RESIDENT & FELLOW SECTION

Section Editor
John J. Millichap, MD

Clinical Reasoning: A complicated case of MELAS

Nikkie Randhawa, MD
Laura Wilson, MD
Sharanpal Mann, MD
Sandra Sirrs, MD
Oscar Benavente, MD

Correspondence to
Dr. Randhawa:
nikkierandhawa@gmail.com

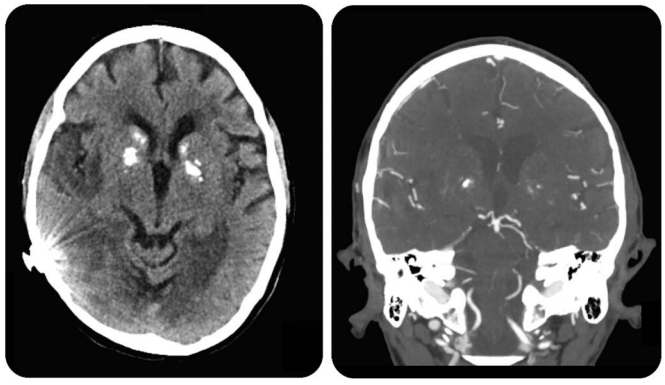
SECTION 1

A 48-year-old right-hand-dominant woman presented to the emergency department with sudden onset of visual loss of her left visual field. She had a complicated medical history—end-stage renal disease requiring renal transplant 6 years prior to presentation secondary to biopsy-proven focal segmental glomerulosclerosis (FSGS), coronary artery disease, left atrial enlargement due to pulmonic stenosis, progressive sensorineural hearing loss 10 years prior and subsequent placement of a right cochlear implant, hypertension, and type 2 diabetes mellitus for the last year. At presentation, the patient's medications included cotrimoxazole prophylaxis, mycophenolate mofetil, tacrolimus, insulin, and folic acid. On examination, she was of short stature and had a low-grade fever and a left homonymous hemianopsia (L-HH). Within the next 3 weeks, she subsequently developed further visual disturbance to the point of being cortically blind in addition to new left upper extremity paresthesias. Initial CT head scan showed a subacute right occipital infarct and bilateral basal ganglia calcification. Subsequent CT imaging done 3 weeks later demonstrated interval development of new left temporoparietal and left occipital infarcts (figure, A). CT angiogram showed intracranial stenoses affecting basilar artery, both posterior cerebral arteries, and to a lesser degree bilateral anterior cerebral arteries and middle cerebral arteries, suggestive of possible atherosclerosis, but were not believed to be hemodynamically significant (figure, B). Due to her cochlear implant, significant streak artifact affected the interpretation of her CT scans and precluded her from obtaining an MRI.

Questions for consideration:

1. What is your differential for stroke in young patients?
2. Which syndromes link renal disease and stroke?

Figure Noncontrast CT head (axial view) and CT angiography (coronal view)



(A) Multiple territory infarcts (R middle cerebral artery and bilateral posterior cerebral artery [PCA] territories) as well as bilateral basal ganglia calcification. Streak artifact is secondary to patient's cochlear implant. (B) Bilateral PCA narrowing suspicious for intracranial atherosclerosis vs vasculitis.

GO TO SECTION 2

From the University of British Columbia, Vancouver, Canada.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

SECTION 2

While stroke in adults under the age of 50 years shares similar risk factors to those seen in older populations (hypertension, dyslipidemia, atrial fibrillation, diabetes mellitus, and smoking), emphasis is placed on investigation of other less common etiologies since stroke in younger adults is generally less frequent.[1] As outlined in the table, these include inflammatory, infectious, genetic, hematologic, mitochondrial, and other vascular pathologies.[1] Other important etiologies in the differential diagnosis of stroke mechanism in young adults are genetic diseases, such as Fabry disease, which is associated with a family history of renal impairment and deafness, and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). Shortly after admission, the patient developed a left, unilateral, throbbing, migraine-type headache and was admitted to the intensive care unit with fever and new-onset generalized tonic-clonic seizures. The recent strokes and possible infectious complications in an immunosuppressed patient were considered in the etiology of the seizures. EEG revealed focal

Table Etiologies of ischemic stroke in young adults

Cardiac
Patent foramen ovale
Atrial septal aneurysm
Atrial myxoma
Atrial fibrillation/flutter
Cardiomyopathy
Myocarditis
Myocardial infarction
Cardiac surgery
Endocarditis
Rheumatic heart disease
Prosthetic valve
Vascular noninflammatory
Arterial dissection
Fibromuscular dysplasia[a]
Hypertension
Radiation vasculopathy
Moyamoya disease[a]
Moyamoya syndrome
Vasospasm
Migrainous infarct
Susac syndrome
Cogan syndrome
Cerebral amyloid angiopathy
Dilative dolichoectasia
Reversible cerebral vasoconstriction syndrome
Eclampsia
Vascular inflammatory
Takayasu arteritis
Giant cell arteritis
Polyarteritis nodosa[a]
Primary CNS angiitis
Behçet disease
Neurosarcoidosis
Kawasaki disease
Vasculitis
Sjögren disease
Wegener granulomatosis[a]
Churg-Strauss syndrome[a]
Rheumatoid arthritis
Systemic lupus erythematosus[a]
Inflammatory bowel disease
Nephrotic syndrome[a]
Scleroderma[a]
Sneddon syndrome
Cryoglobulinemia
Infectious
Varicella
Neurosyphilis
TB meningitis
Fungal meningitis
Cysticercosis
Lyme disease
Chagas disease
HIV
Hepatitis B and C
Metabolic/genetic
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
Fabry disease[a]
Homocystinuria
Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes and other mitochondrial diseases[a]
Ehlers-Danlos syndrome
Marfan syndrome
Sturge-Weber disease
Von Hippel-Lindau disease[a]
Neurofibromatosis
Hereditary endotheliopathy with retinopathy, nephropathy, and stroke[a]
Inherited thrombophilias
Sickle cell disease
Inherited prothrombotic states
Protein C deficiency
Protein S deficiency
Antithrombin III deficiency
Factor V Leiden gene mutation (associated with activated protein C resistance)
Prothrombin gene mutation
Homocystinuria
Lipoproteinemia
Polycythemia vera
Fibrinogen disorders
Acquired thrombophilias
Acquired prothrombotic states
Antiphospholipid antibody syndrome
Pregnancy
Oral contraceptives
Disseminated intravascular coagulation
Leukemias and other malignancies
Protein C and S deficiency
Antithrombin deficiency
Paraproteinemia
Cancer
Iron deficiency anemia
Hemoglobinopathies
Thalassemia
Platelet disorders
Essential thrombocythemia
Diabetes mellitus[a]
Paroxysmal nocturnal hemoglobinuria[a]
Other
Cocaine, amphetamines
Radiation vasculopathy
Lymphomatoid granulomatosis
Hypoperfusion
Intravascular lymphoma
Henoch-Schonlein purpura[a]

[a] Etiologies commonly associated with prominent renal involvement.

right greater than left periodic lateralized epileptiform discharges. The patient was empirically treated with acyclovir but an extensive infectious workup including blood cultures and lumbar puncture were both unremarkable, with CSF showing <1 leukocyte, glucose 4.0, and mildly elevated protein at 474.

Given the patient's age, multiple territory infarcts, and diffuse intracranial vessel narrowing on CT angiography, consideration was given to vasculitis; however, lumbar puncture and serologic markers for systemic inflammation were negative. Workup for possible cardioembolic phenomena showed an incidental right atrial intracardiac mass on both transthoracic and transesophageal echocardiogram attached to anterior lateral wall measuring 10 × 11 mm. No shunt or patent foramen ovale was found with bubble study and a cardiac CT confirmed the mass to be in keeping with a prominent crista terminalis. A 24-hour Holter monitor and repeated ECGs in the hospital were negative for atrial fibrillation or flutter. A malignancy screen including CT chest/abdomen/pelvis and mammogram for hypercoagulable state or related to potential marantic endocarditis yielded negative results.

Question for consideration:

1. What is MELAS and what are the clinical features associated with this disease?

GO TO SECTION 3

SECTION 3

Based on the patient's clinical history of multiple infarcts to the occipital and parietal lobes, history of hearing loss, diabetes mellitus, cardiac disease, and short stature on examination, as well as some mild cognitive impairment, MELAS was considered and genetic testing initiated. L-arginine was started empirically early during the patient's admission while awaiting the results of diagnostic testing. Of interest, the patient had a family history of renal disease and deafness in her father (thought possibly secondary to Alport syndrome) but no family history suggesting mitochondrial dysfunction in her mother.

Questions for consideration:

1. How is MELAS inherited and how is it diagnosed?
2. How is MELAS treated?

GO TO SECTION 4

SECTION 4

The patient's genetic testing confirmed the common m.3243A>G mutation with a heteroplasmy level of 23% in the serum. Given multiple clinical findings of stroke-like episodes (headache, seizure, cortical blindness, and focal lesions on CT scan) in addition to biochemical evidence of mitochondrial dysfunction (elevated serum lactate) and confirmed genetic abnormality, she was given a definitive diagnosis of MELAS.[2] Six weeks after presentation, the patient was no longer cortically blind. She had a mild residual L-HH, mild encephalopathy, and mild optic ataxia. Repeat CT head prior to discharge showed some improvement in low attenuation of the bilateral occipito-parietal regions. The patient was reinitiated on tacrolimus, seizures were controlled with a combination of phenytoin and levetiracetam, and the patient was continued on L-arginine to reduce risk of stroke recurrence in addition to a vitamin cocktail including citrulline, which have been shown to potentially improve mitochondrial function in this patient population.[3]

Question for consideration:

1. What is the pharmacologic role of arginine in the treatment of MELAS?

GO TO SECTION 5

SECTION 5

The stroke-like episodes in MELAS are thought to be the consequence of transient oxidative phosphorylation failure within the brain, resulting in segmental impairment in vasodilation of intracerebral arteries.[4] L-arginine acts as a precursor of nitric oxide (NO) within the arginine-citrulline-NO cycle. It is thought to reduce the severity and frequency of stroke-like episodes through its action as a potent donor of NO, thereby reducing the amount of lactate accumulation in the brain, leading to improved microcirculation and preservation of vascular tone.[4,5] The patient continues to be on this medication without adverse side effects.

DISCUSSION MELAS is a multisystem, maternally inherited mitochondrial disorder with a relapsing and remitting type course which can present with a wide spectrum of manifestations ranging from seizures and stroke-like episodes[5,6] to maternally inherited diabetes with or without deafness. Over 40 causative mitochondrial DNA mutations have been documented, with 80% of cases carrying the m.3243A>G mutation, affecting the respiratory transport chain, and 10% the m.3271T>C transfer RNA mutation.[5,7] The pathophysiology of stroke in MELAS is unclear; however, it appears to involve mitochondrial angiopathy (which appears to respond to L-arginine treatment), mitochondrial cytopathy, and other nonischemic neurovascular cellular mechanisms.[5] The serum and CSF lactic acidosis present in up to 94% and the appearance of ragged red fibers seen on muscle biopsy are thought to be secondary to diffuse mitochondrial cytopathy.[7,8] Based on the MELAS study committee in Japan, a definitive diagnosis of MELAS is met with at least 2 clinical findings of stroke-like episodes (headache with vomiting, seizure, hemiplegia, cortical blindness or hemianopsia, or acute focal lesion observed via neuroimaging) and at least 2 sources of evidence of mitochondrial dysfunction (high lactate levels in plasma ± CSF or deficiency of mitochondrial-related enzyme activities, mitochondrial abnormalities on muscle biopsy, or finding of a definitive gene mutation related to MELAS).[2]

Patients are noted to have a history of short stature, sensorineural hearing loss, and cardiac and renal disease, and present with migraine-type headaches and stroke-like events.[7,9] Given the predilection of these stroke-like episodes for the parietal and occipital lobes, patients typically present with cortical blindness, hemiparesis, or visual field deficits, which typically improve or fluctuate over time. In addition, these patients may develop seizures in the context of acute febrile illness.[1,5] Neuroimaging of patients with this disorder may show classic basal ganglia calcification in addition to cerebral infarcts, which appear to migrate and disappear over time, are not restricted to vascular territories, and show a propensity to occur in occipital and parietal regions with relative sparing of deeper white matter, explaining why many patients present with cortical blindness or visual field deficits.[5,6]

The proportion of mitochondria-carrying mutations known to be associated with MELAS in different tissues of high metabolic demand (notably muscle and brain) is variable, which explains the clinical heterogeneity in onset and presentation of this disease as well as the findings that associated features are not reported in all cases (diabetes, cognitive impairment, hemiplegia, muscle weakness, family history, elevated serum or CSF lactate), making diagnosis difficult.[6] In addition, our case was unique in that in addition to the confounding factors complicating the clinical scenario described above, the patient's family history of possible Alport syndrome in her father was confusing. Furthermore, the patient was not documented to have a peripheral neuropathy (which is present in over 70% of MELAS cases). The patient's FSGS represented a rare clinical manifestation of MELAS that has been reported in other cases.[10] After pedigree analysis, it is possible that her mother, who died at age 50 of melanoma, had a low proportion of affected mitochondria, explaining her relative lack of MELAS features on history. Furthermore, there is emerging evidence to support a broader range of phenotypes of MELAS, including clinical onset after age 40, suggesting that if her mother had survived, she may have developed clinical MELAS.[9]

While our patient did present with classical features of cortical blindness, elevated lactate, stroke-like changes on CT, and seizures in the context of febrile illness with a history of sensorineural hearing loss, diabetes, and cardiac disease, this case was diagnostically challenging given the inability to perform an MRI brain due to cochlear implant, narrowing in multiple intracranial vessels raising the possibility of vasculitis with infarcts in multiple vascular territories, an incidental right atrial mass on transesophageal echocardiogram, possible etiology of tacrolimus-related posterior reversible encephalopathy syndrome (although delayed presentation), multiple active medical issues making it difficult to interpret elevated serial lactate levels in the setting of acute febrile illness, a mildly elevated B_2 glycoprotein immunoglobulin M of unclear significance, and a family history suggesting genetic disease on her father's side rather than her mother's.

Should a patient's history and clinical symptoms raise the possibility of MELAS despite relative lack of a maternal family history, it is important to

empirically treat with L-arginine in the acute setting given its mild side effect profile and efficacy in preventing further strokes in MELAS until genetic studies return or another etiology is established.[3]

AUTHOR CONTRIBUTIONS

Dr. Randhawa: case analysis and interpretation. Dr. Wilson: critical revision of the manuscript for important intellectual content. Dr. Mann: critical revision of the manuscript for important intellectual content. Dr. Sirrs: critical revision of the manuscript for important intellectual content. Dr. Benavente: study/case supervision.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

N. Randhawa, L. Wilson, and S. Mann report no disclosures relevant to the manuscript. S. Sirrs has received funding for travel support and speaking and consultancy fees from Shire Human Genetics Therapies, Genzyme Canada, Actelion, and Alexion, but none of these is relevant to this case report. O. Benavente reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES

1. Mackey J. Evaluation and management of stroke in young adults. Continuum 2014;20:352–369.
2. Yatsuga S, Povalko N, Nishioka J, et al. MELAS: a nationwide prospective cohort study of 96 patients in Japan. Biochim Biophys Acta 2012;1820:619–624.
3. El-Hattab AW, Emrick LT, Chanprasert S, et al. Mitochondria: role of citrulline and arginine supplementation in MELAS syndrome. Int J Biochem Cell Biol 2014;48:85–91.
4. Scaglia F, Northrop JL. The mitochondrial myopathy, encephalopathy, lactic acidosis with stroke-like episodes (MELAS) syndrome: a review of treatment options. CNS Drugs 2006;20:443–464.
5. Koga Y, Povalko N, Nishioka J, et al. MELAS and L-arginine therapy: pathophysiology of stroke-like episodes. Ann N Y Acad Sci 2010;1201:104–110.
6. Goodfellow JA, Dani K, Stewart W, et al. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes: an important cause of stroke in young people. Postgrad Med J 2012;88:326–334.
7. Sproule DM, Kaufmann P. Mitochondrial encephalopathy, lactic acidosis, and strokelike episodes: basic concepts, clinical phenotype, and therapeutic management of MELAS syndrome. Ann N Y Acad Sci 2008;1142:133–158.
8. El-Hattab AW, Adesina AM, Jones J, et al. MELAS syndrome: clinical manifestations, pathogenesis, and treatment options. Mol Genet Metab 2015;116:4–12.
9. Dimaro S, Tay S, Mancuso M. Mitochondrial encephlomyopathies: diagnostic approach. Ann N Y Acad Sci 2004;1011:217.
10. Deva R, Colville D, Savige J. Retinal atrophy associated with FSGS in a patient with MELAS syndrome. Kidney Int 2008;74:252.