McArdle's syndrome:

A review and a preliminary report of four further cases

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INHERITED enzyme deficiencies are increasingly being demonstrated as the underlying abnormality in many hitherto unexplained disease states. Glycogen storage diseases have been shown to belong to this category, and six types have now been described, each apparently the result of a specific enzyme defect in the chain of glycogen breakdown (Mahler, 1966).

In addition to the liver, glycogen is stored in voluntary muscle fibres and is the main source of energy for anaerobic muscular contraction. This is obtained by the generation of adenosine triphosphate from the breakdown of glycogen to lactic acid via the Embden-Meyerhof pathway, a process initiated by the enzyme phosphorylase.

A defect of muscle glycogen breakdown was first suggested by McArdle (1951) as the explanation of a myopathy in a man aged 30 complaining of muscular pain, stiffness and weakness on exertion, symptoms which he had noticed all his life. McArdle found that the expected rise in blood lactate and pyruvate after ischaemic exercise failed to occur. A normal hyperglycaemic response to parenteral adrenaline showed that the breakdown of hepatic glycogen was not impaired and McArdle concluded that the patient suffered from a disorder of carbohydrate metabolism, affecting chiefly, if not entirely, the skeletal muscle.

However, the site of the defect in the glycolytic pathway remained unknown until a preliminary communication from Mommaerts *et al.* (1959) described studies on a muscle biopsy from the thigh of a 19-year-old male who had complained of muscle cramps and fatigability on exertion since childhood, and also the passage of red urine after severe exertion. These workers found the muscle glycogen content to be greatly increased, although the glycogen itself was normal in structure, and there was no detectable myophosphorylase activity. It was again shown that there was no rise in blood lactate and pyruvate

after ischaemic exercise, a normal hyperglycaemic response to parenteral adrenaline, and also an improvement in exercise tolerance after fructose and glucose infusion (Pearson, Rimer & Mommaerts, 1961).

In the same year, Schmid & Mahler (1959) investigated a 52-year-old man who had complained of easy fatigability since childhood. At about the age of 20 he began to experience cramping pains and weakness in the limb muscles after exercise, usually followed by the passage of dark urine, the pigment subsequently being identified as myoglobin. These symptoms were followed over the next few years by a phase of progressive muscular weakness, during which time the attacks of cramp and myoglobinuria subsided. Physical examination revealed marked muscular wasting and weakness, the proximal muscles of the extremities and the shoulder girdle being particularly affected. As in McArdle's patient, there was a failure of the blood lactate to rise after ischaemic exercise, and a normal hyperglycaemic response to parenteral glucagon or adrenaline indicated that hepatic glycogen breakdown was unaffected. Studies of muscle tissue obtained by biopsy showed the glycogen content to be greatly increased, varying from 2.4-3% of the wet weight, and an absence of any significant activity of phosphorylase. Schmid & Mahler concluded that the disorder was due to a defect in the phosphorylase system of skeletal muscle, preventing glycogen breakdown and eliminating anaerobic glycogenolysis as a source of energy for muscular contraction.

The family of this patient was investigated (Schmid & Hammaker, 1961) to try to establish whether the absence of the enzyme was a hereditary defect. The parents were first cousins but neither was clinically affected. Of thirteen children, at least three siblings were affected (including the propositus) but none of the third generation. Schmid & Hammaker concluded that the defect is due to a single rare recessive autosomal gene. By studying the clinical course of these patients, they also suggested that there were three phases of the

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illness: (1) easy fatiguability during childhood and adolescence; (2) the development of cramping pains on exertion followed by transient myoglobinuria during early adult life; and (3) a phase of weakness and wasting of individual muscle groups from the fourth decade onwards.

Mellick, Mahler & Hughes (1962) reported a further case of a 17-year-old male, differing only from the previous patients in that some variations in the levels of serum aldolase and phosphocreatine kinase were detected, and the muscle glycogen content was normal and not increased, as had previously been found. They suggested this might be due to an additional enzyme deficiency tending to reduce the rate of glycogen synthesis from glucose, but not enough material was available to investigate this possibility further.

A patient described in 1963 (Rowland, Fahn & Schotland, 1963) showed no new features, but a report in the same year by Engel, Eyerman & Williams (1963) described a late-onset form of the disease, the symptoms not appearing until the fifth decade. Their first patient was a 52-year-old woman who had been free of symptoms until the age of 49, when she began to complain of progressive generalized muscular weakness and a more profound muscular fatigue after exertion. Generalized weakness and muscle wasting were found on physical examination. The blood lactate failed to rise after ischaemic exercise and histological examination of a muscle biopsy revealed a complete absence of phosphorylase activity, but the glycogen content appeared normal. A second patient aged 60 was the brother of the first, and was also free of symptoms until the age of 49, when he began to experience cramping muscular pain on exertion relieved by rest. These symptoms did not progress in severity and were never associated with pigment in the urine. Muscle bulk and power were normal on physical examination. In this second case there was the usual elevation of blood lactate to four times the resting level after ischaemic exercise. Muscle biopsy studies again revealed a normal glycogen content, but some phosphorylase activity was present (about 35% of that demonstrated in normal controls). Engel and others concluded from these studies that partially affected subjects may occur and that the manifestations may not become apparent until late adult life.

Two further typical cases were described by Hockaday, Downey & Mottram (1964), and in another family study, Tobin & Coleman (1965) reported three cases in a family of six siblings. Both groups of workers accepted these findings as further evidence for an autosomal recessive inheritance of the enzyme defect.

Hitherto it was thought that the metabolic defect was confined to skeletal muscle. However, Ratnov, Baker & Swaiman (1965) described a 19-year-old male who had complained of muscular weakness and cramping on exertion since infancy. He had noticed one episode of dark urine after excessive fatigue, but complained of no other symptoms. Examination revealed a healthy looking well-developed young man, and the only features of note were a sinus bradycardia (pulse rate 48 beats/min) and a grade 1 ejection systolic murmur over the precordium. The diagnosis of McArdle's syndrome was confirmed by finding a failure of the blood lactate to rise after ischaemic exercise, associated with an increased glycogen content and a virtual absence of phosphorylase activity from the skeletal muscle. A chest X-ray showed a normal cardiac shadow, but an ECG revealed sinus bradycardia with marked sinus arrhythmia, a prolonged P-R interval, intraventricular conduction delay, increased precordial voltage and T wave inversion in leads V_2 and V_3 . These ECG features were similar to those noted by Ehlers & Engle (1963) who analysed the tracings from twenty-one proven cases of glycogen storage disease involving the myocardium. Ratnov *et al.* (1965) concluded that the electrocardiographic abnormalities might be related to myocardial phosphorylase deficiency, resulting in increased glycogen stores in the myocardium, and to a deficiency of the glycolytic system upon which the conducting system is believed to be highly dependent. Although this case is certainly suggestive of heart involvement there is still no direct evidence of a reduction or absence of myocardial phosphorylase in McArdle's syndrome.

Earlier, Rowland *et al.* (1963) had speculated as to why there was a lack of clinical evidence of cardiac disorder in this condition. They suggested a difference between muscle and myocardial phosphorylase as a possible explanation, or that glycogen stores play a small part only in myocardial metabolism, or that there might be more than one form of myocardial phosphorylase, so that activity of an alternative enzyme might persist even in the absence of the form corresponding to that in skeletal muscle.

A family study is reported in which four further cases have been discovered, although one appears to be only partially affected. The original patient suffered from attacks of unconsciousness almost certainly epileptic in origin. Salmon & Turner (1965) also reported a case of a boy aged 16, who was shown to suffer from McArdle's syndrome but whose presenting feature was a grand mal convulsion, and the relation of the attacks of

unconsciousness to the biochemical defect will be discussed later.

These patients will be reported more fully elsewhere together with a detailed account of the histological, histochemical and electron microscopic features of the muscle biopsies.

Case reports

Case 1

R.G., age 21, was first seen by a physician at the age of 16 years, when he complained of muscular pain, stiffness and weakness, produced by exertion and relieved by rest. A myopathy was suspected, but physical examination was negative, and a muscle biopsy was reported as normal. No further investigations were performed at that time, and he was not seen again until June 1963, when he was referred to a surgeon because of episodes of alleged haematuria, one of which was preceded by an attack of unconsciousness. Thorough investigation of the urinary tract revealed no abnormality. Further attacks followed by the passage of red urine occurred infrequently over the next few months. He was again referred to a physician and admitted to hospital for further investigation in January 1965.

He still complained of muscular weakness, stiffness and pain after exertion, relieved by resting, and also stated that he had had a total of six attacks, when, after a short bout of severe exertion, he suddenly lost consciousness. Recovery was associated with the complaint of generalized muscle pains and he also noticed the urine was red for the next few hours. One of these attacks of unconsciousness was witnessed, and the description was typical of a grand mal convulsion.

On examination, he was a healthy looking man, with no evidence of muscle wasting or weakness. Examination of the chest, cardiovascular system, abdomen and nervous system revealed no abnormality.

Investigations

Haematology, plasma urea and electrolytes, plasma proteins, urinalysis: no abnormality.

ECG: normal tracing.

Lumbar puncture: revealed crystal clear fluid at a pressure of 110 mm CSF. No excess of white cells.

CSF protein, 18 mg/100 ml. CSF sugar, 80 mg/100 ml. CSF WR negative.

EEG: 'Occasional paroxysmal bursts of abnormality consisting of sharp waves or spikes and slow waves suggesting the possibility of epilepsy' (Dr R. S. Bluglass).

EMG: 'Within normal limits both at rest and after pain had been produced in the quadriceps

femoris muscle by severe exertion' (Dr J. A. R. Lenman).

Glucose tolerance test, glucagon stimulation test, intravenous tolbutamide test: no abnormality.

Blood lactate before and after ischaemic exercise (McArdle, 1951)

	Before exercise	After exercise
Patient	14.5 mg/100 ml	17 mg/100 ml
Control	9.5 mg/100 ml	37.5 mg/100 ml

Muscle biopsy: Histology showed vacuolation of the muscle fibres, many vacuoles containing material giving a positive reaction with stains specific for glycogen (Dr A. Todd).

These features are recognized to be characteristic of McArdle's syndrome (Pearce, 1965).

In view of this finding, the histology of the previous muscle biopsy taken in 1961 was reviewed. Several vacuoles were seen which at that time were thought to be due to fixation artefacts, but in the light of the more recent findings, are now considered to be characteristic of McArdle's syndrome (Dr A. Todd).

TABLE 1
Summary of results of affected siblings

	Age (years)	Blood lactate (mg/100 ml)		Muscle biopsy	
		Before ischaemic exercise	After ischaemic exercise	Glycogen content	Phosphorylase activity
R.G. (original patient)	21	14.5	17.0	3.92	None detected
H.U. (sister)	39	6.5	6.5	4.05	None detected
E.G. (brother)	27	7.0	8.5	1.16	Diminished
C.G. (brother)	38	7.5	8.0	—	—

Glycogen content expressed as mg/100 mg muscle (wet weight). Normal value approximately 1.0 mg.

Histochemical studies (Table 1) revealed an excess of glycogen and no significant phosphorylase activity was detected (Dr G. W. Pearce).

Progress

When the diagnosis was established, the patient was treated with fructose 40 g to be taken thrice-daily or before any severe exertion as suggested by Mellick *et al.* (1961).

However, as this produced no significant improvement and caused considerable weight gain, it was discontinued after a few months.

Since his discharge from hospital, he has had two further attacks of unconsciousness followed on recovery by generalized muscle pain and the passage of red urine. Spectroscopy of the urine on these occasions has confirmed the presence of

myoglobin. One attack was precipitated by exertion, but the other occurred while at rest. When he was examined after the latter, some small tongue lacerations were noted. Otherwise, his general health has been maintained, and the only difficulty encountered has been finding some suitable light employment.

Case 2

C.G., age 38 years, had complained of muscular pain and stiffness on exertion, relieved by rest, since childhood. These symptoms were particularly troublesome during his period of National Service, and as repeated medical examinations were always negative, he was frequently accused of being a malingerer. His symptoms seem to trouble him little at present, and he works as a charge hand in a Midlands steelworks. He has never had attacks of unconsciousness or passed red urine, and he had no other complaints.

Physical examination revealed no abnormality, in particular there was no muscle weakness or wasting.

Investigations

Haematology, plasma urea and electrolytes, blood sugar, plasma proteins, chest film, ECG and urinalysis: no abnormality.

Blood lactate before and after ischaemic exercise (McArdle, 1951)

	Before exercise	After exercise
Patient	7.5 mg/100 ml	8 mg/100 ml
Control	9.0 mg/100 ml	15 mg/100 ml

As this patient lives in the Midlands, muscle biopsy was not possible but the clinical features and blood lactate results are typical of McArdle's syndrome.

Case 3

E.G., age 27 years, also complained of muscular pain and stiffness after exertion and relieved by rest, since childhood, but his symptoms were not particularly severe, and while doing his National Service with the Royal Artillery, he had no real difficulty with route marching and was a keen boxer.

At present he still experiences cramps in the calves while walking up hills although this symptom is rarely severe enough to make him stop walking. He has noticed no pain after use of other muscle groups. Also, he has never had attacks of loss of consciousness or passed dark urine.

Physical examination revealed no abnormality, again there being no evidence of muscular weakness or wasting.

Investigations

Haematology, plasma urea and electrolytes,

blood sugar, plasma proteins, chest film, ECG and urinalysis: no abnormality.

Blood lactate before and after ischaemic exercise (McArdle, 1951)

	Before exercise	After exercise
Patient	7 mg/100 ml	8.5 mg/100 ml
Control	7 mg/100 ml	15.5 mg/100 ml

Muscle biopsy: the routine histological preparation suggested a slight myopathy (Dr G. W. Pearce).

Histochemical studies (Table 1) revealed a slight excess of glycogen and diminished phosphorylase activity.

Case 4

H.U., age 39 years, was well during her early childhood and while at school, but from the age of 13 years began to complain of shortness of breath and tiredness on exertion. A diagnosis of mitral stenosis was made at this time. The complaint of breathlessness on exertion became steadily more marked, and at the age of 30 she was admitted to Dundee Royal Infirmary, and a mitral valvotomy was performed (Professor D. Douglas). The operation was technically very successful, a good valve split being obtained, but she herself felt no real benefit. She was subsequently admitted to hospital for investigation of this failure to improve, but no definite conclusions were reached. When admitted to hospital in February 1966 for further investigation, she complained of still feeling generally unwell with tiredness and shortness of breath precipitated by exertion. She admitted to no attacks of unconsciousness or episodes of passing dark urine. She noticed that the left forearm muscles became painful and hard after exertion, but similar symptoms were not produced after use of other muscle groups.

On examination there was a malar flush but she was not cyanosed or breathless at rest. Examination of the cardiovascular system revealed signs of mitral stenosis. No significant abnormality was found on examination of the chest, abdomen and nervous system, and there was again no evidence of muscular weakness or wasting.

Investigations

Haemoglobin 12.1 g/100 ml. White cell count, 11,300/mm³ (neutrophils at the upper limit of normal). ESR (Wintrobe), 28 mm/hr. Random blood sugar, 90 mg/100 ml. Plasma urea and electrolytes: normal figures. Serum albumin, 3.5 g/100 ml. Serum globulin, 4.3 g/100 ml.

ECG: Normal tracing.

Chest X-ray: showed the transverse diameter of the heart and the vascular pattern of the lung fields to be within normal limits. Oblique and lateral

views with barium showed slight enlargement of the left atrium but no other specific chamber enlargement was shown, and no definite valvular calcification was seen.

Blood lactate before and after ischaemic exercise (McArdle, 1951)

	Before exercise	After exercise
Patient	6.5 mg/100 ml	6.5 mg/100 ml
Control	6.5 mg/100 ml	17.5 mg/100 ml

Muscle biopsy: Histology showed the characteristic features of McArdle's syndrome and histochemical studies (Table 1) revealed a considerable excess of glycogen and an absence of phosphorylase (Dr G. W. Pearce).

Parents and remaining siblings

The parents and remaining two siblings of the original patient (R.G.) were also investigated. None had any muscle symptoms, physical examination was negative, and all had a normal elevation of blood lactate after ischaemic exercise. The blood lactate results are summarized in Table 2.

TABLE 2

Summary of results of parents and unaffected siblings

	Age (years)	Blood lactate (mg/100 ml)	
		Before ischaemic exercise	After ischaemic exercise
Joseph G. (Father)	61	5.3	20.3
Janet G. (mother)	59	5.0	13.5
Mary S. (sister)	40	5.0	12.0
Joseph G. (brother)	30	8.5	17.5

Discussion

Four siblings suffering from McArdle's syndrome are described, although Case 3 (E.G.) appears to be only partially affected. His symptoms are certainly less severe than Cases 1 and 2, and this minor clinical involvement is reminiscent of the second case described by Engel *et al.* (1963), in which muscle biopsy studies also showed diminished rather than absent phosphorylase activity, and a glycogen content of 1.1% (wet weight). The two cases differ, however, in that the symptoms of the latter did not commence until the age of 49, and there was a normal elevation of blood lactate after exercise to four times the resting level.

That the clinical condition is not always a reliable guide in assessing whether there is a partial or total deficiency of phosphorylase is demonstrated by Case 4. Although it might be imagined that

because of the rheumatic heart disease she could not exert herself sufficiently to develop muscular symptoms, the cardiac lesion is not severe, and she works full-time in an electrical appliance factory in addition to performing the usual household duties. As already stated, muscle biopsy studies revealed no phosphorylase activity, and a grossly elevated glycogen content. Despite this she admitted to virtually no specific muscular symptoms, her complaints being rather of tiredness and general malaise.

Evidence that the site of glycogen deposition rather than the total amount present in the muscle is more important in the production of symptoms, has been obtained by Schotland *et al.* (1966). Their electron microscopic studies on muscle from a patient with McArdle's syndrome showed that glycogen was deposited primarily in the intermyofibrillar space of the I band, under the sarcolemma, between the thin filaments within the I band, and occasionally between the filaments in the A band. Similar studies on the cases forming the basis of this report will be published later.

The suggestion from previous family investigations that the biochemical defect is inherited by a single recessive autosomal gene has been confirmed by this study. Parental consanguinity is often a contributing factor, but the parents in this study stated that, to the best of their knowledge, their families were unrelated.

One of the main features of Case 1 was the attacks of loss of consciousness resembling grand mal convulsions, usually precipitated by severe exertion and followed both by generalized muscle pains and transient myoglobinuria. There was no family history of epileptic disorders, but, as already stated, the EEG showed features suggesting this possibility. A similar association of an attack with McArdle's syndrome was reported by Salmon & Turner (1965). They described a boy aged 16 who had a grand mal convulsion 15 min after starting a game of basket-ball, and shortly afterwards passed dark urine, the pigment being identified as myoglobin. He admitted to easy fatigability in the past, but complained of no other symptoms. A sister had had convulsions associated with febrile illnesses during infancy, otherwise there was no family history of seizures. Physical examination revealed no abnormality except for minimal weakness of the shoulder and pelvic girdle muscles, and also of the extensors of the toes and wrists. The blood lactate failed to rise after ischaemic exercise, and histochemical studies of a muscle biopsy revealed no phosphorylase activity, and a normal glycogen content. An EEG on the day of admission showed a paroxysmal slowing of activity, particularly after hyperventilation, and a repeat

examination 7 weeks later showed the abnormality was persistent.

Salmon & Turner considered the following three possible explanations of the association of the seizure with McArdle's syndrome and their remarks apply equally to Case 1 of the present report:

(1) It is conceivable that the association is merely coincidental as idiopathic epilepsy is such a common condition. The seizure might thus have been precipitated by fatigue and the succeeding muscle symptoms and myoglobinuria, the result of the convulsive movements.

(2) The convulsive threshold might be lowered by the effects of circulating muscle breakdown products.

(3) As a result of the enzyme deficiency, glycogen cannot be broken down. Energy for muscular contraction during severe exertion might therefore be obtained by the excessive utilization of glucose which can enter the glycogenolytic pathway beyond the stage where phosphorylase is required. Although hepatic glycogenolysis is unaffected, this might result in hypoglycaemia which could precipitate a convulsion.

The second explanation would seem unlikely as there are no reports of seizures occurring in association with episodic muscle breakdown from other causes similarly resulting in the liberation of myoglobin and other substances. Coincidental idiopathic epilepsy is impossible to exclude, and the recorded EEG abnormalities might be due to an underlying convulsive disorder. However, the third explanation, suggesting an hypoglycaemic basis for the convulsions, is attractive, and the EEG abnormalities could equally well be a reflection of brain damage as a result.

The observation that only some, rather than all, patients with myophosphorylase deficiency experience attacks of myoglobinuria, remains to be explained. Rowland *et al.* (1963) presumed it might be related to an inability to maintain adequate levels of adenosine triphosphate (ATP) to preserve the integrity of the sarcolemmal membrane. However, biochemical studies on muscle biopsies from two patients known to suffer from McArdle's syndrome, both while resting and after the induction of a contracture, showed no significant change in ATP concentration (Rowland, Araki & Carmel, 1965).

As previously mentioned, Schmid & Hammaker (1961) divided the clinical course of patients suffering from myophosphorylase deficiency into three phases—easy fatigability during childhood followed by cramping muscular pains after exertion (with or without myoglobinuria) during early adult life and a final myopathic phase from the fourth

decade onwards. Many of the patients reported with this syndrome have not been observed long enough to confirm this description of the natural history. However, the siblings forming the basis of the present study do not support these conclusions. As Case 3 is only partially affected it can hardly be expected that the typical course would be followed, but Cases 2 and 4, aged 38 and 39 respectively, have shown no variation in their symptoms over the years, and there has certainly been no deterioration in their condition. They may yet progress to a myopathic phase, but this does not seem likely. Case 1, however, is the most severely affected, and the only member of the family to experience attacks of myoglobinuria. This may well represent Schmid & Hammaker's second phase, and the possibility of permanent muscle wasting and weakness in later years seems more probable.

It can be seen from this brief review that since McArdle's original description of the condition (McArdle, 1951), patients have been reported presenting in ways other than with muscular pain and stiffness on exertion. Also partially affected forms may occur, there being a reduction rather than a complete absence of myophosphorylase activity. Even when the presentation is typical, diagnosis is often delayed as physical signs are lacking, and the patients are frequently dismissed as neurotic or hysterical. The possibility of this biochemical defect must obviously be considered in patients complaining of vague pains in the limb muscles, particularly after exertion, for which no neurological, vascular or recognized cause can be found. The measurement of the blood lactate level before and after ischaemic exercise (McArdle, 1951) has proved to be an extremely useful screening test, and if this is suggestive, the diagnosis should be proved by muscle biopsy with a histochemical demonstration of a reduction or absence of phosphorylase activity. The latter is particularly important as a similar picture with a failure of the blood lactate to rise after ischaemic exercise may be produced by the absence of other enzymes involved in glycogen breakdown (Olinier, Schulman & Larner, 1961).

Treatment is at present unsatisfactory, and now that the biochemical defect has been clearly defined it is to be hoped that a method of its circumvention will be discovered in the not too distant future.

Summary

The features of McArdle's syndrome have been briefly reviewed, and four further cases reported, one being only partially affected. The variations in presentation and clinical course, and the possible

relation of the biochemical defect to epileptic seizures are discussed.

Acknowledgments

I would like to thank the many people who helped in this investigation, unfortunately too numerous to acknowledge individually. The patients were admitted under the care of Dr D. G. Adamson, and the muscle biopsy studies were performed by Dr G. W. Pearce.

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