Case in Point

Mitochondrial Myopathy, Encephalopathy, and Lactic Acidosis with Stroke-like Episodes Syndrome

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A presentation of altered mental status, nausea, vomiting, gait difficulty, and a left homonymous hemianopia, in the context of a long history of metabolic and neurologic problems, led clinicians to investigate an underlying mitochondrial disorder. This case highlights the clinical findings that should raise suspicion for these elusive conditions.

Mitochondrial diseases present a unique diagnostic challenge to clinicians because they are relatively rare and tend to affect multiple organ systems, with no single manifestation being pathognomonic. Primary care physicians are likely to recognize common conditions that affect multiple organ systems (such as diabetes), and specialists are likely to have a high index of suspicion for common systemic conditions that affect their organ system of interest (such as diabetic retinopathy or diabetic polyneuropathy). The recognition of rare multisystem diseases, however, requires a familiarity with the salient features of their clinical presentation and a high index of suspicion.

Mitochondrial disorders represent a growing area of clinical and scientific interest. They are probably at least as common as many better-known rare diseases, such as amyotrophic lateral sclerosis.[1] A search of Medline reveals that, of 6,914 articles currently indexed under the major subject heading of "mitochondrial diseases," just over half were published in 2000 or later. Further advances in the understanding of mitochondrial disorders and the development of effective treatment rely upon identification of these disorders by clinicians.

Here, we discuss the case of a woman who presented, over the course of 16 years, to multiple medical facilities and services with some of the classic findings of the mitochondrial myopathy, encephalopathy, and lactic acidosis with stroke-like episodes (MELAS) syndrome before a definitive diagnosis was established. By presenting this case, we hope to raise awareness of mitochondrial diseases among VA health care practitioners across disciplines.

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INITIAL EXAM

A 44-year-old woman was brought to the emergency department (ED) by her husband in December 2007 because she "had not been herself" for three days. She had been in a minor traffic accident three days prior and had driven 10 miles without recalling the event. The next day she developed headache, nausea, and vomiting. Her gait was unsteady, and she seemed not to notice things on her left side. Her mental status waxed and waned, but she had mild persistent confusion. She was admitted to the hospital for further workup.

Patient history

The patient's medical history revealed that she had been experiencing illness for the past 16 years (Table 1). After an unremarkable childhood development, she served in the Marine Corps from 1983 to 1994. At the age of 28 years, she began to notice decreased hearing. She received an otolaryngology evaluation, was diagnosed with idiopathic sensorineural hearing loss, and was fitted with hearing aids.

At the age of 31 years, the patient was diagnosed with diabetes mellitus and began insulin therapy. Her condition was assumed to be late-onset type 1 diabetes, since she was not overweight. A diabetic eye examination revealed some retinal abnormalities. She was referred to a retinal specialist, who diagnosed "a congen-

ital abnormality of the optic nerves likely related to the acoustic nerve abnormalities." (This condition was later diagnosed as a cone-rod dystrophy by the ophthalmology service at the VA.)

Despite her retinal abnormalities, the patient was not visually impaired and worked for the U.S. Postal Service after leaving the Marines. She ceased work in 2000 due to progressive hearing loss that could not be compensated by hearing aids. Otherwise, she was functioning well. She had married while in the Marine Corps and was raising a school-aged son. She had two spontaneous abortions prior to giving birth to her son.

The patient continued in this state of health until April 2005, when she developed acute, bilateral muscle cramping in her thighs and calves. Later the same morning, she had a generalized tonic-clonic seizure and developed status epilepticus. She was taken emergently to a community hospital and was subsequently intubated and transferred to an outside referral hospital. There, she was found to have lactic acidosis and an elevated serum creatine kinase (CK) level (greater than 250,000 U/L; reference range, 40,000 to 150,000 U/L). The patient remained in a coma for several days. She developed acute renal failure and required a short course of hemodialysis. Her seizures were controlled, and her mental status and renal function improved over the following two weeks.

Magnetic resonance imaging (MRI) of the brain was obtained during the admission and revealed "multiple small acute strokes in the left temporal lobe and left paracentral pons." Echocardiogram results were negative for any identifiable source of thromboembolism. Results of blood cultures and multiple viral serologies remained negative throughout her hospital course. Her initial seizures and shock were attributed to "an unidentified viral illness." Her electrolyte abnormalities continued to improve, and her mental status normalized.

Table 1. Timeline of the patient's medical history

Presenting date	Patient age in years	Presentation/diagnosis
1991	28	Idiopathic sensorineural hearing loss
1994	31	Diabetes mellitus
1994	31	Optic nerve abnormality
April 2005	41	Seizures and coma with cryptogenic lactic acidosis; "multiple acute strokes" on magnetic resonance imaging
December 2005	41	Episodic nausea, vomiting, and confusion
2007	43	Confusion, headache, nausea, vomiting, and occipital stroke

The patient was discharged in stable condition three weeks after admission. As she was diffusely weak and could not ambulate or perform any activities of daily living without assistance, she was discharged to a rehabilitation facility. She remained there for three months.

Because she continued to report muscle stiffness, cramping, and pain, she was evaluated by the rheumatology service toward the end of her stay at this facility. Her CK levels were now normal, and rheumatologic laboratory results (erythrocyte sedimentation rate and antinuclear antibodies) were negative. She had mild diffuse symmetric muscle weakness on examination. She was diagnosed with diabetic cheiroarthropathy and deconditioning.

The patient was first evaluated at the Durham VA Medical Center (DVAMC), Durham, NC in October 2005 by the neurology service for hand weakness. She was still taking phenytoin for seizure prophylaxis but had not had any seizures since her April 2005 hospital admission. Although she had been generally improving since her discharge from the rehabilitation facility, she had been "periodically dropping things" for the past month. It was concluded that her problems most likely stemmed from "deconditioning and muscle contracture," but an MRI of the cervical spine was ordered because her reflexes were felt to be somewhat brisk. The imaging results were normal, and no neurologic follow-up was scheduled.

She continued to follow up with the DVAMC's endocrinology and ophthalmology services on an outpatient basis. In December 2005, she presented to the ED, reporting multiple bouts of illness involving nausea and vomiting. These symptoms usually would occur in the morning and often were accompanied by slurred speech, dizziness, confusion, and weakness that would resolve over the course of a day. Results of a computed tomography (CT) scan of the head and lumbar puncture were unremarkable, and she was discharged home with a recommendation for an outpatient gastroenterology workup. A barium swallow was subsequently performed, with normal results.

The patient established primary care at the DVAMC in Janu-

ary 2006. At that time, she reported continued episodic illness similar to that reported at the ED. Because of the confusion that occurred during these episodes, a diagnosis of partial seizures was considered. An electroencephalogram was performed, with normal results.

Throughout 2006 and 2007, the patient visited the DVAMC's neurology and primary care clinics on multiple occasions. She continued taking phenytoin and had no further seizures. During one visit, she was noted to have mild hip flexor weakness but otherwise was described as having full strength. She continued to experience improvements in her functioning following her debilitating illness in April 2005. Before her index presentation, she had been walking without assistive devices and driving with a modified steering wheel (to accommodate hand contractures).

Index presentation

Besides the diagnoses mentioned above, the patient's history was significant for hypertension, hyperlipidemia, and allergic rhinitis. She reported no allergies to medications and currently was taking insulin, hydrochlorothiazide, norethindrone, aspirin, lisinopril, phenytoin, omeprazole, metformin, naproxen, fluticasone nasal spray, simvastatin, and ezetimibe. Her family history was remarkable for cerebral palsy in a brother and psoriasis in her mother. She noted that she was much shorter in stature than other members of her family. She was disabled and living with her husband and son, who was now 17 years old. Her family was supportive. She was not using tobacco, ethanol, or any illicit substances.

Physical examination revealed a short, slender woman (weight 105 lb, height 60 in) in no acute distress. Her blood pressure was 98 mm Hg systolic and 63 mm Hg diastolic. She had a regular pulse at 71 beats/min, regular respirations, and a normal temperature at 98.5° F. Her lungs were clear and her heart sounds were normal to auscultation. Her abdomen was benign, without palpable organomegaly, and her extremities were without edema. Somewhat decreased muscle bulk was noted in the foot intrinsic muscles bilaterally.

Neurologic examination revealed contractures of the deep finger flexors bilaterally. The patient was profoundly hard of hearing but was alert and able to answer orientation questions correctly. She had fluent, spontaneous speech without paraphasic errors, and she was able to name several objects correctly and follow simple commands. The patient did have difficulty following multistep commands, however, whether they were written or spoken, and she had difficulty relating a cogent medical history. Cranial nerve examination revealed a dense congruent left homonymous hemianopia. Muscle tone was normal in both of her upper extremities and increased in both of her legs. Her motor strength was full throughout. The patient was diffusely and symmetrically hyperreflexic, with Babinski signs present bilaterally. She was able to stand with minimal assistance but had a wide-based station and exhibited difficulty initiating gait (gait apraxia).

Results of blood cell counts, serum chemistry studies, and liver enzyme tests were within normal limits, except for a mildly elevated serum glucose level (181 mg/dL; reference range 70 to 110 mg/dL). Urinalysis results were normal, and pregnancy and HIV test results were negative.

A CT scan of the head was performed, which revealed "an evolving large right posterior cerebral artery (PCA) territory infarction." A follow-up MRI of the head was performed (Figure), which also was interpreted as demonstrating a subacute right PCA distribution infarction. Notably, the right PCA was normal in appearance on magnetic resonance angiography, and no changes referable to a prior left temporal or pontine stroke were observed.

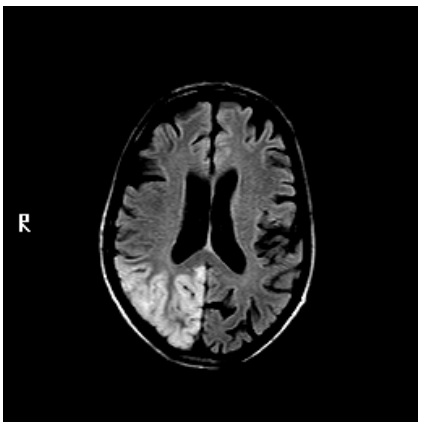

Figure. Axial fluid attenuated inversion recovery (FLAIR) image of the patient's brain, obtained in December 2007. While this image initially was interpreted as evidence of a right posterior cerebral artery (PCA) stroke, note that the area of signal abnormality extends farther anteriorly than the typical PCA distribution—into what is usually middle cerebral artery territory. Typically, stroke-like episodes in mitochondrial myopathy, encephalopathy, and lactic acidosis with stroke-like episodes (MELAS) syndrome are associated with imaging abnormalities that do not conform to a vascular distribution and most often are located in the posterior brain.

Given the radiologic appearance suggesting embolic stroke, the patient was treated with antiplatelet therapy (aspirin and extended-release dipyridamole). A workup for an inherited hypercoagulable state also was initiated. Her encephalopathy could not be well ex-

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Table 2. Selected symptoms of mitochondrial diseases[a]

- Seizures
- Psychomotor regression
- Cryptogenic stroke
- Ataxia
- Sensorineural hearing loss
- Retinopathy or optic atrophy
- Ophthalmoplegia
- Exercise intolerance or weakness
- Lactic acidosis
- Atypical diabetes or other endocrinopathies

[a]Any unexplained combination of these findings should raise suspicion for underlying mitochondrial disease.

plained by a PCA stroke, however, and her complicated medical history suggested an underlying metabolic disorder. A detailed review of her history led to consideration of MELAS syndrome.

To test this possible diagnosis, a serum lactate level was acquired. It was elevated at 3.5 mmol/L (reference range, 0.5 to 2.2 mmol/L). Subsequently, a blood test was sent to Athena Diagnostic Laboratories (Worcester, MA) for a MELAS mitochondrial DNA evaluation. The results returned positive for the A3243G mutation in the mitochondrial leucine transfer RNA gene, and a genetically confirmed diagnosis of MELAS syndrome was made.

TREATMENT COURSE

Supportive management was provided to the patient. Her mental status returned to baseline by discharge. To date, she continues to walk and exercise without assistive devices and cares for multiple children. She continues to be treated through the DVAMC's primary care clinic with routine supportive care.

ABOUT THE CONDITION

Mitochondrial disorders

Mitochondria are ubiquitous organelles responsible for multiple processes of cellular metabolism and, most notably, for the production of adenosine triphosphate through the electron-transport chain and oxidative phosphorylation. Mitochondria are the only organelles apart from the nucleus that contain their own DNA. Mitochondrial DNA (mtDNA) consists of a single, circular, double-stranded DNA molecule encoding 37 genes. There are hundreds to thousands of mitochondria in each cell, and each mitochondrion contains approximately five copies of the mitochondrial genome. Most of the proteins responsible for mitochondrial function are encoded by nuclear DNA (nDNA) and imported into the mitochondria after translation in the cytoplasm. Therefore, inherited mitochondrial defects can follow either a maternal inheritance pattern (involving mtDNA mutations) or a Mendelian inheritance pattern (involving nDNA mutations).[2]

Since mitochondria are ubiquitous, mitochondrial defects typically manifest with abnormalities in multiple organ systems (Table 2). Because nervous tissue and skeletal muscle have high metabolic demand, they often are particularly susceptible to mitochondrial dysfunction. Central nervous system symptoms can include seizures, ataxia, myoclonus, psychomotor retardation or regression, hemiparesis, hemianopia or cortical blindness, headaches, and dystonia. Peripheral nervous manifestations can include peripheral neuropathy, optic atrophy, retinopathy, and sensorineural hearing loss. Muscle disease typically presents with weakness, exercise intolerance, or external ophthalmoplegia. Ragged-red fibers often are seen on muscle biopsy, and lactic acidosis is usually present during symptomatic periods. Cardiac conduction disturbances, cardiomyopathy, endocrinopathies (diabetes, hypoparathyroidism, and short stature), gastrointestinal disturbances, and renal dysfunction also can be present.[2] Ophthalmologic abnormalities are prevalent in mitochondrial disease but do not usually cause profound visual impairment.

Several clinical syndromes attributed to mitochondrial defects have been described. These include progressive external ophthalmoplegia (PEO); Kearns-Sayre syndrome (characterized by PEO with onset prior to age 20, short stature, pigmentary retinopathy, ataxia, heart block, or elevated cerebrospinal fluid protein); MELAS syndrome; myoclonic epilepsy with ragged-red fibers (MERRF); neuropathy, ataxia, and retinitis pigmentosa (NARP); and Leber's hereditary optic neuropathy (LHON).[3] There is considerable overlap among syndromes. In fact, identical genetic mutations can present as different syndromic phenotypes, even among members of the same family.[2]

MELAS syndrome

MELAS syndrome, which may be as prevalent as one case per 6,000 persons in some populations, is typically characterized by episodic headaches (associated with nausea), cognitive dysfunction, and stroke-like episodes (focal neuronal dysfunction with CT and MRI abnormalities resembling acute stroke but often not conforming to a vascular distribution and with atypical features, such as gradual onset). The pathogenesis of the stroke-like episodes in MELAS syndrome is incompletely understood.[4] The events predominantly affect the occipital cortex.

Symptoms of MELAS syndrome typically begin prior to age 40. Short stature, sensorineural hearing loss, and exercise intolerance are encountered frequently. Cardiomyopathy, ataxia, ophthalmoplegia, renal failure, and diabetes are less frequent features of the syndrome. Currently, there are no disease modifying treatments of proven benefit available to treat MELAS syndrome, although several nutritional supplements (such as creatine and coenzyme Q10) are sometimes used on theoretical grounds.[5]

The A3243G mutation

Although several different genetic mutations have been associated with MELAS syndrome,[5] since 1990, a substitution of adenine for guanine in one of two mitochondrial leucine transfer RNA genes (A3243G) has been known to underlie the majority of MELAS syndrome cases.[6] The A3243G mutation alone is not sufficient to cause MELAS syndrome, however. For instance, a recent cross-sectional, genomic study of 2,945 randomly selected residents from a defined geographic area west of Sydney, Australia (99% white) discovered seven study participants with A3243G mutations. All had mild to moderate sensorineural hearing loss on audiometric evaluation, but none had MELAS syndrome.[7]

The phenotype of maternally inherited diabetes and deafness (MIDD) now also has been firmly linked to the A3243G mutation. In 1992, the A3243G mutation was reported in a family of diabetics with maternal inheritance but without neurologic manifestations other than deafness.[8] In a French multicenter study, 40 of 71 patients recruited primarily through a solicitation to diabetes centers had the mutation, although 27% of probands identified by the phenotype of diabetes and deafness had no family history of the disorder. The mean age of diabetes onset was 39 years, and none of the patients were obese.[9]

Clinical approach to suspected disease

Clinical suspicion is key to the detection of mitochondrial disorders, which should be considered in any patient presenting with the clinical dyad of diabetes and sensorineural hearing loss prior to age 50. The discovery of otherwise unexplained retinal abnormalities in a patient with a history of multisystem disease also should prompt consideration of mitochondrial disorders. MELAS syndrome, in particular, should be considered in the differential diagnosis of cryptogenic stroke, and a targeted search for disease should be carried out in patients with other historical features consistent with a mitochondrial disorder.

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There is no universal agreement about the appropriate sequence of diagnostic evaluation in patients with suspected mitochondrial disorders. Hass and colleagues proposed an evaluation that includes a complete blood cell count and testing for serum chemistries, liver enzymes, ammonia, CK, lactate, pyruvate, quantitative plasma amino acids, quantitative urine organic acids, plasma acylcarnitine analysis, and cerebrospinal fluid lactate and pyruvate. They also recommended echocardiography, electrocardiography, ophthalmologic examination, auditory testing, and brain MRI to characterize systemic involvement.[10]

A standardized approach to ordering specific genetic testing has not been established. Screening all young patients with occipital infarcts for the A3243G mutation has proven to be a low yield approach.[11] We advocate the use of selected genetic tests for mitochondrial mutations as a way to potentially confirm diagnosis when there is a high pretest probability of a mitochondrial disorder based upon clinical presentation and laboratory results. Given the evolving state of knowledge of mitochondrial genetics, a negative genetic test result cannot rule out mitochondrial disease. Genetic tests are costly[12] and should be used discriminately. Genetic testing also inevitably raises several ethical issues,[13] an adequate discussion of which is beyond the scope of this report. Furthermore, variable penetrance and clinical heterogeneity in mtDNA mutations make prognostication for subsequent generations anything but straightforward. We recommend referral to a certified genetic counselor to discuss positive results obtained in the course of clinical evaluation or if patients or family members initiate requests for testing.

For the interested reader, DiMauro and Schon give an excellent overview

of the pathophysiology of mitochondrial diseases in their 2003 review.[2] Additionally, the United Mitochondrial Disease Foundation makes several educational resources available to patients and clinicians through their web site (http://www.umdf.org).

IN SUMMARY

Although the mitochondrial diseases are rare, our case demonstrates several of the elements that can alert the vigilant clinician to the possibility of one of these disorders. For example, the patient had cryptogenic stroke presenting at a young age, an unexplained retinal disorder, and the dyad of diabetes and early onset senorineuronal hearing loss. The presence of any of these features should prompt consideration of a mitrochondrial disorder.

Given their complexity and relative rarity, mitochondrial diseases will continue to present a diagnostic challenge for clinicians. As we become better at recognizing and understanding them, however, the hope is that we will be able to provide better care to affected patients. ●

Author disclosures

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