Novel Mutation in the PYGM Gene Resulting in McArdle Disease

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Background: McArdle disease is a common metabolic disorder characterized by marked exercise intolerance, premature fatigue during exertion, myalgia, and cramps. Despite the wide knowledge of the molecular basis of McArdle disease, few studies have used a physiological approach or explored the possibility of improving the exercise capacity of these patients.

Objectives: To describe 3 unrelated patients with McArdle disease with a novel mutation in the PYGM gene and to assess the physical capacity in 1 of them.

Design: Using molecular genetic approaches, we identified the underlying molecular defect in 3 patients with McArdle disease. Physical performance was evaluated in 1 patient by means of an exercise tolerance test on a bicycle ergometer.

Setting: Two university hospitals. Exercise physiology studies were performed in a university department.

Patients: The 3 patients showed common features of McArdle disease. They were definitively diagnosed by histochemistry, biochemistry, or molecular genetic analysis.

Results: All of the 3 patients were genetic compounds for the common Arg50Stop mutation and a novel c.13_14delCT mutation in the PYGM gene. The peak oxygen uptake (VO2peak) of the patient who performed the exercise test was only 20.2 mL·kg⁻¹·min⁻¹.

Conclusions: Together with the novel mutation, there is a markedly decreased exercise capacity in a patient with McArdle disease, which could account for the profound alteration in the capacity for performing normal activities of daily living in this subpopulation.

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METHODS

PATIENTS

The 3 patients showed the clear-cut pattern of McArdle disease: lifelong exercise intolerance, myoglobinuria, and muscle pain and cramps during and following exercise. In 2 patients, muscle histochemistry showed a myophosphorylase deficiency and biochemistry showed a lack of enzyme activity. The third patient was diagnosed by molecular genetic analysis.
**MOLECULAR GENETIC STUDIES**

The DNA was drawn from muscle in 2 patients and from blood in 1 patient. The coding sequence of the entire *PYGM* gene (20 exons) was amplified by polymerase chain reaction and sequenced as described. To confirm the presence of the novel mutation in the 3 patients, we used polymerase chain reaction–restriction fragment length polymorphism analysis (Figure).

**EXERCISE TOLERANCE TEST ON BICYCLE ERGOMETER**

Only 1 patient (a 31-year-old woman) agreed to undergo the exercise test that is described later. After she was informed in detail of the possible discomfort associated with the exercise protocol (leg pain, feeling of tachycardia, breathlessness, and dizziness), she gave her written consent to performing the test. She was eligible to perform the test, as she had reported no history of exercise-induced pigmenturia in the last 5 years. The study was approved by the institutional ethics committee (Universidad Europea de Madrid, Madrid, Spain) and was in accordance with the Declaration of Helsinki for Human Research.

She came to the laboratory at 9 AM after an overnight fast and performed a graded test until volitional exhaustion (workload increases of 10 W/min, starting at 10 W). For ethical and medical reasons, ie, to prevent the occurrence of muscle cramps and exercise-induced myoglobinuria, the exercise test was preceded by the ingestion (30 minutes prior to exercise) of a 660-mL solution containing 75 g of sucrose that was in turn followed by a 15-minute warm-up period (cycle-ergometer pedaling at 10 W). Gas exchange data were collected continuously with an automated breath-by-breath system (Vmax 29C; Sensor-Medics, Yorba Linda, Calif) to determine the VO₂peak.

Heart rates (beats per minute) were also continuously monitored during the test using 12-lead electrocardiographic tracings. Capillary blood samples for the measurement of lactate, glucose (Yellow Springs Instruments, Yellow Springs, Ohio), and ammonia (Menarini Diagnostics, Barcelona, Spain) concentrations were obtained from fingertip pricks every 2 minutes during the test.

**RESULTS**

Sequencing of the *PYGM* gene showed the presence of the Arg50Stop mutation and a novel c.13_14delCT mutation in exon 1 in all of the 3 patients. Results were confirmed by polymerase chain reaction–restriction fragment length polymorphism analysis (Figure). The novel c.13_14delCT mutation presumably causes a frameshift and a premature termination of translation 21 amino acids downstream from the rearrangement.

In the patient who underwent the exercise test, the blood glucose levels were consistently higher than 5.6 mmol/L (100 mg/dL) during exercise. The postexercise creatine kinase level did not exceed 400 IU/L (the reference maximum limit in our laboratory is 170 IU/L). The patient tolerated the exercise relatively well and did not report muscle cramps during the tests. However, she did have overall muscle fatigue and discomfort in both the neck and shoulder muscles due to the cycling position.

The patient’s VO₂peak reached during the graded test was 20.2 mL·kg⁻¹·min⁻¹ whereas her heart rate consistently increased from the start of exercise to reach a maximum value of 157 beats/min. The lactate concentration at baseline (before glucose administration) was 1.0 mmol/L, ie, similar to the values reported for patients with McArdle disease under the same conditions, and consistently increased thereafter to reach a peak value of 2.6 mmol/L, which evidenced the occurrence of glucose-based energy production. The peak ammonia level was 231 µmol/L (324 µg/dL).

**COMMENT**

Our patients had clinical, morphological, and biochemical evidence of McArdle disease. This led us to study the *PYGM* gene, and molecular analysis revealed that the 3 patients were compound heterozygous for the common Arg50Stop mutation (changing an arginine residue for a
The VO2peak of the patient was subjectively improved exercise tolerance following sucrose ingestion, the VO2peak of the patient was reported subjectively improved exercise tolerance following sucrose ingestion, the VO2peak of the patient was, however, higher than those values (approximately 15 mL·kg⁻¹·min⁻¹) previously reported for patients with McArdle disease not receiving previous glucose administration and thus having blocked glycolysis.

The Arg50Stop mutation is the most common alteration in the PYGM gene in Spanish patients with McArdle disease, accounting for 70.0% of patients. Rearrangements are much less frequent, as they represent only 7.4% of patients. Taken together our previous data with results shown here, the novel c.13_14delCT mutation represents 1 of the most usual rearrangements in Spanish patients, accounting for 3.5% of patients and 23.0% of rearrangements. Despite the facts that sucrose was administered to the patient 30 minutes before exercise with subsequent enhanced glycolytic flux (and thus an increased rate of total energy production in working muscles) as evidenced by consistently increasing lactate levels during the graded test and that the patient reported subjectively improved exercise tolerance following sucrose ingestion, the VO2peak of the patient was still low and similar to those values (approximately 20 mL·kg⁻¹·min⁻¹) previously reported after glucose administration in patients of similar age (men and women) with McArdle disease and carriers of the most common Arg50Stop and/or Gly205Ser mutations. This is an important finding, as VO2peak is an integrative indicator that reflects the maximum capacity of different organ systems—lungs, heart, blood, working skeletal muscles—involved in the chain from the delivery of atmospheric oxygen to the mitochondria and is also a powerful, independent predictor of health status and mortality in both healthy persons and those with disease. The patient's VO2peak was, however, higher than those values (approximately 15 mL·kg⁻¹·min⁻¹) reported for patients with McArdle disease not receiving previous glucose administration and thus having blocked glycolysis.

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**Author Contributions:** Dr Martin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study design and concepts:** Rubio, Lucia, Andreu, Martin, and Arenas. Acquisition of data: Rubio, Lucia, Fernández-Cadenas, Cabello, Blázquez, Gámez, and Martin. Analysis and interpretation of data: Rubio, Lucia, Fernández-Cadenas, Cabello, Blázquez, Andreu, Martin, and Arenas. Drafting of the manuscript: Rubio, Lucia, Fernández-Cadenas, Cabello, Blázquez, Gámez, Martin, and Arenas. Critical revision of the manuscript for important intellectual content: Lucia, Andreu, Martin, and Arenas. Obtained funding: Lucia, Andreu, Martin, and Arenas. Financial Disclosure: None reported.

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