of vast amounts of glycogen within the muscle fibres. In the present case the amount of glycogen did not appear to be excessive, although some glycogen was present in subsarcolemmal vacuoles and in vacuoles scattered throughout the sarcoplasm (Figs. 6 and 9). However, examination of sections from the previous biopsy showed abundant amounts of glycogen beneath the sarcolemma and between the myofibrils (Fig. 8).

Turning to the various ultrastructural components of the muscle fibre, the sarcolemma showed a consistent and striking change. The plasma membrane appeared normal throughout but the basement membrane was greatly thickened measuring 1,000 to 3,000 Angstrom units \( (\AA) \) in most sections. This thickening was due to the accumulation of finely granular moderately electron-dense material (Figs. 6 and 7). Although this material appeared to be in linear arrays in some areas, the distribution of the granules was, in general, quite random. Numerous deep invaginations of the sarcolemma were found with many underlying pinocytotic vesicles (Figs. 6 and 7). Many vesicles, some possibly dilated elements of the sarcoplasmic reticulum, together with moderate numbers of lipid bodies were present between individual myofibrils. The mitochondria were generally normal in size and configuration. However, paracrystalline inclusion bodies were found in the mitochondria of one fibre (Fig. 9). No distinctive changes were found in the contractile elements but several foci of fibrillar degeneration and disorientation were seen resembling the so-called peripheral sarcoplasmic masses (Fig. 10). No evidence of Z-band or actin filament degeneration was found.

**BIOCHEMICAL STUDIES** Quantitative analysis of the biopsy

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**FIG. 2.** Cross-section showing subsarcolemmal 'blebs' in muscle fibres (arrows). Haematoxylin and eosin, \( \times 384 \).

**FIG. 3.** Cross-section showing vacuoles within the substance of a muscle fibre. Haematoxylin and eosin, \( \times 650 \).
sample of muscle was performed by Dr. D. Hart-Mercer and showed that the total muscle glycogen content was 2.0% of its wet weight (upper limit of normal in this laboratory 1.0%). Phosphorylase activity was undetectable.\textsuperscript{1}

\textsuperscript{1} The procedure used to assay phosphorylase was a sensitive UV recording method (Hudgson et al., 1968). It was also shown that the patient's muscle preparation did not inhibit phosphorylase activity when added to a rat muscle preparation.

DISCUSSION

The diagnosis of McArdle's disease was suspected on the basis of muscle pain related to exertion and was confirmed by the abnormal ischaemic lactate test and the failure to demonstrate phosphorylase activity in muscle tissue obtained at biopsy. The initial presentation was that of a proximal myopathy but the clinical course was subsequently complicated by the administration of corticosteroids and ACTH.

FIG. 4. (a) Periodic acid-Schiff reaction showing positive staining of several muscle fibres of moderate intensity. The arrows indicate subsarcolemmal vacuoles. $\times$ 250. (b) Periodic acid-Schiff after diastase predigestion showing complete absence of staining of the muscle fibres. $\times$ 375.

FIG. 5. (a) Phosphorylase reaction on muscle from normal control showing deep staining of type II fibres. $\times$ 280. (b) Phosphorylase reaction on patient's muscle showing failure of muscle fibres to stain. $\times$ 250.
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FIG. 6. Second biopsy. Electron micrograph of a muscle fibre showing thickening of the basement membrane (BM) and prominent pinocytotic vesicles (P). Small numbers of glycogen particles are present in the intermyofibrillar spaces and between the thin filaments of the I-bands. V: vesicle associated with a mitochondrion; T: triad. × 35,500.

in high dosage. In view of the clinical improvement when ACTH was substituted for betamethasone and when prednisone was subsequently withdrawn, there seems little doubt that the patient’s deterioration while on corticosteroids was largely attributable to the drugs themselves. The development of a myopathy in patients treated with betamethasone and prednisone is much less frequent than with the 9α-fluorinated compounds such as triamcinolone but has been reported previously (Golding et al., 1961). The high levels of creatine kinase in the blood are not unusual in McArdle’s disease. Schimrigk, Mertens, Ricker, Führ, Eyer, and Pette (1967) found that levels of the enzyme were elevated in all but one of the 15 cases they reviewed in which it was estimated. In the case reported by Gruener, McArdle, Ryman, and Weller (1968) levels ranged from 243 to 2,270 i.u./ml. The first estimation in the present case was performed while the patient was confined to bed before the episode of myocardial infarction, so that the enzyme was probably of skeletal muscle origin. The higher level six weeks after discharge from hospital, during which time the patient was ambulant, suggests that release of the enzyme from the muscles may be related to physical activity.

The histopathological findings, although consistent with the diagnosis of McArdle’s disease, were far less striking than in many of the previously reported cases. McArdle’s disease is generally regarded as a vacuolar myopathy with prominent subsarcolemmal ‘blebs’ (Schmid and Mahler, 1959; Adams, Denny-Brown, and Pearson, 1962; Salter et al., 1967). In the present case only a few small vacuoles were present beneath the sarcolemma or within the substance of small numbers of fibres. Moreover, the amount of glycogen demonstrated histochemically, although greater than in a biopsy from a normal control, was much less than in the cases described by Salter et al. (1967). The changes of non-specific myopathy such as muscle fibre
necrosis, variation in size of muscle fibres, and the presence of excessive numbers of internal nuclei have also been observed in previous cases (Schmid and Mahler, 1959; Pearson, 1968; Salter, 1968). The elevated levels of creatine kinase in the blood may be related to the observed necrosis of muscle fibres. However, the disparity between the degree of necrosis and the levels of creatine kinase suggests that release of the enzyme may occur from fibres which at the light microscopic level appear normal.

The ultrastructural findings also support the view that this patient’s disease was modified by the corticosteroid therapy. In previously reported cases of McArdle’s disease large quantities of glycogen have been found in the muscle fibres lying between myofibrils or in subsarcolemmal deposits (Schotland, Spiro, Rowland, and Carmel, 1965; Salter et al., 1967). In the present case, whereas abundant glycogen was found in sections from the first biopsy, only a small amount was present in sections from the second biopsy taken seven years later. A consistent finding was the presence of considerable thickening of the basement membrane of the muscle fibres. This has also been found by Afifi et al. (1968) in biopsy material from humans with steroid-induced myopathy and by Afifi and Bergman (1969) in an experimental study of steroid myopathy in the rabbit. The other abnormality found in the region of the sarcolemma was the presence of unusually large numbers of pinocytotic vesicles, suggesting that its

FIG. 7. Second biopsy. Electron micrograph showing marked thickening of the basement membrane (BM). Numerous pinocytotic vesicles are present beneath the plasma membrane and between the myofibrils (P). The vesicles (V) are distended elements of the sarcoplasmic reticulum. × 12,000.
membrane transport activity may have been altered in some way. The other ultrastructural findings were quite non-specific. The sarcoplasmic masses and mitochondrial inclusions which were found have been described in a variety of myopathic and neuropathic muscular disorders (De Recondo, Fardeau, and Lapresle, 1966).

Apart from the observations discussed above, there are good theoretical reasons for suggesting that prolonged steroid therapy may modify the course of a skeletal muscle glycogenosis in addition to damaging the muscle fibre in its own right. Adrenal corticosteroids may interfere with the glycolytic pathway at various stages. It has been suggested that cortisone may inhibit activation of phosphorylase by adrenaline or even the activity of the enzyme itself (Kerppola, 1952) although this has not been confirmed by later studies (Leonard, 1957). More recent work (Sie and Fishman, 1964; Young, 1966) indicates that corticosteroids affect the activity of UPDG-glycogen synthetase in the muscle cell. It should also be remembered that prolonged administration of steroids may induce a state of chronic intracellular potassium deficiency which would be likely to damage the
McArdle's disease is characterized by muscle cramps on exercise, sometimes accompanied by myoglobinuria, and eventually by gradual progression to an established proximal myopathy. The patient described presented with the latter, a diagnosis of polymyositis was made at the time and he was subsequently treated with corticosteroids and ACTH for several years. During this time his general condition deteriorated considerably and the proximal muscle weakness became much worse. Subsequent investigation confirmed that he had a proximal myopathy with abnormally low lactate production on ischaemic exercise and deficient muscle phosphorylase activity. However, the glycogen content of the biopsied muscle was only moderately increased and on electron microscopy was much less than in a biopsy performed seven years previously. Ultrastructural studies revealed some of the changes which have been described in steroid myopathy. It is suggested that these changes resulted from the effects of steroids on muscle which was already phosphorylase deficient. The possible mechanisms whereby prolonged steroid therapy could have decreased glycogen deposition in the muscle fibres are considered.

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FIG. 10. Second biopsy. Electron micrograph showing an area of myofibrillar disarray with loss of sarcomere pattern lying between normally oriented myofibrils. Small numbers of glycogen particles are present between the myofibrils and in the I-bands. Triads are also seen (T). × 22,500.

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