

CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

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Case 13-2017: A 41-Year-Old Man with Hearing Loss, Seizures, Weakness, and Cognitive Decline

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PRESENTATION OF CASE

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Dr. Haatem M. Reda: A 41-year-old man was seen in the neurology clinic of this hospital because of seizures, weakness, and cognitive decline.

The patient had a history of migraine headaches, sensorineural hearing loss, and chronic proteinuria. He had been in his usual health until approximately 2 years before presentation to this hospital, when his wife noted subtle changes in his personality and behavior, including short-tempered and argumentative reactions that “didn’t make sense.” One year before presentation to this hospital, headache, malaise, and fatigue occurred for approximately 1 week, followed by the sudden onset of difficulty speaking; over a period of several hours, he progressed from being able to use well-formed but incorrect words to being completely unable to speak and partially unable to write. Later that day, he was admitted to another hospital.

Dr. William A. Copen: Magnetic resonance imaging (MRI) of the brain was performed 1 year, 10 months, and 7 months before the patient’s presentation to this hospital (Fig. 1). All the studies revealed global brain parenchymal volume loss that was far more advanced than would be expected for a patient of this age. On the first study (Fig. 1A), T₂-weighted images showed a mildly expansile, hyperintense intraaxial lesion that was centered in the anterior left temporal lobe and extended posteriorly and superiorly into the inferior parietal lobule. This lesion disproportionately involved the subcortical white matter, although the cortex was also affected. There was no evidence of associated restricted diffusion or magnetic susceptibility effect and no abnormal enhancement on contrast-enhanced images. On the two subsequent studies (Fig. 1B and 1C), the lesion maintained similar signal characteristics but decreased in size; in fact, the third study revealed that the lesion had resolved almost completely. The results of magnetic resonance angiography and venography were normal.

Dr. Reda: On the patient’s admission to the other hospital, 1 year before presentation to this hospital, laboratory testing revealed mild anemia, with a mean cor-

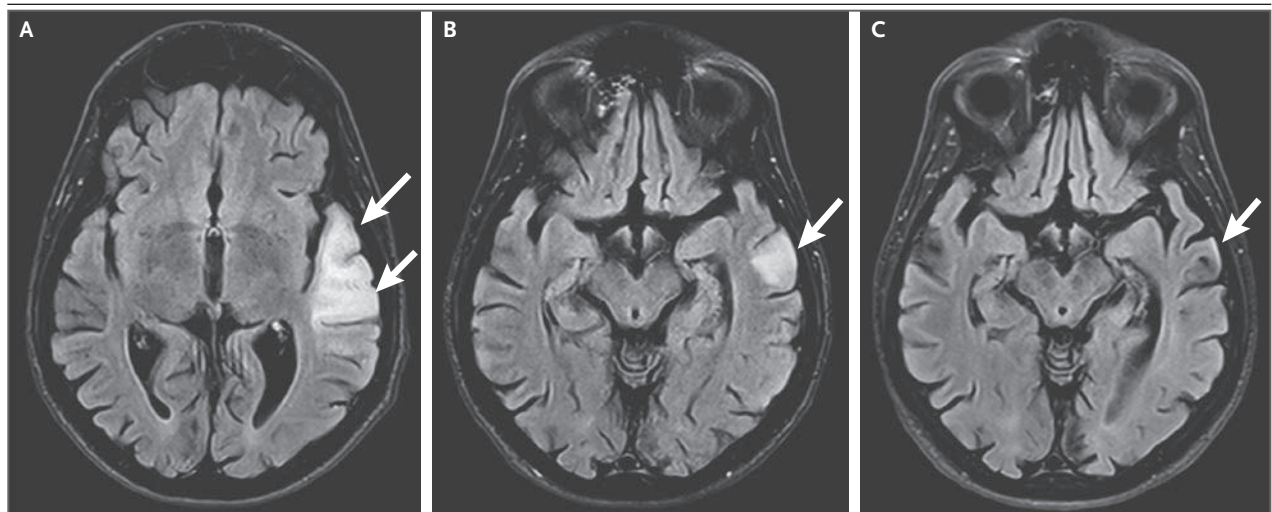


Figure 1. MRI Studies of the Brain Obtained before Presentation.

Axial T₂-weighted fluid-attenuated inversion recovery images of the brain were obtained 1 year, 10 months, and 7 months (Panels A, B, and C, respectively) before the patient's presentation to this hospital. A hyperintense lesion, which is centered in the anterior left temporal lobe (arrows), is largest on the first image, markedly smaller on the second image, and almost completely inapparent on the last image.

puscular volume of 65 fl (reference range, 79 to 92); other test results, including the results of cerebrospinal fluid analysis, are shown in Table 1. A diagnosis of stroke was made, and therapy with aspirin and a lipid-lowering agent was begun. The patient was discharged home. His language abilities gradually improved over the next 2 months but did not return to baseline, and his headaches persisted.

One month after discharge, while the patient was at home, he had a generalized tonic-clonic seizure that was witnessed by his wife. Therapy with levetiracetam was begun, and no further seizure activity occurred. During the next 11 months, he had fluctuating focal neurologic symptoms, rapidly progressive cognitive decline, weakness, and gait instability, along with nearly daily diffuse headaches, muscle cramps in his calves, and weight loss of 11 kg.

One month before the patient's presentation to this hospital, blood levels of cholesterol and lipids and results of liver- and renal-function tests were normal; other test results are shown in Table 1. During the 2 weeks before presentation, the patient's wife noted that his behavior had become more childlike, with rambling speech, impulsivity, and anger. His gait, balance, and coordination worsened, although he did not fall, and swallowing difficulties developed. He was referred to the neurology clinic at this hospital.

The patient was right-handed. He had congenital short stature. When he was 25 years of age, sensorineural hearing loss (worse on the right side than on the left) developed; it gradually worsened and led to the use of hearing aids. Proteinuria was noted when he was 25 years of age. In the past, a clinical diagnosis of gout had been made after an episode of swelling and pain in the left big toe. Medications were levetiracetam, lisinopril, and a multivitamin. He had no known allergies. He was married, had a young child, and had lived in the southwestern United States until 3 weeks before this presentation, when his family moved to be near relatives in New England. He was a lawyer but had been receiving disability benefits since the onset of this illness. He drank alcohol in moderation and smoked tobacco occasionally. His mother was of French Canadian and Irish descent; she had reportedly had lupus nephritis with antinuclear antibodies, diabetes mellitus, and colitis and was described as needing rest frequently when walking. His father was of Hungarian and Italian descent and had diabetes mellitus and coronary artery disease. A maternal aunt and uncle had diabetes mellitus, and the same uncle also had sensorineural hearing loss. He had nine siblings who ranged in height from 150 to 163 cm; some were reportedly well and others had mild gastrointestinal dysmotility or symptoms of the irritable bowel syndrome, senso-

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	1 Yr before This Presentation, Other Hospital	1 Mo before This Presentation, Other Hospital	On Presentation, This Hospital
Blood				
White-cell count (per mm ³)	4500–11,000	13,800 (ref 4000–9600)	8300 (ref 4000–10,000)	7430
Differential count (%)				
Neutrophils	40–70	64	72.3	
Lymphocytes	22–44	29	15.6	
Monocytes	4–11	6	9.1	
Eosinophils	0–8	1	2.7	
Basophils		0	0.2	
Immature granulocytes			0.1	
Erythrocyte sedimentation rate (mm/hr)	0–13			16
Albumin (g/dl)		3.9 (ref 3.5–5.0)	4.3 (ref 3.2–5.2)	
IgG (mg/dl)		784 (ref 758–1612)		
Epstein–Barr virus DNA	Not detected	Not detected		
Cytomegalovirus DNA	Not detected	Not detected		
Antineutrophil cytoplasmic antibodies	Negative			Negative
Antibodies to proteinase 3 and myeloperoxidase	Negative			Negative
Antinuclear antibodies	Negative at 1:40 and 1:160 dilutions			Positive at 1:40 dilution and negative at 1:80 and 1:160 dilutions; speckled pattern
Cerebrospinal fluid				
Color	Clear	Clear		
Turbidity	Colorless	Colorless		
White-cell count in tube 3 (per mm ³)		0 (ref 0–5)		
Albumin (mg/dl)		14 (ref 5–30)		
IgG (mg/dl)		1.7 (ref 0.5–7.7)		
IgG index‡		0.60 (ref 0.25–0.75)		
<i>Borrelia burgdorferi</i> antibodies	Not detected	Not detected		
Herpes simplex virus types 1 and 2 DNA	Not detected	Not detected		
Herpes simplex virus types 1 and 2 IgM antibodies	Not detected	Not detected		
JC virus DNA	Not detected	Not detected		
Varicella–zoster virus DNA	Not detected	Not detected		

* The term ref denotes the reference range at the other hospital.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

‡ The cerebrospinal fluid (CSF) IgG index is the ratio of CSF IgG to CSF albumin divided by the ratio of blood IgG to blood albumin (with both the CSF and the blood albumin levels measured in milligrams per deciliter).

rineural hearing loss, anxiety, and β -thalassemia trait.

On examination, the patient appeared cachectic. The blood pressure was 112/72 mm Hg, the pulse 83 beats per minute, the temperature 36.8°C, and the oxygen saturation 99% while he was breathing ambient air. His weight was 40.5 kg, and his height 152 cm. During the examination, he reached out to grab the examiner's hand and glasses inappropriately. The Montreal Cognitive Assessment score was 25 on a scale ranging from 0 to 30 (with higher scores indicating better cognitive function); points were deducted because the patient made errors of visuospatial function, repetition, and fluency and incorrectly identified a glove as a hand and a feather as a leaf. He had ataxic dysarthria with telegraphic speech and frequent tangential ramblings that were difficult to interrupt. The optic disks were flat and without pallor. The visual fields were normal on confrontation testing. The pupils were round, equal, and reactive, without Horner's syndrome or a relative afferent pupillary defect. Upward gaze was markedly restricted, lateral gaze moderately restricted, and downward gaze mildly restricted in each eye. There was mild bifacial weakness and markedly impaired hearing bilaterally, even while the patient was wearing hearing aids. There was minimal weakness of shoulder abduction bilaterally. The muscle bulk, tone, and strength of the neck and limbs were otherwise normal, without tremor, other adventitious movements, or fasciculations. Finger–nose–finger and heel–knee–shin testing revealed subtle dysmetria; rapid alternating movements were slightly irregular. No truncal ataxia was present while the patient was seated. He swayed prominently while he stood with his feet together and eyes closed. His gait was mildly ataxic, and he could not take more than two tandem steps without losing his balance. The remainder of the neurologic and general examinations was normal.

Laboratory testing revealed a mild secondary carnitine deficiency, which was thought to be dietary. The lactic acid level was initially normal but subsequently increased and remained elevated; the highest level was 8.3 mmol per liter (75 mg per deciliter; reference range, 0.5 to 2.2 mmol

per liter [5 to 20 mg per deciliter]). Other test results are shown in Table 1.

Diagnostic procedures were performed.

DIFFERENTIAL DIAGNOSIS

Dr. Reda: I was involved in the care of this patient and am aware of the diagnosis. This 41-year-old man has findings of a progressive encephalopathy, and the differential diagnosis for this entity encompasses many categories of disease, including vascular, inflammatory, autoimmune, infectious, metabolic, toxic, neoplastic, neurodegenerative, and psychiatric disorders. The presence of a relapsing and remitting course with multifocal brain lesions of the white or gray matter (or both) narrows the possibilities, and accounting for the pace of the disease course helps to narrow them further.

Some of the patient's signs and symptoms — including the proteinuria, sensorineural hearing loss, migraines, and short stature — began many years before this presentation. He had had subtle personality changes for a couple of years. In the differential diagnosis, conditions that progress over a period of years include vascular dementia, multiple sclerosis, dural arteriovenous fistula, CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), moyamoya disease, and mitochondrial diseases, such as MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes).

Although the patient had indolent symptoms for several years, he had a relapsing and remitting but overall rapidly progressive course during the year and a half before this presentation. Conditions on the list that progress over a period of weeks or months include infiltrative primary neoplasms of the central nervous system (CNS) (e.g., primary lymphoma of the CNS), fulminant multiple sclerosis, primary angiitis of the CNS and other vasculitides that tend to involve the CNS (e.g., Susac's syndrome), autoimmune encephalopathies (e.g., neuronal antibody-associated limbic encephalitis and SREAT [steroid-responsive encephalopathy associated with autoimmune thyroiditis]), progressive multifocal leukoencepha-

lopathy, and Creutzfeldt–Jakob disease. During periods of metabolic stress, patients with multisystem mitochondrial diseases have acute or subacute deterioration.

PRIMARY ANGIITIS OF THE CNS

The characteristics of this patient's brain lesions on imaging studies led to an initial diagnosis of stroke. Multifocal ischemic strokes are the hallmark of primary angiitis of the CNS, a rare vasculitis of small and medium-sized blood vessels (arterioles and venules) in the brain. Most patients present after a weeks- or months-long syndrome of varied neurologic and psychiatric symptoms and signs, some of which may be attributable to multifocal ischemic stroke; in some cases, the syndrome progresses in a stepwise manner.¹ Headaches and cognitive decline eventually become the predominant features, although cranial neuropathies, ataxia, seizures, and other focal and diffuse deficits are common.² By definition, this syndrome affects only the CNS; in this patient, the presence of signs and symptoms that refer to the peripheral nervous system and other organ systems rules out the diagnosis of primary angiitis of the CNS.

CREUTZFELDT–JAKOB DISEASE

Brain lesions with characteristics indicative of stroke are occasionally seen in patients with Creutzfeldt–Jakob disease.^{3–5} Although Creutzfeldt–Jakob disease is rare overall, it is relatively common among patients with rapidly progressive dementia.⁶ It is a degenerative prion-related spongiform encephalopathy that is rapidly progressive and ultimately fatal (within months or a few years at most after onset) and is associated with gait and limb ataxia and myoclonus.⁷ Additional clinical features, including the pace of progression, depend on the molecular subtype of the involved prion protein (which may give rise to visual, cerebellar, thalamic, or striatal dysfunction).^{8,9} Patients with Creutzfeldt–Jakob disease would not be expected to have myopathy, renal disease, or hearing loss.

OTHER VASCULAR DISEASES

Lesions with characteristics indicative of stroke or a strokelike condition may occur with other vascular conditions, including venous sinus thrombosis and inherited vasculopathies, such as CADASIL and moyamoya disease. Venous sinus thrombosis in the absence of hypercoagulability is not

expected to be recurrent and is often hemorrhagic. This patient's vascular imaging studies revealed no evidence of an inflammatory or other medium-sized or large vasculopathy affecting the circle of Willis or its branches.

STEROID-RESPONSIVE ENCEPHALOPATHY ASSOCIATED WITH AUTOIMMUNE THYROIDITIS

Patients with SREAT may present with a relapsing and remitting course with recurrent focal neurologic deficits, progressive encephalopathy, personality changes, seizures, and ataxia, but the presence of focal brain lesions would be unusual. Additional features of SREAT include pyramidal signs and myoclonus.¹⁰ Systemic symptoms and signs (except for thyroid dysfunction) and involvement of the peripheral nervous system would not be expected in a patient with SREAT.

MITOCHONDRIAL DISEASES

This patient's presenting symptoms, which began 1 year before his presentation to this hospital, seemed to occur during a febrile illness. He later had further acute deterioration in the context of other infections, including pneumonia. These factors probably indicate a susceptibility to increased metabolic demand. Of the metabolic disorders that can cause strokelike episodes, most are inborn errors of metabolism that occur in childhood. However, patients with a multisystem mitochondrial encephalomyopathy may become symptomatic during their first, second, or third decade.¹¹

In a complex case such as this one, which involves disparate symptoms and diffuse or multifocal (indeed, multisystem) localization, it can help to focus on a syndromic diagnosis in order to refine the differential diagnosis. In addition to a fluctuating but overall progressive encephalopathy that was characterized by impulsivity and psychosis, this patient had seizures and myopathy that was manifested by ophthalmoparesis and proximal muscle weakness. He had migraines, sensorineural hearing loss, short stature, cachexia, and renal dysfunction (proteinuria). Although he did not have diabetes, several of his family members did, and some family members had problems related to gastrointestinal motility. These multisystem derangements are characteristic of mitochondrial diseases, which disproportionately affect tissues that are highly metabolically active, especially during hypermetabolic states (e.g., systemic infection).¹² The patient had recurrent,

acute, and transient episodes of focal neurologic dysfunction that corresponded to reversible, focal cortical and subcortical brain lesions with characteristics indicative of stroke. It is notable that these lesions did not conform to major cerebral arterial territories. Although the patient's lactic acid level was normal when it was first tested, he was not under metabolic stress at the time; subsequent assays performed during hospitalization for acute decline revealed persistent lactic acidosis.

Multisystem mitochondrial disorders that cause encephalomyopathy include the Leigh syndrome, MERRF (myoclonic epilepsy with ragged-red fibers), the Kearns–Sayre syndrome, mitochondrial neurogastrointestinal encephalopathy, and MELAS. The Leigh syndrome is a childhood illness. MERRF may occur in adulthood, but myoclonus is a prominent feature and was not present in this patient. Focal neurologic deficits are rare in the Kearns–Sayre syndrome, and patients with mitochondrial neurogastrointestinal encephalopathy present with gastrointestinal symptoms early in the disease course.^{11,12} At the time of this patient's presentation, MELAS was the most likely diagnosis.

DR. HAATEM M. REDA'S DIAGNOSIS

MELAS (mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes).

PATHOLOGICAL DISCUSSION

MUSCLE BIOPSY

Dr. Derek H. Oakley: The diagnostic procedure was a biopsy of the left quadriceps (Fig. 2). Sections showed muscle with increased variation in fiber

size and occasional regenerating fibers. A Gomori trichrome stain did not show ragged-red fibers. Stains for the enzymatic activity of ATPase showed type 2 fiber predominance and mild fiber-type grouping. A combined stain for the activity of cytochrome *c* oxidase (COX; complex IV) and succinate dehydrogenase (SDH; complex II) was performed to evaluate mitochondrial function. Diminished COX activity and retained SDH activity can be seen in patients with mitochondrial disease; indeed, this patient had scattered COX-negative, SDH-positive fibers. Electron microscopy further revealed occasional enlarged mitochondria and some mitochondria with complex cristae, as well as capillaries with thickened basement membranes. These findings were not specific, but a more detailed mitochondrial evaluation was recommended because of the clinical concern for a mitochondrial disorder in this patient, the presence of more COX-negative fibers than would be expected for a patient of this age, and the subtle mitochondrial abnormalities on electron microscopy.

GENETIC TESTING

Dr. Amel Karaa: MELAS is a genetically heterogeneous disorder caused by at least 32 individual mutations. The most common mutation is m.3243A→G in the *MT-TL1* gene, which encodes transfer RNA Leu(UUR). Since this patient had a phenotype that was highly suggestive of MELAS, targeted analysis of the mitochondrial DNA was performed. Although analysis of tissue samples obtained from the most affected parts of the body provides the highest yield for uncovering mutations in the mitochondrial DNA, this patient underwent whole-blood analysis; given the

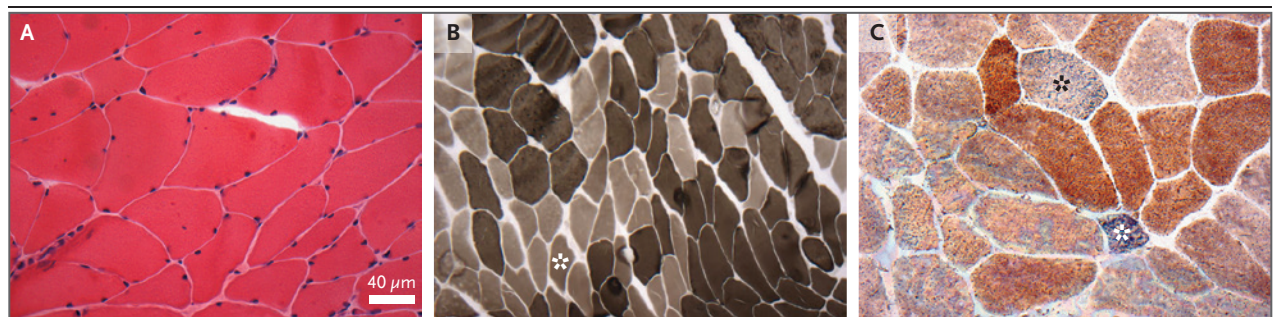


Figure 2. Muscle Specimens Obtained on Biopsy.

A hematoxylin and eosin stain (Panel A) shows mildly increased variation in fiber size. A stain for ATPase activity at a pH of 9.4 (Panel B) shows type 2 fiber predominance (dark fibers) and a single group of type 1 fibers (asterisk). A combined stain for cytochrome *c* oxidase (COX) and succinate dehydrogenase (SDH) activity (Panel C) shows COX-negative, SDH-positive fibers in blue (asterisks).

severity of his disease, we were confident that his heteroplasmy level would be high enough to be detected. Saliva, urine, and muscle samples and buccal swabs may be used for genetic testing for MELAS; blood has the lowest yield because of negative selection and high cell turnover. Thus, a negative blood test for MELAS does not rule out the diagnosis.¹³

This patient had the m.3243A→G mutation in the *MT-TL1* gene, which confirmed the diagnosis of MELAS. His heteroplasmy level was not provided by the diagnostic laboratory.

DISCUSSION OF MANAGEMENT

Dr. Karaa: MELAS is one of the most common mitochondrial diseases caused by a mutation in the mitochondrial DNA, with an estimated prevalence of 8 to 236 cases per 100,000 persons.¹⁴ It affects both children and adults and is characterized by multiorgan involvement. Disease onset varies, but initial symptoms often occur between 20 and 30 years of age; this timeline is consistent with the onset of hearing loss, short stature, proteinuria, and exercise intolerance during adolescence and the early 20s in this patient. The disease course includes episodes of temporary worsening that are triggered by stressors (e.g., infections, fever, dehydration, overexertion, and even emotional distress). This patient started having personality and behavioral changes soon after the birth of his son, which may have been an emotional trigger. Similar to this patient, approximately 40% of patients with MELAS have strokelike episodes by the time they are 40 years of age, with a lifetime prevalence of stroke of 99%.¹⁵ Several other clinical features can be seen in MELAS, including gastrointestinal dysmotility, neuropathy, ataxia, and psychiatric symptoms. It is notable that this patient did not have diabetes, since diabetes is also a common feature of this disease.

There is currently no specific treatment for MELAS, so the focus is on supportive therapy for the chronic symptoms and management of acute events. After the diagnosis is made, a comprehensive survey of organ function is required, followed by periodic monitoring, since complications can be subclinical and, if they are identified, can be treated proactively in a multidisciplinary fashion.¹⁶ After this patient's initial evaluation, a nutrition

consultation was recommended to improve his caloric intake. He was cachectic, and nutritional support in patients with weight loss and failure to thrive is highly recommended to improve energy production. A regular endurance and resistance exercise regimen was advised; such regimens have been shown to promote transfer of wild-type mitochondrial DNA from satellite muscle cells to mature myofibers, thereby decreasing the heteroplasmy level.¹⁶ This patient was counseled on avoiding stressors, getting adequate rest, and minimizing the intake of toxins (e.g., alcohol, tobacco, and certain medications that can cause inhibition of the electron transport chain or worsen lactic acidosis).

The patient's seizure disorder was treated with lamotrigine and levetiracetam (with avoidance of valproic acid, since it can cause severe liver damage), and it was well controlled. He did not receive any specific treatment for headaches other than occasional over-the-counter medications.

Despite the lack of any convincing efficacy or safety data from clinical trials, cofactors and vitamin supplementation that are aimed at increasing ATP production and decreasing oxidative stress have been a mainstay of therapy for mitochondrial diseases.^{16,17} This treatment is known as the "mito cocktail." Infusion of intravenous L-arginine (the precursor of nitric oxide) has recently been shown to prevent or lessen the severity of acute stroke episodes, most likely by inducing vasodilation and improving tissue oxygenation. Also, long-term therapy with oral L-arginine is thought to decrease the frequency of strokelike episodes.^{17,18} This patient was prescribed both oral L-arginine and coenzyme Q10.

Unfortunately, a few days after we saw the patient in clinic (approximately 1 month after presentation to this hospital), he was admitted to this hospital with worsening behavioral changes that led to police intervention, and the recommended end-organ survey tests were not performed. The only abnormalities that were seen on review of his outpatient blood work were a very low vitamin D level of 15 ng per milliliter (39 nmol per liter; reference range, 33 to 100 ng per milliliter [86 to 260 nmol per liter]) and low total and free carnitine levels, which reflected a secondary dietary deficiency. Both abnormalities were treated with supplementation.

During the patient's hospital stay, he received

a plan for the initial management of MELAS. This included intravenous hydration and caloric support with glucose infusion, prompt nutritional evaluation, and electrocardiography and echocardiography for the monitoring of cardiomyopathy and arrhythmias, which can develop suddenly and lead to severe complications or death. Monitoring of kidney function is important, especially in a patient with tubulopathies and proteinuria, which can lead to worsened protein wasting and thus contribute to failure to thrive and weight loss. During the patient's hospitalization, he continued to have stroke-like episodes with behavioral abnormalities. These were attributed to CNS impairment as a result of energy failure, emotional distress (i.e., awareness of health decline with no cure), decreased caloric intake as a result of his erratic eating behavior and gastrointestinal problems, and the increased metabolic demand that was caused by MELAS itself. His dementia, cachexia, and agitation worsened, and the agitation became difficult to control despite the use of multiple therapies. He had an episode of fever due to aspiration pneumonia that was followed by a seizure episode, and he had a urinary tract infection with enterobacter, which was treated with broad-spectrum antibiotic agents (with avoidance of aminoglycosides and linezolid, since they can cause decreased mitochondrial function).

Right ventricular hypokinesia developed, with diastolic dysfunction and congestive heart failure. The patient's ejection fraction was 21%; he had left ventricular hypertrophy, for which he received aggressive diuresis, a treatment that eventually led to acute kidney injury, pulmonary edema, and hyperkalemia. The family decided to change from care measures to comfort measures, and the patient died in the hospital less than 1 month after admission. An autopsy was performed.

Several clinical trials of therapies for the broad group of mitochondrial diseases are under way (ClinicalTrials.gov numbers, NCT02255422 and NCT02805790). These trials are still in early stages (phase 2) and investigate the use of several compounds with different mechanisms of action. A phase 1–2 double-blind, placebo-controlled study (NCT02367014) of elamipretide for primary mitochondrial myopathy recently showed promising improvement in the 6-minute walk-

ing distance among patients in the treatment group, as compared with those in the placebo group.

PATHOLOGICAL DISCUSSION

Dr. Oakley: A postmortem examination of the patient revealed short stature (height, 152 cm) and severe cachexia (body-mass index [the weight in kilograms divided by the square of the height in meters], 15.1). The general autopsy revealed evidence of aspiration pneumonia, acute cystitis, diffuse biventricular interstitial fibrosis of the heart, and bilateral renal hypoplasia with focal segmental glomerulosclerosis and acute tubular necrosis.

Examination of a specimen from the left psoas major muscle (Fig. 3) revealed many small, angulated fibers, including some in groups. Numerous ragged-red fibers were present on a Gomori trichrome stain, although they had not been previously detected on biopsy specimens. Stains for ATPase activity showed type 2 fiber predominance, with pronounced atrophy of type 2 fibers and mild fiber-type grouping. A combined stain for COX–SDH activity showed numerous COX-negative, SDH-positive fibers. The presence of ragged-red fibers in association with COX-negative, SDH-positive fibers is indicative of an underlying mitochondrial cytopathy. The superimposed atrophy of type 2 fibers is consistent with muscle disuse.

On neuropathological examination, the brain weighed 1140 g and its external surface was largely unremarkable. However, examination of cut sections revealed widespread areas of cortical thinning that were most pronounced in the temporal and occipital lobes and the inferior parietal lobule (Fig. 4A). The cerebral cortex in these areas showed focal splitting that resembled laminar necrosis. The white matter and deep gray nuclei were unremarkable on gross examination. The cerebellar vermis was mildly atrophic and had narrowing of folia.

Microscopic examination revealed a pattern of damage characteristic of MELAS (Fig. 4B and 4D). The cerebral cortex had multifocal serpiginous areas of necrosis and gliosis that predominantly involved the deeper cortical layers at the gyral crests. These lesions, which resembled laminar necrosis, contained proliferations of delicate vas-

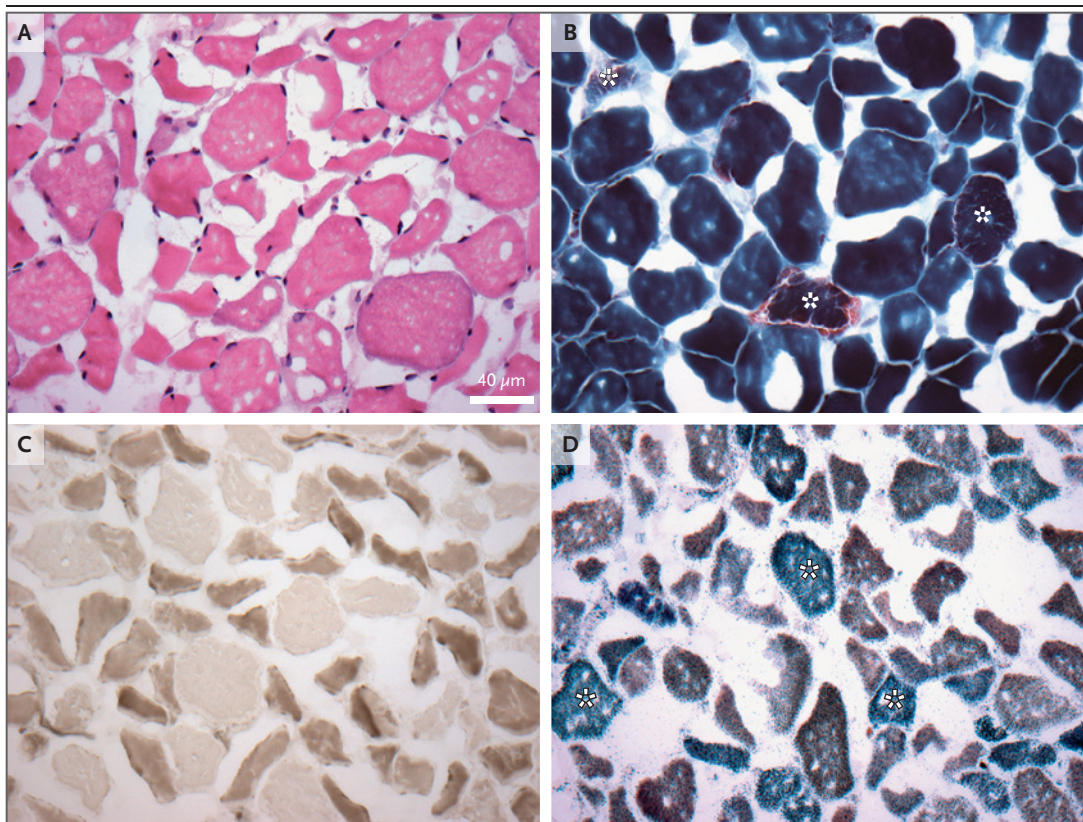


Figure 3. Muscle Specimens Obtained at Autopsy.

A hematoxylin and eosin stain (Panel A) shows markedly increased variation in fiber size. A Gomori trichrome stain (Panel B) shows numerous ragged-red fibers (asterisks). A stain for ATPase activity at a pH of 9.4 (Panel C) shows that the type 2 fibers (dark fibers) are more atrophic than the type 1 fibers (light fibers). A combined stain for COX–SDH activity (Panel D) shows numerous COX-negative, SDH-positive fibers in blue (asterisks).

culature and were surrounded by dense gliosis. There was moderate gliosis of the deep white matter that was most pronounced in the occipital and parietal lobes. The cerebellum had moderate depletion of granule cells and attenuation of neuropil in the molecular layer, predominantly in the vermis. Moderate hypoxic–ischemic changes were present in scattered neurons throughout the brain.

In the frontal cortex, a combined stain for COX–SDH activity revealed occasional COX-negative, SDH-positive neurons (Fig. 4C and 4E). In contrast, numerous COX-negative, SDH-positive endothelial and smooth-muscle cells were present in leptomeningeal and cortical vessels. This pattern of preferential vascular loss of COX activity has been reported previously in association with MELAS.¹⁹

Overall, the autopsy findings, which include a characteristic pattern of damage to the cerebral cortex and muscle abnormalities consistent with a mitochondrial cytopathy, are diagnostic of MELAS.

Dr. Thomas Byrne (Neurology): How do you evaluate patients who have an individual symptom, such as migraine, along with some infarcts on MRI? Do you test for MELAS in all such patients?

Dr. Karaa: For patients to receive a diagnosis of MELAS, they must have all the symptoms listed in the acronym, including strokes or strokelike episodes. When a patient has repeated lesions associated with a strokelike episode that are of an unclear cause, with or without lactic acidosis and other neurologic features (e.g., migraines), MELAS should be considered, especially

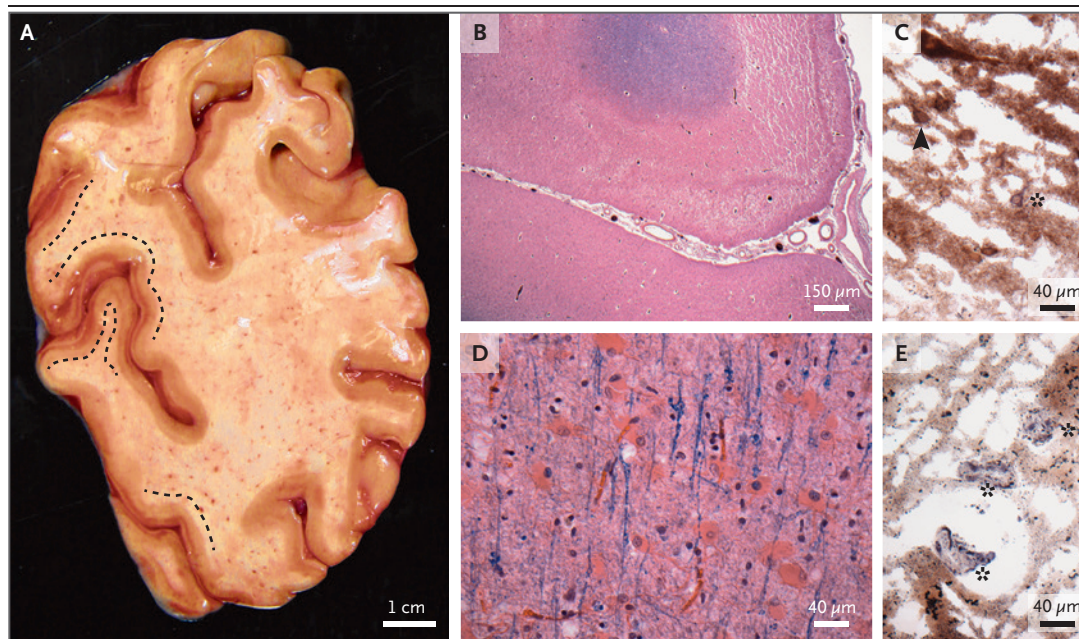


Figure 4. Brain Specimens Obtained at Autopsy.

A photograph of a gross coronal section at the parieto-occipital junction shows cortical lesions that resemble laminar necrosis (Panel A, dashed lines). Combined Luxol fast blue and hematoxylin and eosin staining shows a lesion that resembles laminar necrosis at a gyral crest (Panel B) and neuronal loss and gliosis adjacent to lesions (Panel D). In the frontal cortex, combined staining for COX–SDH activity shows COX-negative, SDH-positive neurons (Panel C, asterisk) and vessels (Panel E, asterisks) in blue; retained COX and SDH activity in neurons is shown in brown (Panel D, arrowhead).

if symptoms associated with the m.3243A→G mutation are present in the family history. In this patient's family, there were 10 siblings, and the patient was the only one with the full MELAS syndrome; other family members had one or two symptoms or were completely asymptomatic. It is possible that cases of diabetes that are hard to control, are associated with features of both type 1 and type 2 diabetes, and lead to early insulin requirement may represent m.3243A→G mutations. It is also possible that some migraine headaches that are difficult to control and have a vasogenic component represent m.3243A→G mutations. It is difficult to know whether to test more patients with these conditions for mitochondrial disease. One thing that may help is obtaining a thorough family history. If other family members have individual symptoms associated with the m.3243A→G mutation — such as hearing loss, diabetes, and migraines — testing for the mutation may be indicated. Although blood testing is available, it may not reveal the

mutation, especially in milder forms. In such cases, DNA testing of tissue may be necessary.

Dr. Joseph C. Glykys (Pediatric Neurology): Given this patient's family history, did you test other family members?

Dr. Karaa: No. I am still in touch with the patient's family, but none of them wish to be tested for now.

ANATOMICAL DIAGNOSIS

MELAS (mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes).

This case was presented at Neurology Grand Rounds.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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