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Mitochondrial Encephalomyopathy With Lactic Acidosis and Strokelike Episodes (MELAS): A Mitochondrial Disorder Presents as Fibromyalgia

Rowena A. DeSouza, MD; Raul J. Cardenas, MD; Tekisha U. Lindler, MD; Francisco A. De la Fuente, MD; Francisco J. Mayorquin, MD; David S. Trochtenberg, MD, FCCP

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Abstract and Introduction

Abstract

This case report describes a patient who presented with symptoms and signs of longstanding fibromyalgia. Routine laboratory tests revealed an elevated anion gap. Evaluation of the elevated anion gap demonstrated elevated lactate and pyruvate levels and a lactate-to-pyruvate ratio greater than 20:1. A muscle biopsy was performed, exhibiting red ragged fibers, pathognomonic for a mitochondrial disorder. The patient was diagnosed with mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes (MELAS). This is the first report describing fibromyalgia as the initial presentation of MELAS. This article outlines the diagnostic process that can assist the physician in distinguishing mitochondrial disorders from other muscular diseases, particularly fibromyalgia.

Introduction

The presenting complaint of diffuse muscular weakness and pain can be a diagnostic dilemma even for the experienced physician. One of the more common causes of these symptoms is fibromyalgia, a common malady frequently managed by the primary care physician. Fibromyalgia is defined as widespread pain not explained by an inflammatory or degenerative muscular disorder.^[1] The diagnosis is made on the basis of the clinical judgment of the examining physician, as there are no definitive laboratory or imaging studies. The hallmark of fibromyalgia is excessive tenderness in at least 11 of 18 points defined by the American College of Rheumatology.^[2] The estimated prevalence of fibromyalgia in the general community is 2%, occurring more commonly in women (3-4%) than in men (0.5%).^[1] The clinical presentation of mitochondrial disease has many similarities with fibromyalgia, making it possible to confuse them with one another. Mitochondrial disease, unlike fibromyalgia, is caused by abnormal oxidative metabolism of glucose within skeletal muscle, resulting in anaerobic conversion of pyruvate into lactate.^[3] The metabolic defect is the result of mutations in mitochondrial DNA. The widespread production of lactate under aerobic conditions can produce objective muscular weakness that differs from the subjective symptoms associated with fibromyalgia. Ultimately, the diagnosis of mitochondrial disease requires a thorough investigation and recognition of symptoms and signs that distinguish it from other muscular disorders, particularly fibromyalgia. The following is a case of mitochondrial disease that was initially confused with fibromyalgia.

Case Report

A 69-year-old white woman presented to the clinic with an acute exacerbation of chronic muscle aches that she had experienced since she was a teenager. She reported worsening muscle fatigue, pain, and weakness, which had begun 1 week previously, and was described as dull achy cramps. The patient complained that the cramps and muscle weakness affected almost every muscle group including the trapezius, deltoids, gluteus muscles, and calves. The pain

was refractory to muscle relaxants, nonsteroidal anti-inflammatory drugs, and narcotics. The only reported alleviating factor was rest, which provided minimal relief. She could not identify a precipitating cause or event, but stated that her job as a factory worker required her to lift large, heavy objects. This episode was the third one she had experienced over the previous 6 months. Review of systems was notable for severe headaches, photophobia, insomnia, and short-term memory loss. She also reported chronic diarrhea that was refractory to both metronidazole and over-the-counter products and was neither bloody nor painful.

Her medical history revealed a history of hypertension, hypercholesterolemia, hypothyroidism, depression, and childhood seizures. She had been seizure free since early adulthood. Her obstetric and gynecologic history revealed G₁ P₁ status, with onset of menopause at age 48. The patient denied drug allergies. Medications included levothyroxine 0.125 mg daily, Premarin 2.5 mg daily, oxycodone 40 mg twice daily, venlafaxine 150 mg twice daily, and colestevam 1,875 mg twice daily. Family history was remarkable for her mother being diagnosed with fibromyalgia early in life. No other family members had myalgias, seizures, or other neuromuscular conditions. The patient reported a 20-pack-year history of tobacco use, but denied alcohol abuse or illicit drug use. She had no risk factors for human immunodeficiency virus.

On physical examination, she was a 69-year-old woman who appeared older than her stated age and was in no apparent distress. Vital signs were notable for a blood pressure of 138/72 mm Hg, a pulse of 72 beats/min, a respiratory rate of 20 breaths/min, and a temperature of 98.6°F. Her head and neck examination was unremarkable. Lungs were clear to auscultation and percussion, bilaterally. Cardiac examination revealed a normal S₁/S₂, without murmurs, rubs, or gallops. Her abdomen was without masses, tenderness, or organomegaly. Her extremities were without clubbing, cyanosis, or edema. There was marked point tenderness in 15 of 18 designated test sites, consistent with a diagnosis of fibromyalgia. Only two control points were tender. Neurologic examination revealed intact cranial nerves, deep tendon reflexes, and sensation (touch, pain, and vibration). Her gait was normal, and 4/5 strength was noted in all muscle groups.

Laboratory evaluation included a normal complete blood count and differential. Also, within normal limits were antinuclear antibodies, rheumatoid factor, creatine phosphokinase, liver function tests, and thyroid-stimulating hormone. Electrolytes included sodium, 142; potassium, 4.0; chloride, 100; and carbon dioxide, 24, with an elevated anion gap of 18 noted. At rest, lactic acid was 60 mg/dl (normal range, 1.5-19.8 mg/dl) and the pyruvate level was 2.9 mg/dl (normal range, 0.3-0.9 mg/dl). The lactate-to-pyruvate ratio was 20:1. Biopsy of the trapezius muscle showed Type 2 atrophy with moth-eaten fibers and occasional red ragged fibers. The laboratory evaluation and biopsy were diagnostic of the mitochondrial disorder known as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS).

Discussion

Mitochondrial disease occurs in 1 of 10,000 newborns.^[4] Mitochondria play a central role in cellular respiration and the synthesis of heme, amino acids, lipids, and nucleotides.^[4] These processes are carefully orchestrated by the mitochondria's own genetic material: mtDNA, mtrRNA, and mttRNA. An A-to-G mutation in the mttRNA^{Leucine(UUR)} gene (A3243G) accounts for approximately 80% of MELAS cases.^[4-6] This mutation also significantly increases the risk of developing Type 2 diabetes mellitus,^[3] one of the common comorbidities seen in MELAS.

The first symptoms of MELAS can occur as early as the third year of life. The classic presentation starts with migraine headaches (in 80% of patients) and seizures (approximately 85% of cases).^[4] Mitochondrial disease should be considered in both juvenile and adult patients with early-onset migraines or refractory partial seizures, especially if the brain magnetic resonance imaging scan is normal.^[3,7] Nearly 90% of patients present with headaches and vomiting; syncopal attacks are seen in 85% of patients. Other symptoms include paresis, mental retardation, sight and hearing disorders, cardiomyopathy, angiopathy, and ataxia.^[4-6] Seizures are usually associated with lactic acidosis.

Characteristic strokelike episodes usually originate in the parieto-occipital region, spreading to other areas of cortex.^[4] Cerebellar ataxia is often observed in patients with MELAS and may precede the development of stroke by many years.^[5] In the course of MELAS, decreased exercise tolerance is observed. A common presenting complaint is diffuse subjective myopathy, which can mimic other musculoskeletal disorders. However, patients are usually asymptomatic until later in life.^[6] Patients with MELAS may die as a result of circulatory and respiratory failure, renal insufficiency, pulmonary embolism, seizures, or metabolic disorders.^[4] Interestingly, antiretroviral therapy with nucleoside analogs may produce lactic acidosis, associated with weakness and other symptoms found in MELAS.^[8]

The syndrome of fibromyalgia originated as an explanation for patients with generalized, persistent idiopathic pain. Mandatory symptoms include widespread pain and characteristic tenderness not explained by an inflammatory or degenerative process. There are no objective markers of disease.^[1] As noted by Goldenberg,^[1] in the past decade, the prevalence of fibromyalgia increased with the age of the population and was commonly associated with comorbid disorders. Fibromyalgia is often seen with other common, ill-defined syndromes such as chronic fatigue syndrome, inflammatory bowel disease, and depression.^[1] A minimal number of laboratory tests, such as erythrocyte sedimentation rate and thyroid function tests, are recommended. More than a century of research has failed to detect consistent abnormalities in the muscle and soft tissues in fibromyalgia. It is now thought that patients with fibromyalgia have a generalized hypervigilance to both pain and auditory stimuli. Levels of both substance P, a neurotransmitter involved in pain pathways, and defective antinociceptive peptides are elevated in the cerebro-spinal fluid of patients with fibromyalgia.^[1]

The biochemical heterogeneity of mitochondrial disorders widens the clinical variability of MELAS and makes the clinical diagnosis of mitochondrial disease difficult.^[7] Thus, a high degree of suspicion is essential to differentiate between MELAS and other similar clinical presentations, such as fibromyalgia. Detection of mitochondrial disorders demands extensive evaluation of any patient with pain, fatigue, weakness, and an elevated anion gap. Phosphorus-magnetic resonance spectroscopy (P-MRS) and magnetic resonance (MR) imaging of muscle are new alternatives that can provide diagnostic information in myopathies associated with defects in glycolysis.^[9] P-MRS of muscle and proton MR spectroscopy of brain can be helpful in the evaluation of mitochondrial encephalomyopathy and, at times, may be diagnostic. P-MRS provides a noninvasive assessment of oxidative metabolism in other myopathies associated with secondary mitochondrial dysfunction, and can be useful for the evaluation of the pathophysiology of exercise intolerance.^[9] Lastly, MR spectroscopy can also be useful for monitoring progression of mitochondrial disorders and their response to therapy.

Due to defects in oxidative phosphorylation, patients with mtDNA disorders are dependent on anaerobic metabolism, which results in a shunt of pyruvate to lactate.^[5] Thus, as demonstrated in our patient, a high lactate level at rest is suggestive of a mtDNA disorder, and a lactate-to-pyruvate ratio of 20:1 or higher is often seen. Metabolic acidosis and elevations of lactate, pyruvate, lactate-to-pyruvate ratio, alanine, tricarboxylic acid cycle intermediates, dicarboxylic acids, or a generalized aminoaciduria can be important diagnostic clues to the presence of an oxidative phosphorylation disease.^[4] High lactic acid levels in combination with a high anion gap are common features of mitochondrial disorders that are often overlooked. They are easy and affordable tests to order in the clinic setting and are effective screening tools when mitochondrial disorders are suspected.

Muscle biopsy findings can suggest the presence of an mtDNA disorder, revealing the pathognomonic ragged red fibers caused by proliferation of abnormal mitochondria.^[4-6] It is important to remember that some patients' defective mitochondria are heteroplasmic (mutation seen in only some of the mtDNA copies); thus, ragged red fibers may not be seen on biopsy.^[4-6] Muscle biopsy is diagnostic when positive, but does not exclude the diagnosis when negative.^[6,10] Genetic testing may reveal the presence of a point mutation most commonly associated with MELAS; however, it is also relatively insensitive.

Therapy for mitochondrial disease is still controversial; however, we know that early recognition and treatment of these diseases can halt their progression. Creatine monohydrate, coenzyme Q, carnitine, and dichloroacetic acid are some of the agents that have been used for therapy.^[4] Tarnopolsky and Martin^[7] demonstrated that a once-daily 10-g dose of creatine monohydrate for 5 days followed by 5 g of creatine monohydrate for 5 to 7 days increased handgrip, dorsiflexion, and knee extensor strength in patients with a variety of neuromuscular disorders including mitochondrial cytopathies.^[7] Although symptomatic improvements have been reported with these agents, no large-scale randomized trials have been performed. The mechanism whereby creatine monohydrate improves strength in the muscle involves increasing phosphocreatine inside the mitochondria, enhancing energy shuttling and thus stimulating protein synthesis.^[8] The overall efficacy and long-term effects of nutritional supplements remain to be determined. Follow-up consists of monitoring the anion gap, lactate-to-pyruvate ratio, and symptomatic management.

Conclusion

An elevated anion gap should prompt the physician to obtain both lactate and pyruvate levels if a patient has chronic myopathy of unknown cause. If the elevated anion gap coincides with an elevated lactate-to-pyruvate ratio (>20:1), a myopathy of mitochondrial origin must be suspected. These are cost effective and simple methods that can be used in any clinic setting to screen for mitochondrial disorders.

Sidebar: Key Points

- Mitochondrial disease may mimic fibromyalgia.
- Unexplained elevation of the anion gap suggests mitochondrial disease.
- An elevated lactic acid level at rest and an elevated lactate-to-pyruvate ratio confirm the diagnosis of mitochondrial disease.
- Muscle biopsy displaying red ragged fibers is diagnostic of mitochondrial disease.

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Authors and Disclosures

Rowena A. DeSouza, MD, Raul J. Cardenas, MD, Tekisha U. Lindler, MD, Francisco A. De la Fuente, MD, Francisco J. Mayorquin, MD, and David S. Trochtenberg, MD, FCCP, Meharry Medical College and Centennial Medical Center, Nashville, TN

Reprint Address

Reprint requests to David S. Trochtenberg, MD, FCCP, Department of Internal Medicine, Meharry Medical College, 1005 Dr. D.B. Todd, Jr. Blvd., Nashville, TN 38208-3599. Email: dtrochtenberg@mail.mmc.edu

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