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Impaired glycogen breakdown and synthesis in phosphoglucomutase 1 deficiency

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ABSTRACT

Objective: We investigated metabolism and physiological responses to exercise in an 18-year-old woman with multiple congenital abnormalities and exertional muscle fatigue, tightness, and rhabdomyolysis.
Methods: We studied biochemistry in muscle and fibroblasts, performed mutation analysis, assessed physiological responses to forearm and cycle-ergometer exercise combined with stable-isotope techniques and indirect calorimetry, and evaluated the effect of IV glucose infusion and oral sucrose ingestion on the exercise response.
Results: Phosphoglucomutase type 1 (PGM1) activity in muscle and fibroblasts was severely deficient and PGM1 in muscle was undetectable by Western blot. The patient was compound heterozygous for missense (R422W) and nonsense (Q530X) mutations in *PGM1*. Forearm exercise elicited no increase in lactate, but an exaggerated increase in ammonia, and provoked a forearm contracture. Comparable to patients with McArdle disease, the patient developed a 'second wind' with a spontaneous fall in exercise heart rate and perceived exertion. Like in McArdle disease, this was attributable to an increase in muscle oxidative capacity. Carbohydrate oxidation was blocked during exercise, and the patient had exaggerated oxidation of fat to fuel exercise. Exercise heart rate and perceived exertion were lower after IV glucose and oral sucrose. Muscle glycogen level was low normal.
Conclusions: The second wind phenomenon has been considered to be pathognomonic for McArdle disease, but we demonstrate that it can also be present in PGM1 deficiency. We show that severe loss of PGM1 activity causes blocked muscle glycogenolysis that mimics McArdle disease, but may also limit glycogen synthesis, which broadens the phenotypic spectrum of this disorder.

1. Introduction

Phosphoglucomutase type 1 (PGM1, EC# 5.4.2.2.) is the predominant isoform of PGM in skeletal muscle and most other tissues. The enzyme catalyzes the conversion of glucose-1-phosphate, generated by glycogen phosphorylase, to glucose-6-phosphate for metabolism in glycolysis, and the reverse reaction for glycogen synthesis. PGM1-generated glucose-1-phosphate is also critical for protein glycosylation [1]. PGM1 deficiency was first described in a patient with exertional muscle cramps and rhabdomyolysis without congenital abnormalities; a defect in glycogenolysis was inferred by exaggerated increase in plasma ammonia despite normal lactate production with forearm exercise [2].

Abbreviations: PGM1, Phosphoglucomutase type 1; CDG, congenital disorder of glycosylation; VO_{2max}, maximal oxygen uptake

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Subsequently, PGM1 mutations were shown to cause a congenital disorder of glycosylation (CDG), and, in some patients, a more severe defect in muscle glycogenolysis with blocked lactate production in forearm exercise [3,4]. Myopathy is a common feature of the phenotype of PGM1 deficiency [5]. We therefore performed detailed exercise assessments in a patient with PGM1 deficiency and prominent muscle symptoms.

2. Patient and methods

We studied the cause and metabolic features of lifelong exertional muscle fatigue, tightness, and rhabdomyolysis in an 18-year-old woman. She had normal intelligence, but multiple congenital abnormalities including Pierre Robin syndrome, a foreshortened esophagus, and partial factor XI deficiency. Continued exercise caused muscle tightness, sometimes with an inability to relax active muscles for minutes to hours with muscle swelling and pain. Resting serum creatine kinase was elevated with values ranging from 2 to 100-fold the upper limit of normal. Pigmenturia had not been noted. Transaminase levels were also elevated. She had normal strength in all major muscle groups, and electromyography and nerve conduction studies were normal. The phenotype of our patient has been reported in detail, by Wong et al. (patient no. 5), and she was classified as being severely affected with a phenotype similar to other severely affected patients in the cohort including congenital malformations and cardiomyopathy [6].

2.1. Exercise testing (Supplemental methods)

Ischemic forearm exercise consisted of 30 maximal effort hand-grips in 1 min using a custom dynamometer with recording of grip force. Blood was sampled from the cubital vein of the exercising forearm for lactate and ammonia at rest and post exercise. Cycle-ergometry exercise was performed in the fasted state, at 70% of VO_{2max} (maximal oxygen uptake) to observe whether the patient developed a second wind. Heart rate and perceived exertion (Borg scale) were recorded, and gas exchange was determined as previously described; results were compared to those of five women with McArdle disease (age 19 [SD 5] years) [7]. Stable isotopes and indirect calorimetry were used to study muscle metabolism during 60 min of cycle-ergometry exercise performed in the fasted state at 60% of VO_{2max}, as previously described (Supplemental methods) [8]. Results were compared to those of four healthy women (age 24 [SD 4] years, data from two of them have been published previously) [8]. We also assessed the effect of IV glucose infusion using the protocol of the stable isotope experiment. To elucidate the effect of oral sucrose on exercise responses, the patient performed two additional 25 min constant workload cycle tests, one after an overnight fast and the second 30 min after consuming a sucrose meal - an intervention that improves exercise capacity in McArdle disease [9]. Blood was sampled at the time points shown in Figs. 1–3 and Supplemental table.

2.2. Muscle and skin biopsies

Histology and glycogen levels were determined in a needle quadriceps muscle biopsy, and phosphoglucomutase enzymatic activity was determined in muscle and in cultured fibroblasts from the patient and healthy controls. Western blots for PGM1 protein were performed in muscle homogenates using a commercial antibody (Santa Cruz Biotech). Serum transferrin isoform analysis was performed by the Mayo Clinic commercial laboratory.

2.3. Genetic analysis

The 11 exons of PGM1 were sequenced in the patient and in her mother. Sequencing of the PGM1 gene on chromosome 1 revealed a c.1264C > T transition in exon 8 that converts a highly conserved arginine to tryptophan (R422W), and a c.1587C > T nonsense mutation in exon 10 that converts a glutamine to a stop codon (Q530X) [3,4]. The patient's mother carried the R422W mutation. The father was unavailable for testing.

2.4. Ethics and statistics

The study was approved by the IRB of the University of Texas Southwestern Medical Center and by The Regional Ethical Committee of The Capital Region of Denmark, # 2010-008 and the study was performed according to the ethical standards of the Declaration of Helsinki. Statistic testing was not performed, but results were considered to be significantly different from healthy controls, if patient values were outside of control ranges.

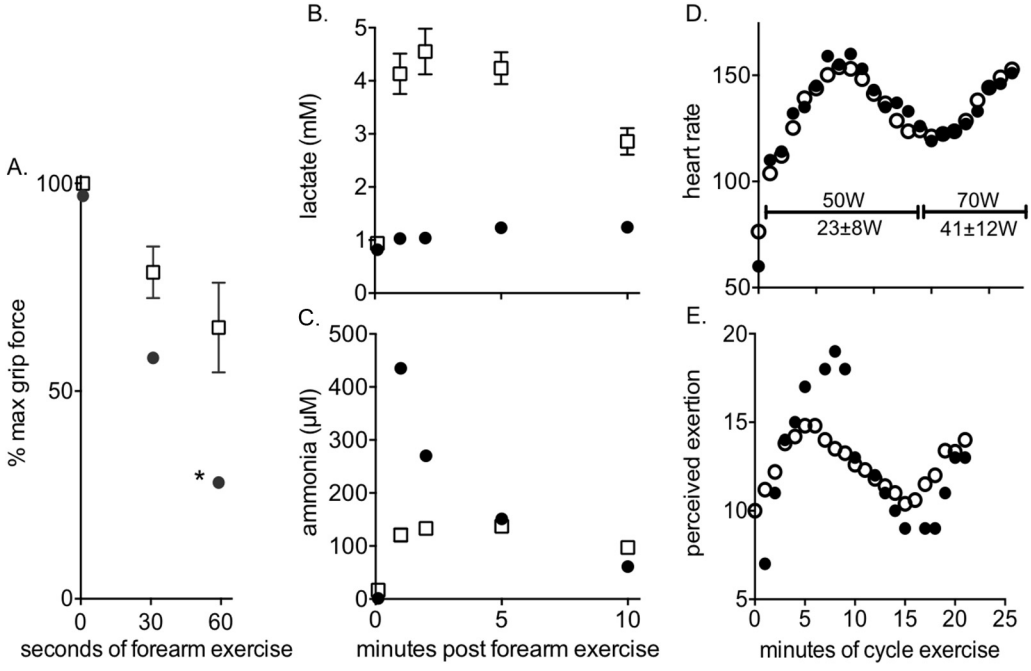

Fig. 1. Forearm and cycle exercise in PGM1 deficiency. A. Grip force during 1 min of ischemic forearm exercise. *Denotes the point at which the patient developed a finger flexor contracture; B. venous lactate, and C. ammonia levels before and after forearm exercise; patient = filled circles; healthy controls (± SD, n = 4) = open squares. D. Heart rate and workload, and E. overall perceived exertion (6–20 Borg scale) during cycle exercise; patient = filled circles; mean value for 5 McArdle women = open circles. During the first 15 min, the 70% VO_{2max} workload for the patient was 50 W and 23 (SD 8) watts for the McArdle women; after 15 min the patient was able to exercise at 70 W, McArdle women at 41 (SD 12) watts.