

# Myophosphorylase Deficiency (McArdle's Disease): Report of a Family

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**SUMMARY:** *The clinical and biochemical findings are presented of two brothers suffering from McArdle's Disease (Myophosphorylase Deficiency). Tissue enzyme estimations and lactate levels were done in affected and non-affected members of the family. Affected members showed absence of phosphorylase enzyme by histochemical and quantitative estimation. No quantitative abnormalities were found in other enzyme systems of glycolytic pathways in the family investigated. Various other aspects of clinical features, biochemical abnormalities and inheritance are discussed.*

**RÉSUMÉ:** *Les faits cliniques et biochimiques chez 2 frères souffrant de la maladie de McArdle (déficience en myophosphorylase) sont présentés. Les analyses d'enzymes dans les tissus et les niveaux de lactate furent faits chez les membres atteints et non-atteints de la famille. Les membres atteints montraient une absence d'enzyme phosphorylase par dosage histochimique et quantitatif. Aucune anomalie quantitative fut trouvée dans les autres systèmes d'enzyme de type glycolitiques dans la famille investiguée. D'autres aspects cliniques, biochimiques et génétiques sont discutés.*

In 1951, McArdle described a 30 year old patient who had suffered from painful muscle cramps on exertion since childhood. Serum lactate and pyruvate levels failed to rise after ischemic exercise in this patient and it was postulated that the condition was due to a defect in glycogen metabolism. In 1959, histochemical studies of muscle showed that the myopathy was associated with the absence of the enzyme phosphorylase (Mommaerts et al., 1959; Schmid and Mahler, 1959). This was accompanied by an increased glycogen content and an absence of phosphorylase activity in the muscle.

Since that time, a number of families have been described with McArdle's disease (Dawson et al., 1968; Cochrane et al., 1973; Salter et al., 1967; Bale et al., 1967; Hockaday et al., 1964; Tobin and Coleman, 1965; Schmid and Hammaker, 1961). This report describes an additional family whose members include two brothers with phosphorylase deficiency.

The propositus K.W. was referred to the Department of Neurology at Wayne State University for evaluation of his complaint of severe muscle spasms during exercise. During his evaluation in hospital, arrangements were made for examination of members of his immediate family consisting of his father, mother, two brothers and a sister. After examination all family members received an ischemic lactate tolerance test and a muscle biopsy. Quantitative enzyme estimation was carried out on a fresh frozen specimen of muscle, using the method described by Fink et al. (1975).

## FAMILY HISTORY

The mother and father of the propositus were born in Alabama but had

moved to Detroit following marriage and had lived in Detroit for many years. The father, J.W., had been healthy all his life. He stated that one of his brothers was a chronic alcoholic who had died at the age of 59, and that he had 4 sisters who are living and healthy.

The mother, L.W., had 3 older siblings. One brother had committed suicide at age 50, another brother had died following traumatic injury, and one sister was alive but was stated to have "kidney problems". L.W. also has 4 younger siblings, 2 younger brothers and 2 sisters, described as healthy. There was no documented immediate or remote relationship between L.W. and J.W. They had 9 children, 5 boys and 4 girls. One boy died in an accident, and another boy died of "kidney problems". Five children, one boy and four girls, are healthy. The remaining 2 boys, K.W. and O.W., are described in this presentation. K.W. is the father of a healthy infant; O.W. is the father of 5 girls who are described as healthy.

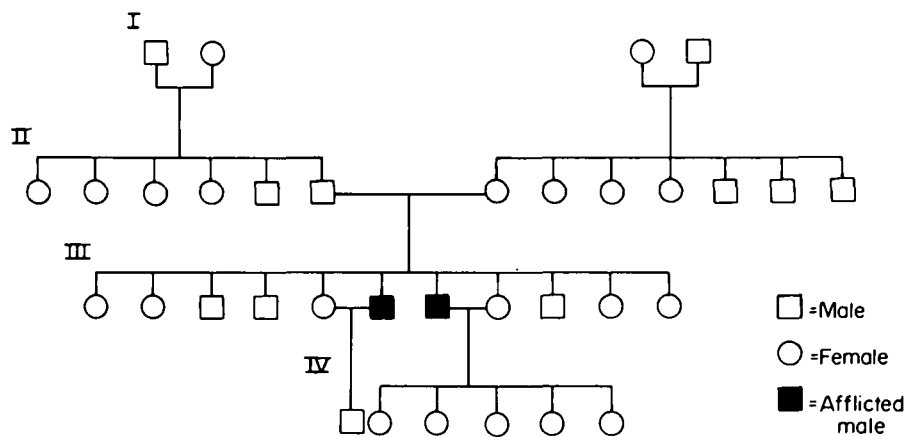
None of the family members gave a history of cramps, muscle stiffness or myoglobinuria on direct questioning except the family members, K.W. and O.W. (Family Pedigree Figure 1.)

## CASE I

K.W. was 21 years of age when first seen in the Department of Neurology, Wayne State University. His mother noticed painful swelling of his muscles when he was an infant. The patient was able to recall having severe spasms and painful swelling of his muscles since the age of 10, after playing and running. The swelling and tightness was confined to the proximal muscles and would prevent him from continuing exercise. Once swelling had developed in the proxi-

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FIGURE I FAMILY PEDIGREE

mal muscles, it would last from 24 hours to 7 days.

The patient recalled that he had passed dark colored urine on at least 4 occasions after strenuous exercise. On each occasion he had had painful spasms in his muscles.

K.W. stated that the pain in his muscles had never been extremely severe. He was never able to improve his exercise tolerance by repeated exercise. He was able to run approximately one block and climb three steps without any problems. He had never had difficulty chewing and had never had double vision.

**Physical Examination**

Physical examination showed a somewhat asthenic, nervous male with a pronounced stammer in speaking. A general physical examination was within normal limits with a blood pressure of 130/80 and a pulse of 80. The neurological examination was also normal.

**Neuropsychological Testing**

Wechsler Adult Intelligence Scale testing revealed a Verbal IQ of 84, Performance IQ of 75, and Full Scale IQ of 79, placing overall intellectual functioning at the upper end of the borderline retardation range. K.W. showed deficits in digital recall and visual sequencing, suggesting bilateral temporal lobe dysfunction. His reading achievement level was only 3.9 grades as determined on the Wide Range Achievement Test. Reitan-

Indiana Aphasia Screening Test revealed evidence of auditory-verbal receptive language difficulty. Copying of geometrical forms was questionably to mildly impaired. It was believed that the patient had a chronic, static cerebral dysfunction with diffuse cortical involvement maximal bitemporally, and had experienced an early learning disability of moderate severity.

**Diagnostic Procedures**

White blood cell count was 6,400 per cubic millimeter with a normal differential count. Hemoglobin 14.6 grams. Sedimentation rate 25 mm/100 ml. VDRL and FTA-ABS negative. RH factor negative. Serum

electrolytes were within normal limits. Routine urinalysis showed absence of protein, reducing substances and bile pigment. Urine was negative for myoglobin. Microscopic examination showed oxalate crystals without additional findings. Electroencephalogram was mildly abnormal with a 9-10 cycle/second alpha maximal posteriorly. The alpha activity was suppressed on the left side where there was a low voltage theta dysrhythmia with occasional 3 cycle/second delta activity extending into the temporal leads. This abnormality was aggravated by hyperventilation.

Electromyography and nerve conduction studies showed a nerve conduction velocity of 66 m/second on the right ulnar nerve and 50 m/second on the left peroneal nerve. Repeated stimulation of 5-10 stimuli/second did not produce a decremental response. Electromyographic examination of muscles bilaterally in both upper and lower extremities did not reveal any abnormalities. It was not possible to produce contracture on ischemic exercise for needle examination because of lack of cooperation by the patient.

Additional biochemical investigations were carried out in this case. The glucose tolerance test was normal. The adrenaline tolerance test and glucagon test showed normal rise in glucose. Serum enzymes before

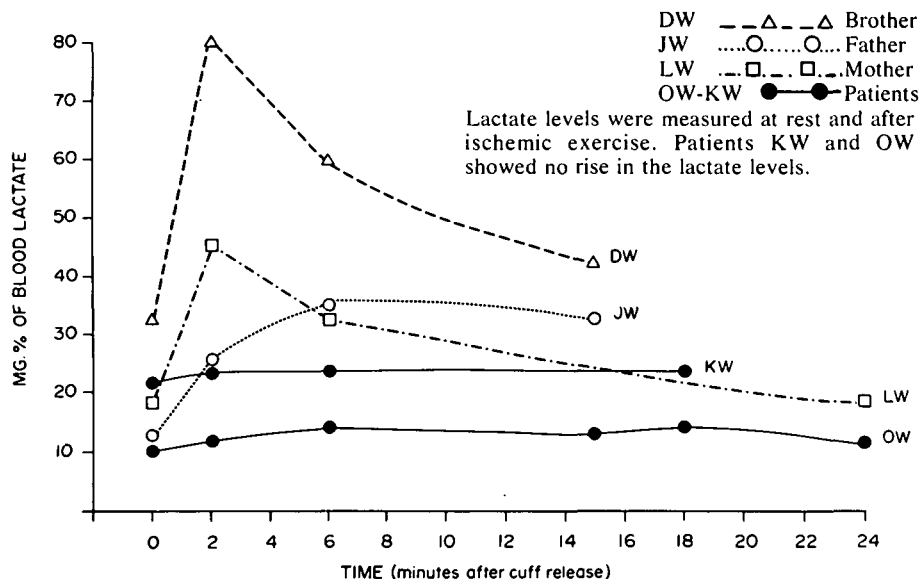


FIGURE II BLOOD LACTATE vs. TIME

and after exercise were measured (Table 1). Serum acid phosphatase activity was normal.

TABLE I

	SGOT	LDH	CPK
Before Exercise	79	145	537
After Exercise	84	152	642
Normal Upper Limit	55 iu	140 iu	50 iu

Serum enzyme levels in patient K. W. before and after exercise.

An ischemic lactate tolerance test was performed by inflating a blood pressure cuff above the systolic blood pressure and having the patient exercise by squeezing a bulb for approximately 90 seconds. Blood specimens were collected before exercise and at intervals after exercise and analyzed for lactate content. The patient developed severe, painful cramps in his hands during exercise and complained of symptoms for approximately 10 minutes after release of the cuff. The patient did not show any rise in lactate level as shown in Figure II.

### Muscle Biopsy

Muscle biopsy was obtained from the left quadriceps muscle and the specimen was prepared using a fresh frozen technique. A modified trichrome stain showed that there was no increase in internal nuclei. Muscle fiber diameter was normal and there was no variation in size. There were no subsarcolemmal blebs or other morphological changes in the specimen. ATPase at pH 9.4 showed good differentiation between Type I and Type II fibers. No fiber type preponderance was seen. PAS stain did not show any increase in the amount of glycogen, although content was elevated on quantitative analysis (see Table II). There was complete absence of muscle phosphorylase enzyme on histochemical staining. Quantitative enzyme data are presented in Table II.

### CASE II

O.W. is a 39 year old brother of K.W. He first developed symptoms of impaired muscle function when he was 5 years old, when he noticed that

he could not keep pace with other children. He had great difficulty walking uphill and any type of exertion produced fatigue. A few years later he noticed painful cramps in the muscles of the lower limbs and stiffness of his muscles following exertion. At age 15 he noticed that he was passing dark burgundy colored urine. Since that time, any strenuous exercise produced pain in the muscles and was occasionally associated with the passage of dark urine. The urine color would always become normal after resting for a few hours when the tenderness in the muscles would disappear.

At age 39 he had reached the stage where any minor exertion would produce symptoms. However, these symptoms were occurring on a background of persistent weakness and his exercise tolerance was markedly decreased.

The patient was a well-nourished, well-developed male. Blood pressure 110/80. The only abnormality detected was generalized weakness in all muscle groups. There was no

TABLE II

	K.W. (patient)	O.W. (brother)	D.W. (brother)	L.W. (mother)	J.W. (father)
Glycogen Content gm/100 gm tissue	1.46	1.42	0.74	0.58	0.63
Alpha-1, 6-Glucosidase (Debrancher) micromoles/min/mgm protein	$9.4 \times 10^{-5}$	$7.22 \times 10^{-5}$	$4.38 \times 10^{-5}$	$5.9 \times 10^{-5}$	$5.7 \times 10^{-5}$
Phosphofructokinase micromoles/min/mgm protein	0.076	0.125	0.090	0.13	0.054
Phosphohexoseisomerase micromoles/min/mgm protein	1.02	3.45	1.77	1.06	0.76
Phosphoglucomutase micromoles/min/gram protein	13	7.74	24	0.020	23
Phosphorylase b kinase	good activity	good activity	good activity	good activity	good activity
Phosphorylase (with AMP) micromoles/min/gram protein	not detectable	not detectable	0.83	0.43	0.45
Alpha-1, 4-Glucosidase (Acid Maltase) Micromoles maltose hydrolyzed min/gram tissue	0.082	1.53	0.052	0.071	0.096
Pyruvic Kinase micromoles/min/gram protein	1.03		1.23	0.47	0.78

Quantitative estimation of the enzymes involved in glycolytic pathways.

muscle wasting. The remainder of the examination was unremarkable.

#### *Diagnostic Procedures*

The ischemic lactate tolerance test was performed and was found to be abnormal (Figure II).

#### *Muscle Biopsy*

Muscle biopsy was obtained from the left quadriceps muscle and showed complete absence of phosphorylase activity on quantitative estimation of muscle enzymes. (The results of other studies are shown in Table II).

#### *Quantitative Estimation of Muscle Enzymes in Family Members*

Muscle biopsies were obtained from 3 members of the family, from K.W. and from his brother O.W. The specimens were analyzed by the techniques previously described. (Fink et al, 1975). The results of analysis for enzyme content are shown in Table II.

### DISCUSSION

A perusal of the literature shows that 48 patients with myophosphorylase deficiency have been described to date. There are 8 female and 40 male subjects. Family studies indicate consanguinity in some cases (Cochrane et al, 1973); (Rowland et al, 1963). A tendency to muscle cramps after exercise has been noted in some of the unaffected members of the families described, which has been suggested to indicate a carrier trait (Dawson et al, 1968). In addition, it has been shown (Bank et al, 1972) that in heterozygous individuals the phosphorylase enzyme activity of muscle is reduced to about half normal using an immunological technique (Schmid and Mahler, 1959). These findings indicate an autosomal recessive mode of inheritance in myophosphorylase deficiency.

The male preponderance which is so apparent in the total group of patients described suggest heterogeneity (Howell et al, 1972) but could also be explained on the basis of sample bias or differential expression of the defect in males and females.

Myophosphorylase deficiency

presents with muscle stiffness and pain after exercise. These symptoms are often associated with myoglobinuria and are always associated with lack of rise of lactate on ischemic exercise testing. A number of other conditions can mimic this syndrome, including phosphofructokinase deficiency (Tauri et al, 1965), phosphohexoisomerase deficiency (Satoyoshi and Yowa, 1967), and amylo-1, 6-glucosidase deficiency (Brunberg et al, 1971). These conditions were eliminated in the study of the 2 patients described in this article by quantitative estimation of muscle enzymes which showed the single enzymatic abnormality of absence of myophosphorylase activity (Table II). There are, however, patients reported in which there is a partial deficiency of myophosphorylase (Fattah et al, 1970). In all cases the normal blood glucose response to subcutaneous injection of adrenalin and intravenous injection of glucagon indicate that the hepatic phosphorylase activity is normal. These enzymes are known to be under different genetic control. The high muscle glycogen content shown in the 2 affected individuals in this series and the specific enzyme deficits are compatible with results of studies in other reported cases (Rowland et al, 1966).

The stiffness, cramping and weakness on exertion seen in patients with myophosphorylase deficiency is due to impaired glycogenolysis. This defect cannot be compensated by glucose input via the hexokinase pathway. An increase in phosphoenolpyruvate carboxykinase activity has been reported in patients with myophosphorylase deficiency and it is thought that this increase in enzyme is probably a compensatory phenomenon (Nolte and Schollmeyer, 1973). One patient described in this presentation was found to have elevated fructose 1-6 phosphate aldolase and phosphorylase b kinase activity which may also be a response to phosphorylase deficiency.

It has been suggested that there are three stages in the course of this disease (Schmid and Mahler, 1959). The first stage consists of easy fatigability appearing in childhood.

The second stage is associated with cramps and myoglobinuria and is often seen in patients within the ages of 20 and 40 years. The third stage is usually seen after the age of 40 years when there is a cessation of myoglobinuria but increased muscle weakness on exertion. This weakness may be so profound that it appears to be present at all times as described in the elder subject, O.W., in this family. An improvement in performance, described as the second-wind phenomenon, has been described in some cases but did not occur in the patients in this series (Pernow and Jennings, 1967; Pearson et al, 1961).

Both patients reported episodes of myoglobinuria after strenuous exercise. This occurs in about half of the patients described in the literature before the age of 18 years and has been associated with renal failure (Fattah et al, 1970; Grunfeld et al, 1972; Bank et al, 1972). It is thought that the elevated muscle enzymes measured after exercise and the myoglobinuria may be the result of cell membrane injury (Salmon and Turner, 1965).

Electromyography is a helpful diagnostic procedure in this condition (Dyken et al, 1967). The contractures produced after exertion are electrically silent. The diminished number of motor unit potentials and their increased size which has also been reported has raised the possibility of a neuropathic process in myophosphorylase deficiency (Upton et al, 1973). Supramaximal repetitive stimulation at 18/second or higher may show detrimental responses in the evoked potentials in some cases.

The patients in this report did not reveal any abnormalities on electromyography. Muscle contractures could not be produced because of lack of cooperation by the patients. Nerve conduction velocities were within normal limits. Electroencephalographic abnormalities have been noted in some patients and there are said to be some associations between myophosphorylase deficiency and seizures (Salmon and Turner, 1965). Patients reported here did not have seizures but were found to have abnormal electroencephalograms

and abnormal neuropsychological test results. It is possible that there is a common etiological basis for the electroencephalographic abnormalities and the muscle membrane abnormalities in this condition.

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