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McARDLE'S DISEASE*
A Case Report

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McArdle's disease is a hereditary, metabolic myopathy characterized by weakness and muscle cramps after exercise, appearing mostly in the second or third decade of life. Due to myophosphorylase deficiency in skeletal muscle, glycogen cannot be used and deposited in the sarcolemmal spaces, leading to lack of endurance to sustained work. The ischemic exercise test is a screening procedure for muscle energy disorders, and the diagnosis is confirmed by reduced enzyme activity in muscle biopsy.

In this report, a family with one child having enzyme assay-proven McArdle's disease and two other children demonstrating a positive ischemic exercise test is presented.
Key words: McArdle's disease, ischemic exercise test.

McArdle's disease (glycogenosis type V) is an autosomal-recessive disorder characterized by exercise-induced weakness and muscle cramps, and sometimes by myoglobinuria as well. Due to deficiency of the enzyme myophosphorylase, energy production by glycolysis is reduced in skeletal muscle, and intolerance after moderate or heavy work ensues. Raised serum levels of creatine phosphokinase (CK) and a positive ischemic exercise test are rapid screening methods for this metabolic myopathy.

The disorder was first described by McArdle in 1951[1] in a 30-year-old man with a life-long intolerance to exercise. Although several cases with late-onset deficiency of myophosphorylase have been published, patients typically experience symptoms during their teenage years[2-4].

In this report, we describe a 17-year-old boy with McArdle's disease and his family members with positive clinical and laboratory features.

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Case Report

A 17-year-old boy was referred to our clinic for weakness and lack of endurance after exercise since childhood. He suffered from muscle pain, cramps and stiffness after moderate to heavy work. He had never experienced darkening of his urine after exercise. His past history was unremarkable. His parents had second-degree consanguinity and were asymptomatic. The propositus was the second child of the family and had three sisters and one brother. One sister and brother had similar symptoms, though milder than his. This sister, who was 15 years old, had experienced weakness since five years of age, but only after a long-distance walk or heavy exercise. His three-year-old brother's symptoms had appeared recently; he complained of tiring easily.

On examination, these three children's physical and electromyographic findings, including neurological examination, did not reveal any abnormality. The patient's serum creatine phosphokinase (CK) level was extremely high (27,960 U/L). During the ischemic exercise test he developed cramps and could not complete the exercise; his serum lactate concentration increased by only 1 mg/dl, while it would normally be expected to increase by more than 20 mg/dl. The serum CK levels and the results of the forearm exercise test of the patient and his family members are shown in Table I. The exercise test was performed as follows: after a resting period of 30 minutes, venous blood samples were collected for baseline ammonia (NH_3) and lactic acid levels. Following five minutes of exercise with rapid flexion and extension of the forearm, blood samples were obtained again for post-exercise NH_3 and lactic acid levels.

Table I: Laboratory Findings and Exercise Test Results of Patient and Family Members

			NH_3 (mg/dL)		Lactic acid (mg/dL)	
	Age (years)	CK* (U/L)	Before Test	After Test	Before Test	After Test
Propositus	17	27,960	82	155	20.6	21.6
Mother	38	111	98.4	120	9.6	28.3
Father	38	90	63.8	104.6	20.8	46.9
Sister	19	156	109	187	8	13.3
Sister	15	1,262	160	218	8.1	8.9
Sister	9	98	137	174	8.7	8.9
Brother	3	243	73.8	150.7	12.1	8.8

* Creatine kinase (range: 5-130).

The patient had severe pain and contracture after a very brief period of exercise and could not complete the test. His mother had slight weakness during the exercise but completed the test. No other family members reported pain or cramping during the test.

Muscle biopsy was performed in the propositus. The muscle glycogen content was increased (patient 4.4 g/100 g muscle, control $\bar{X}$: 1.1, range: 0.7-2). Muscle phosphorylase activity was diminished (patient 1.4 E/g muscle, control $\bar{X}$: 89.3, range: 69.0-121.5).

Discussion

McArdle's disease is a glycogen storage disease. These diseases result from deficiency or absence of specific enzyme activity in glycogen's metabolic pathway. Patients with McArdle's syndrome have deficiency of muscle phosphorylase. McArdle's disease has a wide clinical spectrum varying from asymptomatic cases to recurrent myoglobinuria with attacks of rhabdomyolysis and unremitting muscle pain with exercise. There have also been a few reports of acute renal failure secondary to intense myoglobinuria[5,6]. The majority of patients present with symptoms during the second or third decade of life. However, the past history usually reveals muscle weakness and lack of endurance since childhood. The severity of symptoms varies with the percentage of enzyme activity. The propositus complained of weakness, exercise-induced cramps and pain since childhood. He had no pigmenturia.

Brief exercise of great intensity or less intense but sustained activity produces symptoms in patients. Because muscle depends almost exclusively on endogenous glycogen for intense exercise, pain and cramping are experienced. Many patients experience a second wind, that is, when they rest briefly after the cramps first appear, they can continue without further symptoms. For moderate exercises with long duration, the fatty acids seem to be the most important source of energy. This may explain the tolerance in patients to moderate exercise[7]. In patients with suspected muscle energy disorders, the ischemic exercise test is the first step and should be performed when cramps develop on exercise. In most normal individuals, serum lactate concentrations increase by more than 20 mg/dl and serum ammonia concentrations increase by more than 100 µg/dl over baseline. Failure to raise the serum lactate level more than 5 mg/dl along with a normal rise in ammonia concentration is diagnostic of a glycogen storage disease[8]. The abnormal increase in the concentration of serum creatine kinase and the exercise test reslts in our patient led us to perform a muscle biopsy. The findings of increased muscle glycogen content and low phophorylase activity confirmed the diagnosis of McArdle's disease. Electromyographic (EMG) findings demonstrate myopathic units in late-onset forms of McArdle's disease; however, this feature has been noted rarely in the early-onset disorder. Our patient's EMG findings were also normal.

In McArdle's disease, myophosphorylase is only deficient in skeletal muscle; the activity in liver and smooth muscle is normal. The glycogen concentration is increased by up to four percent, and excess glycogen is deposited in

subsarcolemmal and intermyofibrillar spaces with disruption of the myofibrillar structure at the level of the I band[9]. Due to insufficient ATP production and accelerating recycling of muscle purine nucleotides, blood ammonia, inosine, hypoxanthine and uric acid level increase[10, 11]. Though infrequent, muscle phosphofructokinase deficiency, muscle phosphoglycerate kinase deficiency, muscle phosphoglycerate mutase deficiency and lactate dehydrogenase deficiency produce symptoms and glycogen deposition similar to that in McArdle's disease; thus, a definitive diagnosis can only be reached by enzyme assays[8].

Being mildly symptomatic, the three-year-old brother and 15-year-old sister of the propositus had serum CK and lactate levels consistent with the disease. The patient's nine-year-old sister had a normal CK concentration but her lactate levels also did not increase normally during the test; she needs further evaluation for the enzyme activity. The mother, feeling weakness during the test, had normal results. The father was completely asymptomatic. These findings are consistent with the autosomal-recessive transmission of the disease. Although biochemical studies have failed to show any differences in the severity of the enzyme defect or in the concentration of muscle glycogen, some rare clinical variants of the disease have been described[12, 13]. There have been reports of late-onset disease with no symptoms until the age of 74 years, and of a fatal presentation before four months of age[3, 4, 14, 15]. Though the enzyme level of the propositus was extremely low, he was able to maintain his daily activites; the symptoms appeared only after heavy exercise.

For carrier studies, evaluation of enzyme activity in muscle biopsy or phosphorus magnetic resonance imaging (^{31}P MRI) is recommended. ^{31}P MRI is a noninvasive diagnostic procedure demonstrating pH, ATP and reduction in phosphocreatinine concentration in response to both aerobic and ischemic exercise[17, 18]. The gene for muscle phosphorylase has been cloned and mapped to chromosome 11q 13-q ter[19]. The most common mutation is the C to T transition at codon 49 in exon 1 of the gene, changing an encoded arginine to a stop codon[7]. Genetic counseling in this disorder is possible by chromosomal analysis and MRI.

McArdle's disease is a relatively benign metabolic disorder. There is no need for specific therapy, as avoidance of vigorous exercise prevents the symptoms. A high-protein diet was found to increase exercise tolerance[19]. Oral intake of glucose or fructose can also augment tolerance to heavy work.

In conclusion, patients having weakness, pain or cramps after exercise should be evaluated for muscle energy disorders. A positive ischemic exercise test along with increased CK levels help to establish the defect in carbonhydrate utilization and indicates the need for biochemical analysis of muscle biopsy for definitive diagnosis.

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