Clinical Reasoning: A 62-year-old woman with deafness, unilateral visual loss, and episodes of numbness

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SECTION 1

In May 2007, a 62-year-old woman presented with two episodes of right-hand numbness. The episodes were accompanied by profound fatigue. Each event lasted 5 minutes, and both occurred within a 2-week period. She also recalled an episode of right-sided numbness 30 years previously. She had a past medical history of hypothyroidism, hypertension, hypercholesterolemia, and multiple miscarriages. About 15 years ago, she began losing hearing in her left and then right ear, and she had been completely deaf for the last 8 years. Prior testing had revealed that the patient had sensorineural hearing loss, but the etiology could not be determined. Family and social history were unremarkable.

Questions for consideration:

1. What is the differential diagnosis for episodic neurologic abnormalities?
2. What diagnostic testing would you perform?

GO TO SECTION 2

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SECTION 2

The differential diagnosis of transient sensory dysfunction is broad and includes TIA, complicated migraine, seizure, metabolic derangement, peripheral nerve compression, compressive myelopathy, multiple sclerosis (MS), and conversion disorder.[1] Particularly in patients over the age 55, transient neurologic attacks that are focal, nonfocal, or a mixture of both are associated with an increased risk of stroke. Therefore, an evaluation of our patient should include carotid ultrasound, transthoracic echocardiogram, and head CT or MRI of the brain.[2] The history of multiple miscarriages raises the suspicion for antiphospholipid syndrome, which may cause a hypercoagulable state. Anticardiolipin antibodies, anti beta-2 glycoprotein antibodies, and lupus anticoagulant assays could be performed to investigate this possibility. An EEG may be considered to identify epileptiform discharges, especially given the patient's post-event fatigue.

A diagnostic evaluation for the cause of her two episodes of numbness was unrevealing. Then, in January 2008, the patient noted blurred vision in her left eye that progressed over 3 days. She denied pain on eye movements, photopsia, metamorphopsia, or other neurologic deficit. Initial eye examination showed a left relative afferent defect and a normal-appearing left optic nerve head. An MRI of the brain was performed and revealed T2 and fluid-attenuated inversion recovery (FLAIR) signal abnormality in the subcortical and deep white matter, without enhancement with gadolinium. A diagnosis of optic neuritis was made and the patient received high-dose IV steroids for 5 days. However, her visual function did not improve over the next 2 months. At this time she came under our care.

Question for consideration:

1. What is the differential diagnosis for the constellation of episodic numbness, new visual loss, and progressive hearing loss?

GO TO SECTION 3

Table Clinical features of mitochondrial diseases[3,10]

Features	LHON	MELAS	MERRF	CPEO	Pearson	NARP	MILS
CNS							
Developmental delay/ regression	−	+	+/−	+	−	+	+
Seizures	−	+	+	−	−	−	+/−
Ataxia	−	+	+	+	−	+	+/−
Myoclonus	−	+/−	+	−	−	−	−
Stroke-like episodes	−	+	−	−	−	−	−
Dystonia	+/−	+	−	−	−	−	+
Migraine headaches	−	+	−	−	−	−	−
Nerve							
Neuropathy	−	+	+/−	+/−	−	+	−
Muscle							
Myopathy	−	+	+	−	−	−	−
Ophthalmoplegia	−	−	−	+	+/−	−	−
Ptosis	−	−	−	+	−	−	−
Eye							
Optic atrophy	+	+/−	−	−	−	+/−	+/−
Pigmentary retinopathy	−	+/−	−	+	−	+	+/−
Heart							
Cardiomyopathy	−	+/−	−	+/−	−	−	+/−
Conduction abnormality	−	+/−	−	+	−	−	−
Ear							
Sensorineural hearing loss	−	+	+	+	−	+/−	−
Endocrine							
Diabetes	−	+/−	−	+/−	−	−	−
Short stature	−	+	+	+	−	−	−
Exocrine dysfunction	−	−	−	+/−	+	−	+/−
Blood							
Sideroblastic anemia	−	−	−	+/−	+	−	−
Kidney							
Fanconi syndrome	−	+/−	−	+/−	+/−	−	−
Ancillary tests							
Lactic acidosis (serum)	−	+	+	+	+	−	+/−
Ragged-red fibers (muscle biopsy)	−	+	+	+	+/−	−	−

LHON = Leber hereditary optic neuropathy; MELAS = mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; MERRF = myoclonic epilepsy with ragged-red fibers; CPEO = chronic progressive external ophthalmoplegia; NARP = neuropathy, ataxia, and retinitis pigmentosa; MILS = maternally inherited Leigh syndrome.

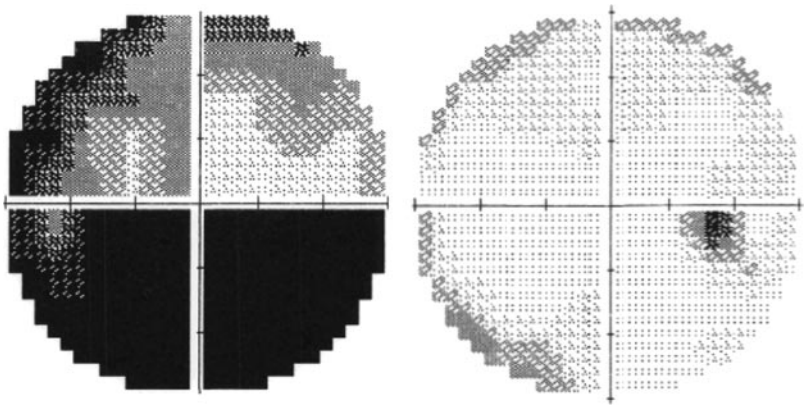
SECTION 3

Our patient has had episodes of transient neurologic dysfunction, visual loss, and a past history of sensorineural deafness. Few conditions can completely account for this symptom complex. Wolfram syndrome is a rare, heterogeneous, inherited neurodegenerative disorder characterized by diabetes insipidus, diabetes mellitus, optic atrophy, and sensorineural deafness. While this syndrome would tie together visual and sensorineural hearing loss, it would not account for her transient numbness. Furthermore, she had no evidence of diabetes, and there was no family history of a similar disorder. Late onset MS was also considered but the clinical course of the visual loss was atypical for optic neuritis given the absence of pain and the lack of subsequent visual improvement. Bilateral hearing loss is also rare in MS. Another possibility was vitamin B1 deficiency. This condition can cause optic neuropathy and sensorineural hearing loss, but usually in combination with confusion, ataxia, and nystagmus, which our patient did not demonstrate. We also considered Susac syndrome, which consists of the triad of encephalopathy, branch retinal artery occlusions, and hearing loss. This condition is due to a microangiopathy affecting the precapillary arterioles of the brain, retina, and inner ear. However, an interval of 30 years between the onset of her progressive hearing loss and her current symptoms would be uncharacteristic of this disorder.

Several mitochondrial disorders can account for her major symptoms and would be highest on the differential at this point. Mitochondrial disorders in general have clinical heterogeneity, in part due to heteroplasmy (differential amounts of mutated DNA and normal DNA within each tissue). Also, each tissue has a different threshold at which the proportion of mutant mitochondrial (mt) DNA causes symptoms.[3] Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibers (MERRF), and chronic progressive external ophthalmoplegia often include sensorineural hearing loss; on the other hand, Leber hereditary optic neuropathy, neuropathy, ataxia, and retinitis pigmentosa, and maternally inherited Leigh syndrome often involve vision, but not hearing (table).[3] Given the history of sudden onset numbness, MELAS stands out as a possible culprit. This disorder can present with a wide range of clinical symptoms including seizures, ataxia, stroke-like episodes, neuropathy, myopathy, sensorineural hearing loss, and encephalopathy.[3] Although our patient is older than the typical age at presentation, with greater than 90% of patients presenting with a severe course before the age of 40, there are many reports of patients with MELAS and other mitochondrial disorders presenting later in life.[4] Although our patient did not have a family history suggesting maternal inheritance, spontaneous mutations occur in a subset of patients with MELAS.

Physical examination revealed that the patient was cachectic and had short stature. She weighed 65 pounds. Her blood pressure and heart rate were

Figure 1 Humphrey visual fields revealing an inferior altitudinal defect in the left eye



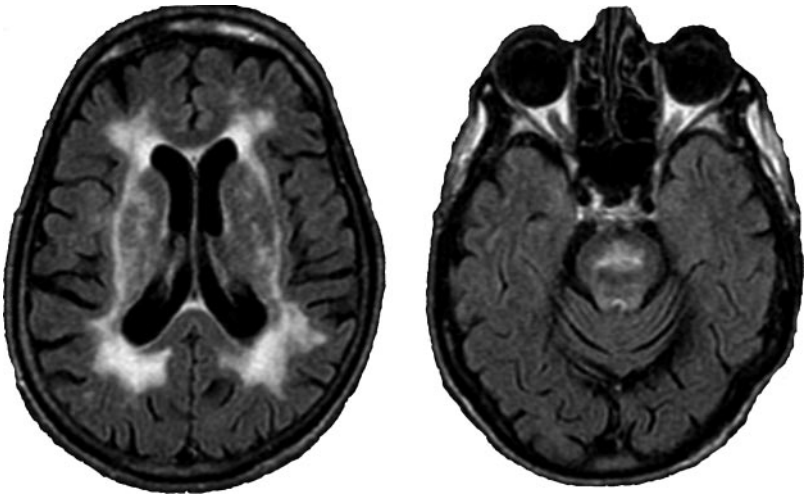
normal. Mental status testing revealed normal orientation, attention, concentration, memory, and language. Acuity was 20/20-2 in the right eye with 8/11 color plates, and she could count fingers at 4 feet in the left eye with 0/11 color plates. With pinhole, she was occasionally able to see the 20/200 line with the left eye. Confrontation and computerized visual fields were normal in the right eye, and revealed a central scotoma and inferior altitudinal defect in the left eye (figure 1). The pupillary light response was brisk on the right and sluggish in the left eye, and there was a left relative afferent pupil defect. Her ocular motility examination revealed mildly restricted upgaze for saccades, pursuit, and oculocephalic movements. Ductions were otherwise full. Funduscopic examination revealed myopic changes bilaterally and optic atrophy in the left eye. There was subtle right optic nerve atrophy. She was deaf bilaterally. She had dysarthric speech, but facial strength and sensation were normal. She had 4/5 strength proximally and 5/5 strength distally. On sensory examination, she had evidence of a length-dependent neuropathy with decreased vibration and temperature sensation up to her elbows and mid-thighs. There was no dysmetria. She had slight difficulty with tandem walk. There was no Romberg sign. Her deep tendon reflexes were absent.

Question for consideration:

1. Which features of the examination aid in narrowing the differential diagnosis?

GO TO SECTION 4

Figure 2 MRI of the brain: Fluid-attenuated inversion recovery (FLAIR) sequences



MRI of the brain showed prominent symmetric T2 and FLAIR signal abnormality in the subcortical and deep white matter and stippling of the basal ganglia. There was no enhancement with gadolinium. The pons had significant T2 and FLAIR abnormality as well.

SECTION 4

Three features of this examination are particularly important. First, short stature is seen in many mitochondrial disorders and suggests a longstanding disorder affecting growth and development. Second, the patient has proximal weakness, fitting a myopathic pattern. Mitochondrial disorders commonly involve multiple organ systems, and are particularly likely to cause myopathy. Finally, she has absent reflexes and length-dependent sensory loss indicative of neuropathy. Among disorders that cause concomitant neuropathy and myopathy, mitochondrial disease is on a fairly short list which also includes rheumatologic conditions such as Sjögren syndrome, sarcoidosis, toxicity from agents such as colchicine, amyloidosis, thyroid disease, or critical illness.

The patient's brain MRI was reviewed at our institution and revealed prominent, symmetric T2 and FLAIR signal abnormality in the subcortical and deep white matter and stippling of the basal ganglia. There was no enhancement with gadolinium (figure 2).

Electromyography revealed excessive low amplitude, short duration, polyphasic motor units with a decreased recruitment ratio and early interference pattern consistent with a mild myopathy. There was also evidence of a mild axonal polyneuropathy on nerve conduction studies.

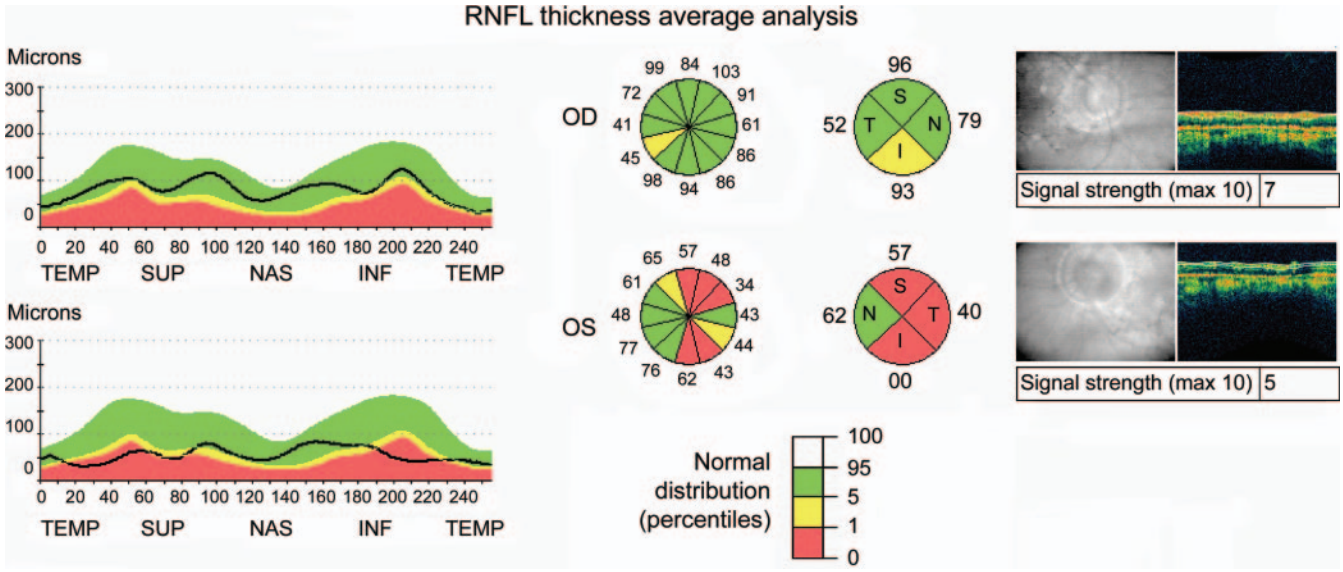
Optical coherence tomography (OCT) (figure 3) showed a retinal nerve fiber layer thickness of 80.03 μm in the right eye and 54.79 μm in the left eye (normal, 104 μm $\pm$ 12). An electroretinogram (ERG) had normal results.

Questions for consideration:

1. How does the MRI of the brain change the differential diagnosis?
2. Why is the electromyography important?
3. What does the combination of the OCT and ERG tell us about the localization of the patient's visual loss?
4. What additional diagnostic tests would you order?

GO TO SECTION 5

Figure 3 Ocular coherence tomography showing a retinal nerve fiber layer (RNFL) thickness of 80.03 μm in the right eye and 54.79 μm in the left eye (normal, 104 μm $\pm$ 12)



The retinal nerve fiber layer in the left eye is thinnest in the superior, inferior, and temporal regions. TEMP = temporal; SUP = superior; NAS = nasal; INF = inferior.

The brain MRI revealed diffuse and symmetric abnormality in the white matter with pathologic changes in the basal ganglia. This patient was treated for optic neuritis earlier in her clinical course but it should be noted that the white matter abnormalities on the MRI were atypical for MS. Symmetric, nonenhancing lesions of the subcortical and deep white matter without enhancement of the optic nerves would be unusual for a patient with MS and acute optic neuritis. This fact underscores the importance not only of brain imaging in the diagnosis of MS but also the proper interpretation of the scan results. Furthermore, the patient was treated with 5 days of IV steroids, whereas the current standard of care based on the Optic Neuritis Treatment Trial is 3 days of IV steroids followed by an oral prednisone taper. On the other hand, the combination of the MRI abnormalities might suggest the diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which results from a *NOTCH 3* gene mutation. Patients with CADASIL typically present with multiple subcortical infarcts, migraines, dementia, and psychiatric symptoms. The MRI abnormality in this condition reveals T2/FLAIR abnormalities in the subcortical and deep white matter including the anterior temporal lobe and external capsule.[5] Although our patient's MRI suggested this condition, other clinical features such as optic nerve and cochlear nerve dysfunction did not.

In MELAS, there can be a wide variety of MRI abnormalities. Classically, the prominent abnormality is in the cortical gray matter, extending across vascular territories, without restricted diffusion. In addition, there is high T1 signal in the basal ganglia.[6] However, there have been several reports where the MRI abnormality was limited to the white matter.[6]

Our patient's electromyography and nerve conduction studies confirmed the coexistence of myopathy and neuropathy, in keeping with a mitochondrial disorder with multiorgan involvement. One study found that almost all patients with MELAS had clinical findings suggestive of neuropathy, with confirmation on nerve conduction studies in 77%.[7]

The OCT and ERG results confirmed that our patient has dysfunction of the left optic nerve with normal retinal function. OCT measures the thickness of the retinal nerve fiber layer to quantify the extent of axonal loss.[8] ERG measures the electrical responses of photoreceptors in the retina and therefore provides an indication of retinal integrity and function.

There are a few ancillary tests that can be helpful in the diagnosis of MELAS. Magnetic resonance spectroscopy of the brain can identify lactate peaks when considering mitochondrial disorders. Serum lactic acid levels are often abnormal in MELAS. Our patient had a lactate level of 16 mg/dL (normal range, 4–16) and a pyruvate level of 0.14 mg/dL (range, 0.3–0.7). Her lactate was at the high end of normal and her lactate/pyruvate ratio was elevated. These values are consistent with the metabolic disturbance found when mitochondrial oxidative phosphorylation is not functioning properly. For definitive diagnosis, a test was sent for the common MELAS mutations and she was found to have the A3243G mt DNA mutation.

Although there is no established treatment for MELAS, rational therapeutic approaches based upon the associated biochemical abnormalities include supplementation with levocarnitine, coenzyme Q10, and vitamin B complex.[4] MELAS causes dysfunction of complex I of the respiratory chain and, therefore, decreased beta oxidation of long-chain fatty acids. Levocarnitine aids in the transport of long-chain fatty acids into the mitochondrion, and supplementation may help increase fatty acid oxidation. Coenzyme Q10 transfers electrons from complexes I and II to complex III and also stabilizes these complexes within the mitochondrion membrane. These functions may provide a beneficial antioxidant effect. Vitamin B complex contains thiamine, riboflavin, and nicotinamide, which all have proposed biochemical mechanisms to aid in repairing oxidative phosphorylation.[4] Additionally, there are new data suggesting that arginine therapy may also benefit these patients, possibly by increasing nitric oxide levels and thereby reversing the impairment of vasodilation in this disorder. In a controlled clinical trial, arginine therapy reduced the severity, frequency, and disability resulting from stroke-like episodes in MELAS.[9] Side effects of arginine therapy, however, may include severe hypotension. Therefore, more data are clearly needed to propose this treatment in all patients.

Patients with MELAS must also receive appropriate genetic counseling. Typically, there is a maternal inheritance pattern, in which all children of an affected mother are also affected. Given the clinical heterogeneity in mitochondrial disorders, these affected children can have a wide spectrum of phenotypes. In addition, there are rare autosomal mutations that can also cause the MELAS phenotype. Our patient had the most common mitochondrial mutation. As a result, all of her children would be expected to be carriers and she should be counseled appropriately. Since her parents were not affected, she most likely had a de novo mutation in her mitochondrial DNA.

Our patient had bilateral sensorineural deafness, acute optic neuropathy, and transient episodes of numbness. These clinical features coupled with her

ancillary testing including the MRI of the brain, electromyography, and ocular testing allowed for the final diagnosis of MELAS. Genetic testing confirmed this hypothesis.

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