McArdle’s Disease: a Review

M. MICHAEL LUBRAN, M.D., PH.D.

Department of Clinical Pathology,
Habor General Hospital Campus, UCLA School of Medicine,
Torrance, CA 90509

ABSTRACT

The clinical features of McArdle’s disease (inherited deficiency of skeletal muscle phosphorylase) and the histological and biochemical changes are described. Their possible causes are discussed in the light of recent knowledge of the biochemistry of muscular contraction. Diagnostic tests are detailed. Attention is drawn to the possibility that the disease may be due to a primary defect of motoneurons.

Introduction

McArdle’s disease, described in 1951, was the first example of a hereditary primary myopathy shown to be due to an enzyme deficiency, although it was not until 1959 that the enzyme concerned was identified independently by Schmid and Mahler and Mommaerts et al as skeletal muscle phosphorylase. Forty-two cases have been described in the English language literature through the first half of 1974; it is probable, however, that many mild cases have passed unrecognized or have been incorrectly diagnosed. Thus, in 1948, Kreutzer et al described a case of spontaneous myoglobinuria, which was very probably an example of McArdle’s disease.

The enzymatic defect results in a failure to convert glycogen to lactate. Glycogen accumulates in the skeletal muscles, but only to about twice or three times the normal amount. Other types of glycogen storage disease owing to enzyme defects are known; some of these (phosphofructokinase deficiency, limit dextrinosis, amylo-1,6-glucosidase deficiency, phosphohexoseisomerase deficiency, result in failure to convert glycogen to lactate and present a clinical picture identical with that of McArdle’s disease. However, skeletal muscle phosphorylase is present.

Inheritance of the enzymatic defect in McArdle’s disease is due to a single recessive autosomal gene. In most cases, absence of muscle phosphorylase is complete; in a few cases the defect has been partial and the clinical effects mild. The activities of the other enzymes concerned in glycogen synthesis and degradation are normal; however, an increase in the activity of phosphoenolpyruvate carboxykinase has been described, probably an adaptive mechanism providing phosphorylated intermediates.

Clinical Features

The disease is about three times as common in males as in females. Patients typically present themselves in adolescence or
early adult life, although a few have been as old as 60 years. In almost every case, symptoms can be traced back to early childhood. Family studies of affected subjects have occasionally revealed the enzymatic defect in very young symptomless siblings.

The main symptoms are muscle pain, easy fatigue and stiffness of muscles (cramps) on moderate exertion. Aching of the calves on walking is a common early symptom, although any muscle can be affected by exercise. Pain, which is usually the most prominent symptom, is proportional to the severity of the exercise and its duration. Patients learn to exercise within the pain-producing limit, but may exceed it on occasions. Symptoms are then rapidly relieved by rest, but they recur as soon as moderate exercise is resumed. Pain is increased in severity and may persist for many minutes after the exercise has stopped. A characteristic finding is the inability of the patient to extend the fingers fully after powerful, long sustained or frequently repeated gripping movements. The muscles are then in a state of physiological contracture (i.e., electromyographically silent).

The phenomenon of “second wind” occurs in a few patients who are able to continue moderate exercise in spite of the pain. Pain and stiffness disappear and the exercise may be continued for some time before they recur. Second wind is due to an increased blood flow through the muscle and an increase in the concentration of fatty acids in the blood, which provide an alternative source of energy to glycogen.

A slight degree of muscle wasting, particularly in the upper limbs, occurs in about one third of the patients. It may be more severe and progressive in older patients. Even when muscle wasting is not apparent, the upper limbs are not as well developed muscularily as the lower limbs. The ability to perform work is reduced in all muscles (because of pain); the tolerance to exercise varies widely among the patients. Exercise tolerance has been improved in some patients by the prior administration of glucose or fructose. Heart muscle is not affected (cardiac muscle metabolism is aerobic). Slight exertion in elderly subjects may result in tachycardia, dyspnea and exhaustion. Rarely, an abnormal electrocardiogram has been observed, indicative of some blockage of the conduction pathway. Epileptiform seizures have been described.

About two-thirds of the patients have had occasional episodes of myoglobinuria after unusually severe exercise, although many athletic patients can undergo short bursts of vigorous exercise without the production of myoglobinuria. In a small number of patients, myoglobinuria has been the presenting feature of the illness. Rarely, acute renal failure has supervened; most commonly, however, the myoglobinuria is symptomless and transient.

Apart from the features described, the patients show no physical abnormality, are healthy and live normal lives within the limits of their exercise tolerance. Carbohydrate metabolism is normal, except for the defect in skeletal muscle glycogenolysis. The liver is normal in size and function (hepatic and skeletal muscle phosphorylases are not identical). Pregnancy has been described in one patient. Delivery was normal and uterine contractions were unaffected.

**Biochemical Features**

The inability to produce lactate from glycogen during ischemic work is the principal biochemical finding in McArdle’s disease, although it is also found in the rarer enzyme deficiency diseases listed in the Introduction. Elevations of serum creatine-phosphokinase (CPK) and aldolase activities, even at rest, are common; after exercise, activities may be very great. Lactate
dehydrogenase (LDH) and glutamate-oxaloacetate transaminase (SGOT) activities are also elevated in the serum. The diagnostic feature of the disease is the demonstration of the absence (in most cases) or great reduction (in a few cases) of skeletal muscle phosphorylase activity. The demonstration is best made by biochemical methods; histochemical methods may also be used but they are difficult and do not always work. Absence of the enzyme has been confirmed in a few cases by immunological methods. In one case there was evidence of immunologically reactive but biochemically inactive phosphorylase.

One of the remarkable features of McArdle's disease is the ability of the patient to perform light exercise without discomfort and the production of a painful contracture of the muscle when moderate or severe exercise is carried out. These observations can be explained in part by current knowledge of the biochemistry and biophysics of muscular contraction, but many problems still remain unanswered.

Skeletal Muscle Contraction

Skeletal muscle contraction depends upon an adequate supply of adenosine triphosphate (ATP) to provide the energy required by the contractile elements of the muscle fiber. During exercise, the demand for ATP is increased many hundred times. Skeletal muscle at rest or during light exercise depends mainly on the oxidation of fatty acids and aminoacids, especially alanine, for the generation of ATP. However, the amount of ATP that can be formed is limited by the availability of oxygen and substrates, which reach the active muscle by diffusion. Additional ATP is generated in normal muscle by glycolysis, the first step of which is the conversion of glycogen and inorganic phosphate to glucose-1-phosphate and degraded glycogen; phosphorylase is required for this step. The remaining steps, as far as the production of lactate, are anaerobic and take place rapidly in exercised muscle. Lactate is eventually converted by the liver to glucose or oxidized to carbon dioxide and water. Lack of muscle phosphorylase, in McArdle's disease, becomes clinically obvious, therefore, only during strenuous or prolonged exercise. Increasing the blood supply to the muscle and providing more substrate for ATP production (glucose, fructose or non-carbohydrate substances such as fatty acids) will allow more exercise to be performed before the lack of phosphorylase makes itself felt. On the other hand, ischemic exercise will bring on rapidly the effects of phosphorylase lack; furthermore, no lactate will be produced. Phosphorylase activity in skeletal muscle is essential to allow for adequate glycolysis with ischemic work.

Phosphorylase is part of a complex enzyme system involved in muscular contraction. It exists in muscle in two forms, a tetramer, phosphorylase a, and a dimer, phosphorylase b, the latter predominating in resting muscle. Although phosphorylase b can, in vitro, act directly on glycogen, the reaction requires an adequate amount of adenosine monophosphate (AMP). In resting muscle, ATP is greatly in excess of AMP and inhibits phosphorylase b action on glycogen by reducing its affinity for this substrate and also for inorganic phosphate.

Phosphorylase Activation

During anaerobic muscular activity, there is a rapid and almost complete conversion of phosphorylase b to phosphorylase a, which acts on glycogen to produce glucose-1-phosphate and degraded glycogen. The conversion is brought about by an enzyme, phosphorylase b kinase, in the presence of ATP, magnesium ions and a non-enzymatic protein factor of as yet unknown nature. The serine of phosphorylase a becomes phosphorylated. This may ex-
plain the greater affinity of phosphorylase a for glycogen.

Phosphorylase b kinase is present in an inactive form in resting or lightly exercised muscle. It is activated during strenuous exercise by the events of muscle contraction, or it may be activated by means of the sympathetic nervous system through the production of catecholamines, particularly norepinephrine. Muscle contraction results in the production of calcium ions in a concentration about $10^{-8}$ M. This concentration activates the kinase in the presence of protein factor. The kinase can also be activated by low concentrations of calcium ions ($10^{-6}$ M) in the presence of ATP, magnesium ions and a trace of cyclic AMP. The last substance is important in the activation of phosphorylase kinase b by catecholamines. These stimulate the production of cyclic AMP from ATP in the presence of adenyl cyclase and magnesium ions. Cyclic AMP activates a protein kinase which is identical with glycogen synthetase kinase involved in glycogen synthesis. The activated protein kinase activates phosphorylase b kinase. The protein kinase consists of two portions, a catalytic part and a regulatory part which inhibits the catalytic action. Cyclic AMP combines with the regulatory part, thus allowing the catalytic activity to occur.

Active phosphorylase b kinase is deactivated by phosphorylase phosphatase, which is present in muscle. Deactivation is inhibited by glycogen and AMP. The latter substance accumulates in an anaerobic contraction of muscle, thus protecting phosphorylase b kinase. In addition, AMP activates phosphorylase b to act directly on glycogen and enhances the activity of phosphorylase a by 30 percent to 40 percent through an allosteric effect. The activity of phosphorylase b is also increased through the action of $5'$-AMP, derived from cyclic AMP by the action of cyclic phosphodiesterase.

Absence of phosphorylase kinase does not give rise to the signs and symptoms of McArdle's disease. Several cases of this rare genetic disorder have been described in which phosphorylase b kinase has been absent or deficient. Evidently, some of the phosphorylase b kinase-independent activating mechanisms become operative in this disease.

**Histological Features**

**Light Microscopy**

No abnormalities can be seen in hematoxylin and eosin or trichrome stains of muscle biopsy specimens. Best-carmine and periodic acid-Schiff stains reveal increased glycogen content. Blebs containing granular material may be seen under the sarcolemmal membrane. Longitudinal rows of small granules are seen within the fiber, often near the I band; free granules may occur in the interstitial space. The granules, which disappear after treatment with amylase, are probably glycogen.

**Electron Microscopy**

There is a marked increase in glycogen, mainly in vacuoles under the sarcolemma and in the intermyofibrillar space of the I band and, occasionally, the A band. Increased amounts of glycogen also occur between the thin filaments in the I band; myofibrillar structure is disorganized. The sarcolemmal membrane is deeply invaginated. Muscle examined in contracture shows contracted myofibrils, localized mitochondrial swellings and dilatation of portions of the sarcoplasmic reticulum. Necrosis of fibers may occur, especially after exercise.

**Electromyography**

Electromyographic changes do not appear until repeated muscular contractions have led to fatigue and hypoxia of the muscle. There is then a marked and progressive decrease in amplitude of the inter-
ference pattern of discharge during full effort and in the force of the contraction until the muscle goes into contracture; electrical activity is then completely absent. The interval between the cessation of motor unit potentials and onset of relaxation is unchanged during exercise and does not decrease as contracture develops, thus suggesting that the relaxation mechanism is intact.

Contracture can also be induced by supramaximal stimulation of the ulnar nerve (18 per sec), potentials being recorded from the first dorsal interosseous muscle. Potentials fall to zero and painful contracture develops, lasting several minutes. The test need not be carried to completion. The motor response to the stimulation decreases to 50 percent or less within 40 seconds in patients with McArdle’s disease, but not in those with other myopathies.

Cause of the Contracture

Contraction and relaxation of muscle fibers are related to changes in calcium ion concentration of sarcoplasm, mediated by a calcium pump mechanism. Calcium is stored in the terminal cisternae of the sarcoplasmic reticulum, presumably bound to some carrier. Action potentials resulting from stimulation of the muscle by its motor nerve travel down into the fiber along the membranes of the transverse tubule to the region of the triad. In some way, this causes the terminal cisternae to release rapidly significant amounts of calcium ions into the sarcoplasm. Resting muscle is kept in a relaxed condition by a mechanism termed “relaxing factor,” which is a system of regulatory proteins. Myosin and actin, in the presence of magnesium ions and ATP, interact to form a superprecipitate (a compact gel) and split the ATP. If troponin and tropomyosin (other myofibrillar proteins) are present, actin and myosin do not combine; ATP is not broken down. The inhibitory effect of these regulatory proteins results in relaxation. Calcium ions added to the sarcoplasm as a result of muscle stimulation combine with troponin and overcome its inhibitory effect; the fiber contracts. At the same time, the ions are removed by a competing process which involves active transport of calcium ions (calcium pump) from the sarcoplasm across the walls of the longitudinal tubules into their lumens, from which they pass by diffusion into the terminal cisternae. ATP is required for the calcium pump. When the calcium ion concentration has fallen below a critical value, the regulatory proteins once more exert their inhibitory effect and produce relaxation. Calcium ions also move into and out of the mitochondria.

The cause of the contracture in McArdle’s disease is unknown. It is probably not due to changes in relaxing factor, as electromyographic evidence suggests that this is normal. It is not due to ATP deficiency, as concentrations of ATP are normal in muscles of patients with the disease. It is not due to changes in propagation of action potentials along the sarcolemmal membranes, or changes in the membrane, as contracture develops in fibers stripped of sarcolemma. Biopsy of muscle before and during contracture reveals a normal uptake of calcium under both conditions. The contracture appears to be related to changes in the muscle fiber itself, due to the deposition of glycogen; or ATP may be compartmentalized and thus be inaccessible to enzymes.

Diagnosis

This depends upon clinical alertness and awareness of the existence of the disease. The condition should be suspected if muscle pain occurs during moderate exercise in a young person, otherwise healthy, with normal physical and neurological findings. The diagnosis of McArdle’s disease should
also be considered in otherwise healthy subjects exhibiting spontaneous myoglobinuria related to strenuous exercise. Elevated muscle enzyme activities in serum (CPK, aldolase, SGOT, LDH), even at rest, may be present. Urinary creatine and creatinine excretion are normal.

The ischemic exercise test results in no significant increase in lactate, thus distinguishing McArdle’s disease from other conditions associated with muscle pain or myopathy (except the other glycolytic enzyme deficiency diseases). To perform the test, a sphygmomanometer cuff is wrapped around the upper arm and another around the wrist. Each is inflated to about 200 mm of mercury and the patient made to flex and straighten the fingers by repeated squeezing of a sphygmomanometer bulb or similar object for about 45 seconds. The cuffs are released and venous blood collected from the antecubital vein at once and at further intervals of about two or three minutes for a total of about ten minutes. Blood is taken from the same vein before the exercise is started. It is convenient to use an indwelling catheter in the vein. Blood samples are collected directly into protein precipitant solutions to prevent the formation of lactate from blood glucose by glycolytic enzymes in the blood. Lactate should be measured by an enzymatic procedure.

The ischemic exercise test is painful; nevertheless, it should be carried out if the condition is strongly suspected on clinical grounds. In screening patients (e.g., in family studies), the ulnar nerve stimulation test, described in the section on electromyography, is convenient and well-tolerated by the subject. There is unfortunately, no easily accessible cell which can be examined to establish the diagnosis. Phosphorylase activity is present in epidermal cells, skin fibroblast cells in culture, and platelets obtained from patients with McArdle’s disease.

The definitive test, which diagnoses the disease and differentiates it conclusively from other glycolytic enzyme deficiency diseases, is the examination of fresh muscle, obtained by biopsy, for phosphorylase activity. Histochemical and direct biochemical tests should be used. Muscle should be obtained by a non-traumatic surgical procedure, immediately flash-frozen in isopentane, and kept at −170° to −180° in liquid nitrogen. Appropriately stained sections should be examined for glycogen and phosphorylase activity. These should also be measured by standard biochemical procedures. Several methods have been described for determining phosphorylase activity. It is advisable to use two methods, employing different principles, to minimize the risk of technical error. Absence of phosphorylase histochemically and biochemically confirms the diagnosis of McArdle’s disease.

Treatment and Prognosis

There is no treatment of value which prevents muscle pain and permits strenuous and prolonged exercise. Administration of glucose or fructose before exercise leads to obesity. Pyridoxal phosphate is present in the phosphorylase molecule. However, there is no evidence to suggest that there is a deficiency of this substance in McArdle’s disease and treatment with pyridoxal phosphate is without effect. Patients learn to adjust their activity to prevent pain. Although myopathy may occur, it is rarely progressive; when it is progressive, it does not threaten the life of the patient. The prognosis is good and patients should be encouraged to lead a normal life. The episodes of myoglobinuria are transient and require no treatment, except in the rare cases when acute renal failure occurs.

Etiology

Although the clinical features of McArdle’s disease are due to a deficiency of
phosphorylase in skeletal muscle, there is some evidence which suggests that the enzyme deficiency is not the primary defect. Roelofs et al. have shown that phosphorylase activity could be demonstrated histochemically in regenerating muscle fibers from patients with McArdle’s disease. Mature fibers were deficient in the enzyme. These results suggest that phosphorylase activity is lost with fiber maturity. Upton et al. have investigated a patient with biochemically proved McArdle’s disease using a technique for estimating the number and size of motor units in a muscle. In the muscles examined, Upton and coworkers found a definite reduction in the number of motor units and enlargement of the surviving units. This finding has not been observed in other myopathic disorders and would not be expected in them. A differential involvement of motor neuron pools was observed. The investigators state that the muscle wasting observed in McArdle’s disease may be due to an inability of increasingly “sick” motoneurons to maintain an increased or normal number of muscle fibers. There may be a primary defect of motoneurons, leading to a loss of muscle phosphorylase activity. Loss of phosphorylase activity is known to follow severance of the motor nerve.

These observations would account for the mild nature of the disease in childhood and adolescence, the delayed onset in many cases, the varying degree of muscle wasting, its uneven distribution and the muscle hypertrophy occasionally seen in the early stages of the disease. Still to be explained are the uneven sex distribution, the cause of the contracture and the cause of the pain.

References


