Mitochondrial Myopathy Presenting as Rhabdomyolysis

David C. Patchett, DO
Michael L. Grover, DO

A 37-year-old white woman presented with acute bilateral hamstring pain after hiking. She had a creatine kinase level of 11,144 U/L. Rhabdomyolysis was diagnosed and the patient was admitted for intravenous fluid hydration. The patient continued to have exercise-induced myalgias and elevations in her creatine kinase level. Rheumatologic causes were ruled out and results from electromyogram testing were nondiagnostic. A muscle biopsy revealed a mitochondrial myopathy. The 22 mitochondrial DNA and transfer RNA genes were sequenced. An A-to-G transition was found at nucleotide position 4281 in the transfer RNA isoleucine gene. The patient was placed on a regimen of riboflavin, vitamin C, and coenzyme Q10, which provided mild relief. The patient returned to the emergency department 2 more times after vigorous exercise, with creatine kinase levels as high as 2800 U/L. At last follow-up, the patient was using a fentanyl citrate transdermal patch, which enabled her to perform moderate exercise without pain.

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Mitochondrial myopathies are diseases of the muscle associated with enlarged and abnormal mitochondria. The lifetime incidence of mitochondrial myopathy is 1 in 5000 live births. More than 200 disease-related mitochondrial DNA point mutations have been reported. These myopathies have various clinical presentations and implications and may present at any age. However, when they present in adolescence or adulthood, they tend to present with myopathic symptoms, cardiomyopathy symptoms, or both. Adults may present with fatigue, proximal muscle weakness and soreness, exercise intolerance, or ptosis. Mitochondrial myopathies can be difficult to diagnose; included in the differential diagnoses are myositis, dermatomyositis, rhabdomyolysis, electrolyte abnormality, thyroid disease, Guillain-Barré syndrome, and myasthenia gravis. In addition, the diagnosis of mitochondrial myopathy requires a muscle biopsy, which some individuals may decline.

We describe a case of a woman who presented with acute rhabdomyolysis caused by a variant of mitochondrial myopathy that to our knowledge has not been previously reported. The present case illustrates the steps to diagnose mitochondrial myopathy as well as some common missteps in the diagnostic process.

Report of Case

A 37-year-old white woman presented to the emergency department with a 1-day history of bilateral hamstring pain and cramping after a vigorous hike. Her medical history included a ductal carcinoma in situ of the breast at age 24 years, depression, anxiety, and herpes simplex virus. She had no medical history of neurologic or rheumatologic disease, but her family medical history was notable for a maternal uncle with polymyalgia rheumatica. Physical examination showed tenderness in the bilateral hamstrings with normal strength; findings from the remainder of the physical examination were normal.

Laboratory findings showed the following: creatine kinase, 11,144 U/L; alanine aminotransferase, 70 U/L; aspartate aminotransferase, 286 U/L, with a creatine level of 0.6 mg/dL; and potassium, 4.4 mEq/L. Erythrocyte sedimentation rate was 1 mm/h and C-reactive protein level was 1.10 mg/L.

The patient was diagnosed as having rhabdomyolysis secondary to excessive exercise and poor hydration. She was admitted to the Mayo Clinic Hospital for intravenous (IV) fluid hydration, pain control with morphine sulfate, and observation. During her 2 days at the hospital, the patient’s peak creatine kinase level was 13,487 U/L. The week after discharge, she was followed up by a rheumatologist who diagnosed exertional rhabdomyolysis based on physical examination, the patient’s history of increased activity in a hot climate with inadequate hydration, and the patient’s elevated creatine kinase level, which responded to fluid hydration.

After discharge, the patient continued to have intermittent various myalgias. Approximately 2 months after her first visit to the emergency department, the patient presented with a 1- to 2-day history of right shoulder pain and thoracic spine discomfort. At presentation, she indicated that she had not participated in any exercise out of the normal for her. She had been very careful to stay well hydrated and avoid excessive activity.
Physical examination showed tenderness of the right paraspinal muscles in the thoracic region (T3-T6) and of the right deltoid muscle. A nonspecific erythroderma was present on the chest and scattered on the face. The rest of the physical examination findings were normal.

Results of laboratory tests showed a creatine kinase level of 277 U/L, aldolase level of 111.5 U/L, and antinuclear antibody level of less than 0.09 U. The patient was given IV fluid hydration and her pain was managed with IV morphine sulfate. Myositis, dermatomyositis, and metabolic myopathies were suspected. The patient was examined by a rheumatologist the next week, who ruled out a rheumatologic cause. She was then seen in the family medicine clinic within the same week and muscle biopsy was recommended, but she declined. The patient was referred to the neurology department and she was seen 2 weeks later. Muscle biopsy was discussed again, but the patient still declined.

The next week, the patient underwent an electromyogram, the results of which showed only minimal short duration potentials in the proximal arms, legs, and paraspinal muscles. Within the next 2 weeks, she was referred to the physical medicine and rehabilitation department, where she underwent magnetic resonance imaging of the thoracic and lumbar spine because of ongoing complaints of midthoracic and low back pain. Magnetic resonance imaging results showed tiny right-sided disk herniations at T6 through T7 and T11 through T12 that were of no perceived clinical significance. Approximately 1 month after presenting to the emergency department, the patient was told her pain was myofascial.

Within the next month, the patient returned for follow-up in the family medicine department on 2 separate occasions and requested osteopathic manipulative treatment (OMT) for her myofascial pain. She primarily complained of right shoulder and midthoracic pain. Somatic dysfunction was found primarily in the midthoracic spine (T4-T7) and in the right ribs (4-7). Poor mobility of the right scapula was also noted. The patient was treated with high-velocity, low-amplitude and direct myofascial release OMT techniques. The OMT provided temporary pain relief for the patient. However, the pain and somatic dysfunction returned quickly.

The patient returned for follow-up 2 weeks later. She had experienced another episode of severe muscle pain and had been evaluated at another emergency department, which had measured an elevation in her creatine kinase levels. The patient agreed to the muscle biopsy of the left gastrocnemius muscle. Results showed high levels of ragged red, ragged blue, and cytochrome c oxidase–negative fibers.

The patient was diagnosed as having mitochondrial myopathy and was started on a megavitamin routine of riboflavin (100 mg, 3 times per day), vitamin C (500 mg, twice daily), and ubiquinone (300 mg, 3 times per day). The patient felt the megavitamin regimen was mildly effective and stopped taking the vitamins.

Mitochondrial enzyme analysis was normal. The 22 mitochondrial DNA and transfer RNA genes were sequenced. A change was found that had not been previously reported that had pathologic potential: an A-to-G transition at nucleotide position 4281 in the transfer RNA isoleucine gene. The patient and her family denied further genetic testing.

Within 3 months after biopsy, the patient had returned to the emergency department 2 times, with creatine kinase levels being as high as 2800 U/L after strenuous exercise. At last follow-up, the patient was on a regimen of a 25 mcg fentanyl citrate transdermal patch for pain management. She was able to perform moderate exercise; however, strenuous exercise caused her pain to resume. No further follow-up was available because the patient moved out of state.

Comment
Mitochondrial myopathies can present as rhabdomyolysis or exercise-induced muscle pain, particularly in adolescents and adults. Diagnosis is made by muscle biopsy, but genetic testing is required for genetic counseling, which allows patients to make decisions about potential reproductive issues. Knowing the type and degree of genetic abnormality allows individuals to understand the likelihood that they may pass mitochondrial myopathies to their children and the degree to which their children might be affected.

Various vitamins, minerals, and supplements have been used in the treatment of patients with mitochondrial myopathies with variable success. In particular, coenzyme Q10 and creatinine monohydrate have shown promise at improving exercise tolerance in individuals with mitochondrial myopathies. Physical activity has also been shown to improve exercise tolerance and quality of life scores; though long-term studies are needed in this area. Pain management is warranted for patients with mitochondrial myopathies to enable physical activity. In the future, mitochondrial gene therapy may be a treatment option for patients with mitochondrial myopathies.

Conclusion
Mitochondrial myopathies should be considered in patients presenting with recurrent muscle pain and elevation of creatine kinase after exercise.