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Clinical Study

Clinical and laboratory features of patients with myophosphorylase deficiency (McArdle disease)

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ABSTRACT

Mutations of *PYGM*, the gene encoding human myophosphorylase, produce a metabolic myopathy characterised by exercise intolerance and, in some patients, myoglobinuria. To illustrate the clinical and laboratory features of myophosphorylase deficiency, we describe 10 patients diagnosed in Auckland, New Zealand, between 1989 and 2009. We review the clinical, biochemical, and histologic features and the results of mutation analysis. All patients reported exercise intolerance since childhood or the teenage years, starting within minutes of moderate or intense exertion. The "second wind" phenomenon, or myoglobinuria, were each reported in about half the patients. The serum creatine kinase concentration was elevated in all patients where this had been measured. Muscle biopsies revealed subsarcolemmal vacuolation and histochemical absence of myophosphorylase. Analysis of *PYGM* showed mutations in all alleles, most commonly Arg49Ter or Gly204Ser. One patient harbored a novel mutation, Pro488Arg, predicted to seriously disrupt the tertiary structure of the enzyme. Myophosphorylase deficiency produces a fairly uniform set of symptoms, and consistent elevation of the serum creatine kinase concentration. The diagnosis can be confirmed in most patients by mutation analysis using a blood sample.

1. Introduction

In 1951, McArdle described a 30-year-old man who developed pain and stiffness after exercise. He noted that the cramps were electrically silent, and that his venous lactate level failed to increase after ischaemic activity. He astutely concluded that the patient had a metabolic defect that prevented the breakdown of muscle glycogen.[1] In 1959, three groups independently described deficiency of the enzyme myophosphorylase in patients with this syndrome.[2]

Glycogen phosphorylase (EC 2.4.1.1) removes 1,4-glycosyl residues from the glycogen molecule, liberating glucose-1-phosphate, which can enter the glycolytic pathway. Deficiency of myophosphorylase, the muscle-specific form of glycogen phosphorylase, is due to mutations of *PYGM*, the gene which encodes the enzyme.[3] Myophosphorylase deficiency is also known as McArdle disease and glycogenosis type V. Other organs have different phosphorylase isozymes and are not affected in myophosphorylase deficiency.[4]

Exercise intolerance is the cardinal symptom in myophosphorylase deficiency. Patients experience a variable combination of myalgia, early fatigue, stiffness and weakness of exercised muscles, often with disproportionate dyspnoea and tachycardia. This may be superseded within minutes in some patients by the so-called "second wind" phenomenon, consisting of a decrease in perceived exertion due to exercise-induced enhancement of muscle glycolysis. Rhabdomyolysis, a dramatic syndrome characterised by prolonged myalgia, muscle swelling, markedly elevated creatine kinase (CK) levels, and myoglobinuria (often described by patients as cola-colored urine), occurs in some patients.[5]

To demonstrate the typical features of myophosphorylase deficiency and to review our experience with molecular analysis of *PYGM*, we describe 10 patients diagnosed in Auckland between 1989 and 2009.

2. Methods

2.1. Patients

Patients were identified from the personal files of the authors and from a search of laboratory records at Auckland City Hospital. These patients were diagnosed with myophosphorylase deficiency in Auckland between 1989 and 2009. We reviewed the clinical notes, laboratory results and muscle biopsies (where applicable) on each patient. The study was approved by the Northern Regional Ethics Committee.

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2.2. Muscle biopsies

Muscle biopsies were obtained under local anaesthesia from biceps (five patients), tibialis anterior (two patients) and from an unknown muscle (one patient). Patients 9 and 10 did not undergo muscle biopsy. Cryostat sections from flash-frozen muscle were stained or reacted for haematoxylin and eosin, modified Gomori trichrome, NADH-tetrazolium reductase, ATPase (after preincubation at pH 4.3, 4.6, and 9.4), periodic acid-Schiff (PAS), acid phosphatase, oil red O, and myophosphorylase using standard methods. Myophosphorylase histochemistry was always performed concurrently on a normal control section.

2.3. DNA analysis

In all but patients 9 and 10, DNA analysis was performed after myophosphorylase deficiency had been diagnosed already from the clinical features and muscle biopsy. Genomic DNA was extracted from whole blood (patients 3, 9 and 10) or frozen muscle by a guanidine thiocyanate method[6] and all 20 exons of the *PYGM* gene, including the intron–exon boundaries, were amplified using the polymerase chain reaction (PCR) as previously described.[7] All PCR products were sequenced in both directions on an 3130*xl*Genetic analyzer using a BigDye® Terminator v3.1 Cycle Sequencing kit in accordance with the manufacturer's instructions (Applied Biosystems, Foster City, CA, USA). Sequences were compared to the Genbank reference NC_000011.8.

3. Results

3.1. Clinical features

The clinical and laboratory features of the patients are summarised in Table 1. All patients reported exercise intolerance, with onset of symptoms in childhood except for one. Different patients volunteered (in descending order of frequency) "pain", "tightness", "stiffness", "seizing up", "burning", "aching" or "weakness" in exercised muscles, generally triggered by several minutes of moderate or intense exercise. The amount of exercise required to precipitate the symptoms was fairly uniform: jogging (usually several hundred meters), sprinting (30–100 m), ascending stairs or a slope, or vigorous activity during sport (e.g. netball) were cited precipitants. The symptoms usually forced the patients to interrupt the activity. Milder exercise, such as sustained walking on level ground, was usually well tolerated. The second wind phenomenon was reported by six of the nine patients where this question was asked. Five of the patients reported discomfort in the jaw muscle with forceful mastication. One or more episodes of myoglobinuria had occurred in five patients. Limb weakness, usually mild, was found in three patients.

3.1.1. Illustrative patients

3.1.1.1. Patient 1. This 24-year-old man gave a history of exercise intolerance for as long as he could remember. He would develop a painful tight discomfort in his legs when he ran for more than 2 minutes or climbed 5 flights of stairs. These symptoms faded over several minutes with rest. At school he was able to sprint two but not three runs when playing cricket. There was no second wind phenomenon. Walking on level ground did not produce symptoms. At age 25 he was admitted to hospital with chest pain. His CK concentration was 9160 U/L, falling to 1218 U/L 2 days later. Investigations excluded cardiac disease. He had never had myoglobinuria. One of his two brothers had similar exertional muscle symptoms. Examination showed mild bilateral weakness of shoulder abduction. Random CK was 1757 U/L (60–220 U/L).

3.1.1.2. Patient 2. This 36-year-old woman said that her muscles had always felt "unfit". Since her teens, all forms of exercise had been limited by muscle symptoms. More than 10 steps uphill would cause pain and stiffness in thigh muscles, forcing her to stop. Resting for 5 minutes often allowed her to continue without recurrence of symptoms (second wind). Similar symptoms affected her arms with activities such as hanging out the washing, and her jaw with forceful chewing. She often had a low-grade feeling of exhaustion in her legs at the end of the day. She had been aware of mild weakness of her arms for several years. She reported

Table 1
Clinical characteristics and laboratory data of patients with myophosphorylase deficiency (McArdle disease).

Patient no./age at diagnosis (years)/sex	Symptom onset	Muscle symptoms	Precipitant	Second wind	Jaw symptoms	Myoglobinuria	Muscle weakness	Serum creatine kinase[a] (U/L)	*PYGM* mutations	
									Allele 1	Allele 2
1/24/M	Child	Pain, tightness	Running > 2 minutes; climbing 5 flights stairs	No	NA	No	Shoulder abduction	1757	Arg49Ter	Arg49Ter
2/36/F	Teens	Pain, stiffness	Uphill 10 steps; hanging out washing	Yes	Yes	Yes	"Diffuse"	ND	Gly448Arg	Pro488Arg
3/14/F	5 years	"Seizing up", tightness	Brisk walk > 300 m; walking up hill	No	NA	No	None	ND	Arg49Ter	Gly204Ser
4/32/M	8 years	Burning, tightness	Climbing 4 flights stairs	NA	NA	No	Neck flexion	641–9560	Arg49Ter	Arg49Ter
5/52/F	Child	Pain, tightness	Jogging > 1 min; walking up hill	Yes	Yes	No	None	700–11,000	Arg49Ter	c.2260_2262delA
6/19/M	Child	Pain, stiffness	Sprinting 100 m, jogging 200 m, lifting weights	Yes	Yes	Yes	None	14,018	Arg49Ter	Gly204Ser
7/22/F	Child	Pain, stiffness	Sprinting 100 m; jogging 500 m	No	No	Yes	None	564–826	Arg49Ter	Gly204Ser
8/36/F	Child	Stiffness, "seizing up"	Sprint 30 m, weight training	Yes	Yes	No	None	248–12,952	Arg49Ter	Arg601Gln
9/25/F	Child	"Seizing up", weakness	Netball, rock climbing, stairs, jogging 500 m	Yes	Yes	Yes	None	706–43,455	Arg49Ter	Arg49Ter
10/27/F	Child	Pain, cramps	Hill climbing, rowing	Yes	NA	Yes	Mild limb girdle	308	Arg49Ter	Arg49Ter

NA = not available; ND = not determined.
[a] Normal = 60–220 U/L male, 30–180 U/L female.