A 41-Year-Old Man With New Headache and Altered Mental Status

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A 41-year-old man with a history of diet-controlled diabetes mellitus developed acute-onset confusion and mild holocephalic headache relieved by acetaminophen. His confusion worsened over the course of 5 days, and he was subsequently brought to his primary care physician by his family, where he was noted to have an altered mental status. He was admitted to a local hospital for evaluation. Magnetic resonance imaging (MRI) of the brain showed an area of restricted diffusion on diffusion-weighted imaging in the left temporal cortex, consistent with a subacute infarction. Diagnostic testing with lumbar puncture, computed tomography (CT) angiogram of the head and neck, transthoracic echocardiogram (TTE) without saline contrast bubble, fasting lipid analysis, hypercoagulability analysis, and routine laboratory analysis showed only a hemoglobin of 11.9 g/dL (ref 14.0-17.5 g/dL), an elevated creatine phosphokinase (CPK) at 510 U/L (ref 55-380 U/L), elevated postprandial glucose at 252 mg/dL, a low-density lipoprotein (LDL) cholesterol of 122 mg/dL (ref 1-100 mg/dL), and a high-density lipoprotein (HDL) cholesterol of 32 mg/dL (ref 40-85 mg/dL). The patient was diagnosed with a subacute ischemic stroke in the left temporal lobe, producing a Wernicke aphasia, and was discharged home on aspirin and pravastatin with primary care follow-up to better control his elevated blood glucose.

Over the course of the next 9 months the patient was readmitted to the hospital 4 times for progressively worsening mental status, aggressive behaviors, right-hand side weakness, and seizures. Brain imaging on each admission showed progressive infarcts in multiple vascular territories (Figure 1). During this time, a transesophageal echocardiogram (TEE) with saline contrast bubble was performed, which showed flow across the interatrial septum with Valsalva maneuver, consistent with a small patent foramen ovale (PFO). However, lower extremity doppler ultrasound and MR venogram of the pelvis failed to show evidence of deep vein thrombosis. The patient was placed on aspirin and warfarin for presumed paradoxical embolus and transferred to this facility for further evaluation.

Other than impaired glucose tolerance, his medical history was significant only for hearing loss, requiring the use of hearing aids. The patient worked in a cannery until he became ill, with

no known exposures to chemicals or infectious agents while at work or at home. He did not smoke tobacco, drink alcohol, or use illicit drugs. The patient's mother, father, and one of his brothers had diabetes. Of his 5 sisters, 4 had early miscarriages. His paternal aunt and first cousin both had a seizure disorder.

On admission to this hospital, temperature was 36.8°C, blood pressure 107/61 mm Hg, pulse 103 beats/min, respiratory rate 18/min, and oxygen saturation 97% on room air. General physical examination showed a cachectic patient in no apparent distress, with anicteric sclerae, a clear oropharynx, a regular cardiac rhythm with normal s1 and s2 heart sounds, lungs clear to auscultation, a nontender and nondistended abdomen, urinary incontinence requiring a diaper, and ecchymosis on the right anterior shin. Neurologic examination showed an alert patient able to regard the examiner but oriented only to person, without dysarthria but speaking in 1- to 3-word sentences with perseveration and echolalia, unable to follow commands, normal cranial nerves, antigravity strength in all 4 extremities but favoring the left over the right, 3+ deep tendon reflexes throughout, with slightly brisker reflexes on the right-hand side compared to the left, withdrawal to pain in all 4 extremities, and a narrow but unsteady gait.

A repeat MRI of the brain with and without contrast was unchanged from the most recent study performed at the referring hospital (Figure 1E). The patient was placed on telemetry monitoring. A repeat TEE with saline contrast bubble showed no evidence of right-to-left shunt, atrial or ventricular thrombus, or pathology within the aortic arch. A diagnostic cerebral angiogram was performed, which showed no evidence of atherosclerosis or vasculitis within the cerebral arteries. An extensive serum laboratory analysis was performed, the results of which are shown in Table 1.

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Figure 1. Imaging of progressive multifocal infarcts. A, Noncontrast CT scan of the brain 10 days after initial presentation showing a focal area of encephalomalacia in the left temporal lobe, representing an old infarct as well as an area of low attenuation and cortical effacement extending into the left parietal lobe, representing new ischemia. B, Further extension of the infarct into the left parietal lobe, as well as an area of new ischemia in the right anterior temporal lobe 1 month later. C, Progression of the infarctions to involve the left occipital lobe approximately 4 months after initial presentation. D, 4 months later, the areas of infarction have enlarged and now involve the right parietal lobe. E, Fluid-attenuated inversion recovery sequence (FLAIR) MRI of the brain 9 months after the patient's initial presentation showing multiple confluent areas of extensive infarction involving bilateral temporal, parietal, and occipital lobes, with associated volume loss. CT indicates computed tomography; MRI, magnetic resonance imaging.

The patient underwent a repeat lumbar puncture. The cerebrospinal fluid (CSF) was clear and colorless, with 2 white blood cells and 650 red blood cells, glucose of 69 mg/dL (serum glucose 153 mg/dL), elevated protein at 89 mg/dL (ref 15-50 mg/dL), lactate dehydrogenase level of 15 U/L, elevated lactate at 6.5 mmol/L (ref 1.1-2.8 mmol/L), normal pyruvate, no oligoclonal bands present, and an elevated immunoglobulin G (IgG) index at 0.8 (ref 0.3-0.6). Polymerase chain reaction on the CSF for varicella zoster virus and herpes simplex 1 and 2 viruses was negative. Cerebrospinal fluid cryptococcal antigen, *Borrelia burgdorferi* antibodies, and venereal disease research laboratory (VDRL) test for syphilis were also negative. A diagnostic test was performed.

Stroke in the Young

Discussant: Nerissa U. Ko

In this case of recurrent ischemic stroke in a 41-year-old man, an expanded evaluation for stroke in the young is warranted. In addition to the standard evaluation for ischemic stroke, which typically includes vascular imaging of the cervical and cerebral arteries by CT or MR angiography, assessment for a cardioembolic source with echocardiogram and telemetry monitoring, and measurement of traditional vascular risk factors such as hypertension, hyperlipidemia, and diabetes, there are a number of special diagnostic considerations in those who present with stroke at a young age. Stroke in the

Table 1. Serum Laboratory Tests^a

Metabolic	Hypercoagulable	Autoimmune/Inflammatory	Infectious
LDL 49	Antithrombin III >140% (79-120%)	ANA	Blood cultures
HgA1c 5.6%	Free protein S 24% (53-137%)	RF	Tuberculin test
Lipoprotein-a 77 (<75 nmol/L)	Protein C	C3 complement 162 (71-159 mg/dL)	HIV Ab
CPK 803 (55-380 U/L)	Factor V Leiden mutation	C4 complement	Hep B serologies
Lactate ^b	MTHFR mutation	Anti-myeloperoxidase Ab (p-ANCA)	Hep C Ab
TSH 0.31 (0.4-4.0 mIU/L)	Prothrombin 20210A mutation	Anti-proteinase 3 Ab (c-ANCA)	RPR
Free T4 7 (9-24 pmol/L)	Homocysteine	Anti-SSA Ab	Cryptococcal Ag
	Anti-cardiolipin Abs	Anti-SSB Ab	Coccidioides Ab
	Anti- β_2 glycoprotein I IgG and IgM	Anti-TPO Abs	Borrelia burgdorferi Ab
	Lupus anticoagulant	Anti-Tg Abs	
		Cryoglobulins	
		ESR 41 (<10 mm/h)	

Abbreviations: Ab, antibody; Ag, antigen; LDL, low-density lipoprotein; HgA1c, hemoglobin A1c; CPK, creatine phosphokinase; TSH, thyrotropin; MTHFR, methylenetetrahydrofolate reductase; Ig, immunoglobulin; ANA, antinuclear antibody; RF, rheumatoid factor; ANCA, antineutrophil cytoplasmic antibodies; SSA, Sjögren syndrome antigen A; SSB, Sjögren syndrome antigen B; TPO, thyroperoxidase; Tg, thyroglobulin; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; Hep B, hepatitis B; Hep C, hepatitis C; RPR, rapid plasma reagin.

^a Tests that are highlighted in boldface are abnormal, with the normal reference range given in parentheses after the abnormal value.

^b Serum for test was drawn after making the patient walk.

young, usually defined as occurring before age 45, has broad differential considerations including hematologic disorders, infectious and inflammatory conditions, vascular dissection and atypical vasculopathies, as well as rare genetic and metabolic disorders.

Disorders of coagulation are a common cause of ischemic strokes in the young. Screening patients for the most common coagulopathies that may lead to stroke is imperative, especially if a prior history or family history of thrombosis (including history of miscarriage in women) is elicited. Standard evaluation includes measuring protein C, protein S, and antithrombin III activity; assessing for the presence of factor V Leiden, methylenetetrahydrofolate reductase, and prothrombin 20210A gene mutations; measuring homocysteine levels; and testing for the presence of antiphospholipid antibodies. Caution should be used when testing the activity of proteins in the coagulation pathway, as they can be altered in the acute phase of stroke.^{1,2} Screening for hemoglobinopathies in certain patient populations is also warranted. In this case, the patient had elevated antithrombin III activity, reduced protein S activity, and a positive lupus anticoagulant. Warfarin decreases protein C and protein S levels, which may explain the patient's low free protein S activity.

Structural heart disease is more prevalent in children and young adults with ischemic stroke.³ Transesophageal echocardiography may be superior to TTE in evaluation for valvular and septal cardiac pathology that have been associated as a cause of cardioembolic strokes.⁴⁻⁶ Performing TEEs routinely on all stroke patients is neither feasible nor cost-effective as part of a routine stroke evaluation. However, in young patients who present with ischemic stroke, a TEE with saline contrast bubble study should be performed to better assess for aortic arch disease, valvular disease, atrial appendage thrombus, and

right-to-left shunt.⁷ In this case, a TEE with saline contrast suggested the presence of a small PFO, although this was not confirmed on a repeat study. The risk of paradoxical embolus increases with the size of the atrial or ventricular septal defect and the degree of cardiac or pulmonary right-to-left shunting. Recurrent ischemic strokes in those with right-to-left shunt and documented deep vein thrombosis should be treated with anticoagulation. Secondary prevention of ischemic strokes in those with small PFOs remains controversial, and a number of clinical trials are currently comparing treatment with PFO closure versus medical management in this patient population.^{8,9} Regardless of the outcome of these current studies, a stroke in the presence of a small PFO should prompt evaluation for etiologies other than paradoxical embolus.

Multifocal Strokes

In this case, the patient had recurrent ischemic strokes in multiple vascular territories in the absence of vascular lesions, structural heart disease, or other known vascular risk factors other than a mildly elevated LDL cholesterol level and impaired glucose tolerance. Evaluation for proximal embolic sources and diffuse processes that can affect multiple vessels is warranted. Cardiac arrhythmia such as atrial fibrillation can be difficult to detect, and prolonged cardiac rhythm monitoring with a 21- or 30-day event monitor has been shown to have a higher diagnostic yield compared to standard evaluation.¹⁰ Strokes that cross multiple vascular territories should include assessment of both primary and secondary causes of CNS vasculitis and infectious vasculopathies. Workup includes CSF and serum studies, cerebral angiogram, and likely tissue biopsy.

Autoimmune vasculitis associated with systemic lupus erythematosus, Sjögren disease, and antiphospholipid antibody syndrome can cause ischemic stroke. In this case, the patient's lupus anticoagulant test returned positive, and the erythrocyte sedimentation rate (ESR), a general marker of inflammation, was mildly elevated. His altered mental status could be a neuropsychiatric manifestation of CNS lupus, but he had no other stigmata of lupus, and the rest of his autoimmune serologies, notably the antinuclear antibody (ANA), are negative. Primary CNS vasculitis can be challenging to diagnose and often leads to both ischemic and hemorrhagic strokes in multiple vascular territories. The patient underwent a diagnostic cerebral angiogram that did not show changes in the caliber of the intracranial vasculature, but the elevated protein in his CSF would be consistent with CNS vasculitis. Definitive diagnosis of this disease often requires a brain biopsy for pathologic confirmation. Bacterial, viral, mycobacterial, syphilitic, fungal, and borreliosis infections of the CNS can all cause vasculopathies, leading to ischemic stroke. In this case, the time course of the patient's strokes over 9 months rules out bacterial causes for stroke, and all other infectious etiologies are essentially ruled out with a noninflammatory CSF profile on lumbar puncture in an immunocompetent patient. Appropriate diagnostic testing for selected infectious agents can assist in the evaluation where the presence of inflammation in the CSF is in question.

Atypical stroke presentation with headaches, seizures, and cognitive changes should raise the suspicion for nonarterial etiologies such as venous sinus thrombosis, dural arteriovenous fistulas, and metabolic or genetic/mitochondrial disorders. Sinus thrombosis can cause venous ischemia in atypical vascular territories, often presenting with nonspecific headache, seizure, and encephalopathy. Standard cross-sectional imaging can easily miss these subtle vascular changes. In this case, the normal cerebral angiogram rules out CNS venous thrombosis and dural arteriovenous fistula as a cause for the patient's strokes.

Although rare, genetic and metabolic disorders such as Fabry disease, homocystinuria, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and mitochondrial disorders can cause recurrent ischemic strokes in younger patients. Family history, unusual provocative symptoms, and involvement of other organ systems can provide more evidence for further testing. Although these disorders tend to occur in patients younger than the one presented here, laboratory and imaging data that support a mitochondrial disorder in this patient include an elevated CPK and CSF lactate level (although CSF lactate can be elevated after ischemic stroke), and the presence of mild basal ganglia calcifications and mild cerebellar atrophy (both of which are nonspecific findings in the elderly, but more unusual if found in the young). Data that would argue against this diagnosis include a normal serum lactate after walking and a normal CSF pyruvate level. Further assessment with tissue biopsy and, ultimately, genetic testing is needed.

Diagnostic Result

Nerve conduction studies were performed in the left lower extremity and were normal. An electromyogram of the left upper and lower extremities was also normal. The patient underwent a right temporal lobe brain biopsy and a right quadriceps muscle biopsy. The results are shown in Figures 2 and 3, respectively. Pathologic examination of these specimens showed no evidence of vasculitis, or a metabolic or mitochondrial disorder. Elevated CSF lactate was confirmed with proton MR spectroscopy. The *MT-TL1* mitochondrial gene was sequenced and showed the presence of the A3243G mutation, confirming the diagnosis of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS).

Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes

Discussant: Jonathan B. Strober

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes is a mitochondrial disorder that has been linked to a number of mutations in the mitochondrial genome and rare nuclear mutations (Table 2). Approximately 80% of patients with MELAS have the A3243G mutation in the mitochondrial DNA (mtDNA) leucine transfer RNA gene, which leads to dysfunction in mitochondrial protein synthesis and consequent problems with aerobic energy metabolism. How MELAS leads to stroke is not known. Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes typically presents in patients 4 to 15 years old, but the clinical presentation is highly variable. Because of heteroplasmy, different tissues, or even different populations of cells within the same tissue, can be affected to varying degrees. This not only causes phenotypic variability but can also make diagnosis challenging, even by pathologic examination. Histology often shows "ragged red fibers" in muscle on Gomori trichrome stain, and enzymatic testing can show respiratory chain defects. In addition, electron microscopy can show morphologic abnormalities of mitochondria. In this case, pathology did not show obvious changes in muscle or brain tissue, and the diagnosis was confirmed only on genetic testing. A significant finding in this case was a markedly elevated CSF lactate, much higher than one typically finds even in cases of ischemic stroke.¹² The CSF pyruvate level was normal but caution should be exercised when interpreting pyruvate levels as the analyte is unstable and will significantly degrade prior to measurement. Finally, the patient's CPK level was persistently elevated, likely an indication of the myopathy associated with MELAS.

Other than the problems for which the syndrome is named, MELAS can also be associated with migraine headache, seizures, endocrinopathies including diabetes mellitus, exercise intolerance, cardiac disease, hearing loss, growth retardation, and neuropsychiatric dysfunction. In this patient, MELAS likely led to the development of headaches, hearing loss, hypothyroidism, diabetes, seizures, and perhaps neuropsychiatric manifestations,

Figure 2. Brain biopsy. A, The hematoxylin and eosin (H&E) stain is normal. B, The glial fibrillary acidic protein (GFAP) stain shows associated astrogliosis. C, The CD68 stain shows no macrophages. D, The neuronal nuclei (NeuN) stain shows focal neuronal loss. Alcian blue/periodic acid Schiff and trichrome stains were normal (not shown). Level sections showed no evidence of vasculitis. These findings are nonspecific and represent astrogliosis and focal neuronal loss.

although the latter 2 problems could also have been caused by metabolic stroke. The spreading lesions seen on imaging are typical of MELAS. Another clue in this case is the family history, which is significant for early miscarriages in 4 of the 5 sisters. Because MELAS is largely due to mtDNA mutations, it is almost always inherited through the mother.

There have been no randomized clinical trials demonstrating a benefit in the treatment of MELAS. Primary treatment goals are to increase adenosine triphosphate production and flow of electrons through the electron transport chain. To this end, treatment with nicotinamide, succinate, cytochrome C, coenzyme Q10, and idebenone (a synthetic analogue of CoQ10) has been tried with variable success.¹³ Dichloroacetate, which increases consumption of pyruvate and lowers lactate levels in MELAS, failed in a randomized placebo-controlled treatment trial for MELAS and had significant peripheral neurotoxicity side effects.¹⁴

Supplementation with L-arginine, which is an important precursor to nitric oxide and is decreased during stroke-like episodes in MELAS, has shown promise in decreasing the severity of symptoms during stroke-like episodes and the frequency with which they occur.^{15,16} Aerobic exercise has also been shown to have some benefit in MELAS but concern has been raised about the possibility of increasing the number of mtDNA mutations after significant exercise. Medications that can worsen the disease and should be avoided include haloperidol, valproic acid, and inhaled general anesthetics. In general, prognosis is poor, with progressive neurologic deterioration and cardiac dysfunction.

Declaration of Conflicting Interests

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Figure 3. Muscle biopsy. A, The hematoxylin and eosin (H&E) stain is normal. B, Nicotinamide adenine dinucleotide tetrazolium reductase (NADH) staining shows scattered moth-eaten fibers. C, ATPase staining shows only mild variation of muscle fiber diameters (~40% type I and 60% type 2) with small type 2 fiber groups and scattered angulated atrophic fibers. D, Succinic dehydrogenase (SDH) staining is normal. The trichrome stains were also normal (not shown). These findings demonstrate nonspecific and minimal myopathic changes with no evidence of a mitochondrial abnormality. No ragged red fibers and no subsarcolemmal crescents were identified.

Table 2. Most Common Mitochondrial DNA Mutations Associated With MELAS^{11,a}

Percentage of Affected Individuals	Mutation	Mitochondrial Gene	Affected Gene Product
~80%	A3243G	MT-TL1	tRNA-Leu
~7.5%	T3271C	MT-TL1	tRNA-Leu
<5%	A3252G	MT-TL1	tRNA-Leu

^a The presence of these mutations can be tested for through targeted mutation analysis. In all, 23 other mutations have been identified that require sequence analysis/mutation screening for identification. These tests are available through multiple different laboratories, a list of which can be found at http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/clinical_disease_id/53880?db=genetests.

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Keywords

MELAS syndrome, mitochondrial diseases, stroke, paradoxical embolism, patent foramen ovale, thrombophilia, CNS vasculitis, cerebral thrombosis

References

1. Van Cott EM, Laposata M, Prins MH. Laboratory evaluation of hypercoagulability with venous or arterial thrombosis. *Arch Pathol Lab Med.* 2002;126(11):1281-1295.
2. Khor B, Van Cott EM. Laboratory evaluation of hypercoagulability. *Clin Lab Med.* 2009;29(2):339-366.
3. Williams LS, Garg BP, Cohen M, Fleck JD, Biller J. Subtypes of ischemic stroke in children and young adults. *Neurology.* 1997; 49(6):1541-1545.
4. de Bruijn SF, Agema WR, Lammers GJ, et al. Transesophageal echocardiography is superior to transthoracic

- echocardiography in management of patients of any age with transient ischemic attack or stroke. *Stroke*. 2006;37(10):2531-2534.
5. de Abreu TT, Mateus S, Carreteiro C, Correia J. Therapeutic implications of transesophageal echocardiography after transthoracic echocardiography on acute stroke patients. *Vasc Health Risk Manag*. 2008;4(1):167-172.
 6. Gupta N, Lau C, Al-Dehneh A, et al. Importance of performing transesophageal echocardiography in acute stroke patients older than fifty. *Echocardiography*. 2010; Jun 7, PMID 20546010 (Epub ahead of print).
 7. Leung DY, Black IW, Cranney GB, et al. Selection of patients for transesophageal echocardiography after stroke and systemic embolic events. Role of transthoracic echocardiography. *Stroke*. 1995;26(10):1820-1824.
 8. Messe SR, Silverman IE, Kizer JR, et al. Practice parameter: recurrent stroke with patent foramen ovale and atrial septal aneurysm: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2004;62(7):1042-1050.
 9. O'Gara PT, Messe SR, Tuzcu EM, Catha G, Ring JC. Percutaneous device closure of patent foramen ovale for secondary stroke prevention: a call for completion of randomized clinical trials: a science advisory from the American Heart Association/American Stroke Association and the American College of Cardiology Foundation. *Circulation*. 2009;119(20):2743-2747.
 10. Tayal AH, Tian M, Kelly KM, et al. Atrial fibrillation detected by mobile cardiac outpatient telemetry in cryptogenic TIA or stroke. *Neurology*. 2008;71(21):1696-1701.
 11. Brouns R, Sheorajpanday R, Wauters A, De Surgeloose D, Marien P, De Deyn PP. Evaluation of lactate as a marker of metabolic stress and cause of secondary damage in acute ischemic stroke or TIA. *Clin Chim Acta*. 2008;397(1-2):27-31.
 12. Ikejiri Y, Mori E, Ishii K, Nishimoto K, Yasuda M, Sasaki M. Idebenone improves cerebral mitochondrial oxidative metabolism in a patient with MELAS. *Neurology*. 1996;47(2):583-585.
 13. Kaufmann P, Engelstad K, Wei Y, et al. Dichloroacetate causes toxic neuropathy in MELAS: a randomized, controlled clinical trial. *Neurology*. 2006;66(3):324-330.
 14. Koga Y, Ishibashi M, Ueki I, et al. Effects of L-arginine on the acute phase of strokes in three patients with MELAS. *Neurology*. 2002;58(5):827-828.
 15. Koga Y, Akita Y, Nishioka J, et al. L-arginine improves the symptoms of strokelike episodes in MELAS. *Neurology*. 2005;64(4):710-712.
 16. MELAS. NCBI GeneReviews, 2005. <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=melas>. Accessed July 31, 2010.