

MELAS Masquerading as a Systemic Vasculitis

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Abstract: Mitochondrial encephalomyopathy, lactic acidosis, and stroke (MELAS) is a mitochondrial genetic disorder caused by a point mutation, resulting in the substitution of guanine for adenine at nucleotide 3243 (A3243G). It is a multisystem disorder with variable manifestations and typically presents between the first and third decades of life. It should be suspected if a patient exhibits stroke-like episodes before age 40, encephalopathy characterized by seizures, dementia, or both, and lactic acidosis, ragged-red fibers in muscle, or both.

We present the case of a 26-year-old white man suspected with primary central nervous system vasculitis admitted to our facility with profound constipation from severe intestinal dysmotility. Although his gastrointestinal and neurologic symptoms did not meet criteria for a specific vasculitic syndrome, his symptoms and blood test abnormalities were concerning for such a process. MELAS was included in our differential diagnosis because his symptoms failed to fit a defined vasculitic process. When genetic testing documented the presence of the point mutation A3243G, his diagnosis was changed. This case illustrates the importance of considering a mitochondrial genetic disorder in the differential diagnosis of patients who present to Rheumatologists with suspected unusual or atypical vasculitic symptoms.

Key Words: MELAS, systemic vasculitis, stroke-like events, encephalopathy, ragged red fibers, headache, lactic acidosis

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Mitochondria are subcellular organelles on which all mammalian cells are dependent for the production of energy. Mitochondrial dysfunction can have a tremendous impact on cellular function. We present the case of a patient with MELAS, or mitochondrial encephalomyopathy, lactic acidosis, and stroke-like events, a clinical syndrome caused by a mitochondrial DNA (mtDNA) point mutation whose initial presentation mimicked a vasculitis. Deficient adeno-

sine 5'-triphosphate (ATP) production from faulty electrochemical gradients inside mitochondria leads to widespread cellular dysfunction, especially in tissues heavily dependent on oxidative metabolism, such as the brain and skeletal muscle. It is important for a rheumatologist to recognize MELAS because the protean clinical manifestations of this disorder can mimic conditions treated by our specialty.

CASE

The Rheumatology Service at our hospital was consulted to evaluate a 26-year-old white man admitted for profound constipation. At the time of his presentation to the emergency room in mid-April 2006, the patient reported having anorexia and diarrhea for about 2 weeks along with nausea and feculent vomiting for 2 to 3 days. During his initial evaluation, he was febrile and abdominal X-ray film revealed a profuse amount of stool. The results of several serologic tests at the time of presentation are listed in Table 1. The patient's elevated white blood cell count and C-reactive protein were concerning, and a serum lactate level drawn to screen for bowel ischemia or infarction was also elevated (see Table 1). This prompted further evaluation with a CT abdomen/pelvis, which revealed massive dilation of the sigmoid colon caused by densely packed stool throughout the large intestine and secondary blockage of the small intestines. The patient was taken to the operating room and 18 pounds of feces removed. Biopsies of the stomach, small intestine, and colon were obtained. Review of the biopsy specimens revealed a patchy but marked neutrophilic infiltrate and scattered eosinophils within the vessel walls of capillaries and small vessels of the colon only. Larger vasculature throughout the stomach and intestines were spared. Histologically, the vessel wall inflammation suggested a small vessel vasculitis, and thus rheumatology was consulted.

Just 6 weeks earlier, the patient had been hospitalized at our facility by the neurology service for evaluation of acute encephalopathy. He had been in his usual state of health up to early February 2006 when he experienced new migraine-like headaches and patchy cortical blindness. His mother reported that during this time the patient also had a personality change, noting a new interest in gambling. The patient was hospitalized when he experienced a rapid decline in his mentation, developed a new left facial numbness and experienced a brief loss of consciousness associated with bizarre eye movements and head jerking. A very thorough evaluation was performed; however, most of his work-up was unremarkable with the exception of an initially elevated cerebrospinal fluid protein level and an electroencephalogram testing that demonstrated periodic lateralized epileptiform discharges and continuous

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TABLE 1. Results of Serologic Tests at the Time of the Patient's Presentation to the Emergency Room

	Patient's Value	Normal Range
White blood cell count	14.6 ($\times 10^9/L$)	4.3–10.0 ($\times 10^9/L$)
Hemoglobin	13.9 g/dL	13.5–17.5 g/dL
C-reactive protein	27.5 mg/dL	0–1.0 mg/dL
Lactate level	3.5 mmol/L	0.5–2.2 mmol/L
Blood urea nitrogen	7.14 mmol/L	1.79–7.85 mmol/L
Creatinine	70.7 $\mu\text{mol/L}$	61.9–132.0 $\mu\text{mol/L}$

arrhythmic slow activity in the right hemisphere. Magnetic resonance imaging (MRI) of his brain confirmed the presence of a right hemispheric process revealing gyral edema and regions of laminar cortical necrosis within the right parietal and occipital lobes (Fig. 1). Magnetic resonance angiography however showed normal intracranial vasculature without evidence of aneurysm or intracranial stenosis. Brain biopsy was performed, which revealed marked lymphohistiocytic inflammation of pia-arachnoid and Virchow-Robin space with numerous capillaries and small vessels demonstrating neutrophilic infiltration. Hemosiderin laden macrophages suggested the extravasation of blood. Associated reactive changes were noted without dural involvement. Based on these abnormalities, a diagnosis of primary central nervous system vasculitis was made. No treatment was instituted since the patient had gradually started to improve, and he was discharged for further monitoring.

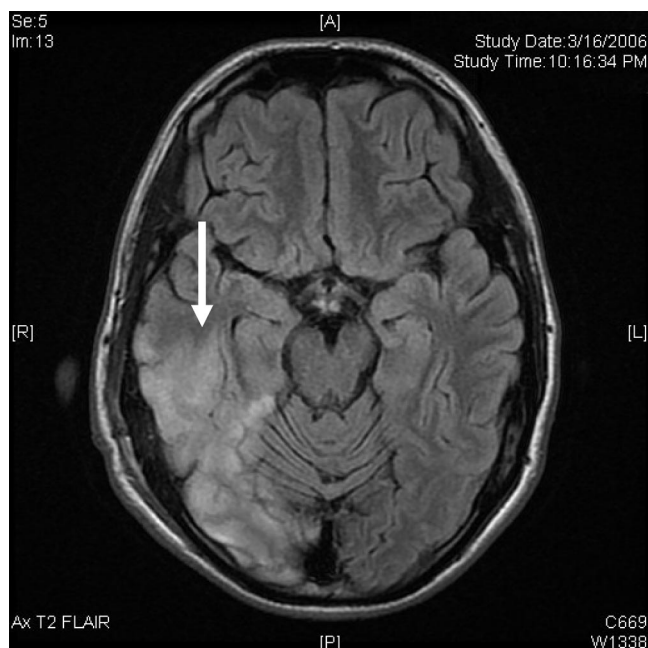


FIGURE 1. Axial T2 weighted FLAIR magnetic resonance image of the brain. Gyral edema and regions of laminar cortical necrosis within the right parietal and occipital lobes are noted (arrow). At the time of the study, a new area of restricted diffusion was seen within the optic radiations of the right temporal lobe.

TABLE 2. Results of Key Autoimmune and Infectious Serologic Tests Performed During Patient's Hospitalization

Test	Patient's Result
ANA	Negative
RPR	Nonreactive
PR3-ANCA	Negative
MPO-ANCA	Negative
Rheumatoid factor	Negative
Hepatitis B virus surface antibody	Negative
Hepatitis C virus antibody	Negative

Although the patient had no chronic medical conditions, he did have a history of 2 previous bouts of intestinal dysmotility. In March 2001, he was hospitalized for sigmoid volvulus and underwent laparoscopic surgery. Postoperatively, he remained in the hospital for 2 months because of difficulty advancing his diet, recurrent vomiting, and ileus. In January 2002, he was hospitalized for laparoscopic correction of a superior mesenteric artery syndrome. Again, his postoperative course was complicated by difficulty tolerating advances in his diet, episodic vomiting, but this time by constipation and colonic dysmotility as well. Evaluation failed to reveal an etiology for his complicated postoperative course. He had a normal developmental history, meeting age appropriate goals and progressing through school without limitations. He had no difficulty meeting the physical demands of military basic training or fitness testing. He did not smoke tobacco routinely but did have an occasional alcoholic drink. The patient had 2 older siblings who were in a good state of health, and his mother and father were both alive and well.

Upon our evaluation, the patient was found to have an unremarkable clinical examination. He had no organomegaly, no synovitis, no evidence of skin tightening, no digital ulcerations, and no cutaneous findings to support a vasculitic or autoimmune condition. The results of various serologic tests are shown in Table 2. Despite having initially elevated markers of inflammation, he had no proteinuria, hematuria, renal dysfunction, or evidence of hemolysis. He did have a persistently mild elevation in his serum lactic acid. Initially, on the basis of the results of his colon biopsy and previous diagnosis of primary central nervous system vasculitis, our service felt that the patient had evolved to an unspecified systemic vasculitis. In our differential diagnosis, we included MELAS because his symptoms failed to meet a specific vasculitic condition and his history of encephalopathy/seizures, elevated lactic acid levels, and stroke-like event seemed unusual for a previously healthy adult. Although genetic testing for MELAS was being performed, cytotoxic therapy was considered but the patient suffered multiple consecutive infections, persistent encephalopathy, and pulmonary embolism. As a temporizing measure, IVIg 400 mg/kg was given for a total of 5 days. When genetic testing for MELAS returned with the detectable presence of the characteristic A3243G point mutation, his diagnosis was definitively made. L-carnitine therapy was instituted shortly after his diagnosis but with no obvious immediate clinical effect.

TABLE 3. Common Initial Clinical Manifestations of MELAS

Initial Symptom or Sign	Frequency (%)
Seizures	28
Recurrent headaches	28
Gastrointestinal symptoms (recurrent vomiting, anorexia)	25
Short stature/stopped growth	18
Stroke	17
Altered consciousness/impaired mentation	12
Hearing loss	10
Exercise intolerance	10
Visual symptoms	8
Developmental delay	5

Modified from DiMauro S, Hirano M. MELAS [Myopathy, Mitochondrial-Encephalopathy-Lactic Acidosis-Stroke; Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes]. October 13, 2005. Available at <http://www.geneclinics.org>. Accessed May 15, 2006.

DISCUSSION

MELAS is a disorder of mitochondrial genetics characterized by a point mutation in the gene *MT-TL1*, which encodes tRNA^{Leu(UUR)}.¹ This tRNA gene sequence encompasses 78 nucleotides of the 16,569 positions found in normal mitochondrial DNA. To date, 5 point mutations have been found to occur in the *MT-TL1* gene, but the 2 most common are the adenine to guanine substitution at nucleotide position 3243 (A3243G) and the thymine to cytosine substitution at nucleotide position 3271 (T3271C). In combination, both of these point mutations are found in nearly 90% of patients diagnosed with MELAS, with the A3243G point mutation responsible for nearly 80% of cases. With either point mutation, a taurine modification deficiency at the anticodon wobble position occurs leading to a codon specific translational defect and likely translational depression of ND6, a component of Complex I (NADH-coenzyme Q reductase) of the respiratory chain.² Complex I gathers electrons from reduced cofactors such as NADH and FADH₂ formed by the metabolism of carbohydrates, fats, and proteins. These electrons then flow down an electrochemical gradient, and energy liberated in the process is used to pump protons out of the mitochondrial matrix into the intermembrane space. The proton gradient established is then used by Complex V (ATP synthase) to synthesize ATP.³

Since all cells rely on mitochondrial synthesis of energy to perform daily functions, the symptoms and signs of MELAS are protean and can reflect a multisystem disorder.¹ Typically, patients present during childhood but presentation over the age of 20 can occur as in our patient. It is exceptionally rare to be diagnosed over the age of 40, although there are patients in the medical literature who have manifested other nonspecific symptoms years before the full syndrome was recognized.⁴ Early development is typically normal with the exception that some patients have short stature. Common initial clinical manifestations of MELAS are listed in Table 3.¹ Seizures can be accompanied by stroke-like episodes of transient paresis, cortical blindness, or altered mentation. Headaches eventually occur in most affected individuals, have a migrainous quality, and can be severe at the

beginning of a stroke-like event. Recurrent vomiting and anorexia are also common symptoms, with pseudo-obstruction of the bowel possible. To our knowledge, our patient's acute and profound intestinal blockage was the most severe documented. Over time patients with MELAS may also develop sensorineural hearing loss, diabetes mellitus, congestive heart failure from cardiomyopathy, cardiac conduction blocks, or progressive external ophthalmoplegia. When symptoms are focal, as they initially were in our patient, an autoimmune disorder, vasculitic process, or myositis may be confused with MELAS.

To diagnose a patient with MELAS, criteria established by Hirano et al in 1992 are used. On the basis of their review of 69 cases in the literature and the 2 common point mutations associated with the disorder, they stated that a diagnosis of MELAS should be suspected based on 3 invariant criteria⁵:

1. stroke-like episode before the age of 40,
2. encephalopathy characterized by seizures, dementia, or both, and
3. lactic acidosis, ragged red fibers, or both.

Ragged red fibers refer to the appearance of muscle fibers on light microscopy when stained with succinate dehydrogenase. Sporadic muscle fibers accumulate mutant mtDNA which leads to massive mitochondrial proliferation and markedly increased staining.⁶ The diagnosis could be considered "secure" if a patient also had at least 2 of the following:

1. normal early development,
2. recurrent headaches, or
3. recurrent vomiting.

Although some patients with MELAS may have clinical manifestations that overlap with other mitochondrial genetic disorders, Hirano et al maintained that "clinical differences can almost always be discerned."⁵ Sporadic cases of MELAS or relatives of a patient with MELAS who have the same mtDNA mutation may have an incomplete syndrome or just one finding (such as diabetes or hearing loss) rather than the cardinal MELAS features. Acknowledging this limitation of their clinical definition, Hirano et al recommended analysis of mtDNA in partial or confusing cases.⁵ Although our patient met the established clinical criteria, we pursued serum genetic testing fearing misdiagnosis. Serum genetic testing currently available for MELAS can potentially yield false-negative tests because of the mitochondrial genetic phenomenon called heteroplasmy. Heteroplasmy refers to the mixture of mutant and wild-type mtDNA that can occur in a cell. The amount of mutated mtDNA can vary widely from organ to organ and even between cells. It is possible for leukocytes or platelets in a serum sample to have too low to detect levels of mutant mtDNA, thus yielding a negative test result. Submitting a different specimen, with the most reliable being muscle tissue, can potentially yield a different though more accurate result.

Although typical pathologic changes in MELAS can be found on muscle biopsy, in our patient tissue samples were obtained only from involved organs. Case reports of antemortem brain biopsy specimens have demonstrated changes

specifically in cerebral small vessels (smaller than 250 μm in diameter) while sparing larger vessels. Arterioles, specifically pial arterioles, show narrowing of the lumen from metabolic damage to the endothelial cells. Secondary smooth muscle hypertrophy may occur. Surrounding cortex and white matter demonstrate changes such as gliosis, presence of reactive gemistocytes, spongiiform degeneration, and pyknotic appearing neurons suggestive of apoptosis.⁴ On MRI, signal changes involving both the gray and white matter with preferential involvement of the posterior temporal, occipital, and parietal tissues is noted. Newer MRI techniques, which use an apparent diffusion coefficient, have shown that this coefficient is elevated after a clinical event and is consistent with the presence of extracellular edema.^{7,8} Such changes reflect cortical injury and vasogenic edema in the white matter and suggest the presence of a metabolic disorder.⁸ Similar vascular and cortical changes were noted on our patient's brain biopsy specimen and on his MRI. The marked lymphohistiocytic inflammation and involvement of only small vessels on biopsy, and cortical laminar necrosis on imaging, suggest a nonvasculitic process. Somewhat confounding was the extravasated blood and the hemosiderin laden macrophages noted on brain biopsy. Although the specimens were reviewed twice with our Pathology department who felt strongly about the presence of a small vessel vasculitis, the significance of this remained unclear, especially since similar extravasation was not noted on the bowel biopsy specimens. It is possible this was artifactual or a local hemorrhagic complication. In contradistinction, the histopathologic abnormalities seen in focal arterial ischemic events reflect cellular necrosis, with widespread cell swelling and an acute inflammatory response. MRI shows perfusion deficits in established vascular territories and typically involves larger vessels. Additionally, the apparent diffusion coefficient is depressed, which reflects cellular edema and impending necrosis.⁷

The prognosis for patients with MELAS is variable but in general worse than that seen in other mitochondrial disorders.⁹ Patients typically die between 10 and 35 years of age, often from intercurrent infections, intestinal obstruction, recurrent stroke-like events, or status epilepticus. In an 8-patient follow-up series from Taiwan, 50% died within 7 years of presentation, with 25% having significant mental deterioration and 25% remaining stable. Substantial morbidity occurs from the cumulative effects of the stroke-like episodes and seizures. Deafness, if it develops, further contributes to the morbidity of this disorder. Treatments to date have mainly focused on dietary supplementation of vitamins or cofactors, specific coenzyme Q10, L-carnitine, and L-arginine. Efficacy for dietary supplementation is currently limited to case reports, although some observational studies suggest that L-arginine, a substrate for the synthesis of nitric oxide and creatine, may reduce the severity and frequency of acute

stroke-like episodes.¹⁰ A randomized, placebo controlled trial published in 2006 assessing the efficacy of dichloroacetate was ended early because of peripheral nerve toxicity, which lead to a high rate of medication discontinuation.¹¹ Our patient was started on L-carnitine 100 mg twice a day shortly after diagnosis, but as of the writing of this case report, it was too early to assess the efficacy of this therapy.

In summary, MELAS is a mitochondrial genetic disorder with multiorgan involvement but which can present with atypical symptoms. Examination as well as serologic and radiologic studies may often show nonspecific findings, further confounding the diagnosis. This was the case with our patient's elevated white blood cell count and C-reactive protein. It is possible both were abnormal because of the stress of his dysmotility or concomitant infection complicating his presentation. Our patient was a diagnostic enigma during the 3-week period it took his genetic testing results to return to our facility. Fortunately, his results returned before the institution of cytotoxic therapy for a presumed unspecified systemic vasculitis. With population-based studies suggesting that mitochondrial disorders may be at least as common (1 case per 8500 people) as other sporadic or inherited neurologic illnesses, they should be more frequently incorporated in our differential diagnosis as Rheumatologists.⁸

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