Mitochondrial Encephalomyopathy With Lactic Acidosis and Strokelike Episodes Presenting Before 50 Years of Age: When a Stroke Is Not Just a Stroke

Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome is one of the most common maternally inherited mitochondrial diseases. However, its pleomorphic clinical manifestations and the fact that the maternal relatives carrying the same mutation may be asymptomatic or only oligosymptomatic makes the diagnosis sometimes elusive.

Report of a Case | A man in his 50s presented with a 5-year history of stepwise loss of executive and somatosensory functions in relation to what was interpreted as 2 previous stroke episodes. He had no vascular risk factors apart from mild dyslipidemia.

The first strokelike episode, when he was in his late 40s, presented with left homonymous hemianopsia. Head computed tomographic scan depicted a right parieto-occipital lesion compatible with recent ischemic stroke. Diagnostic workup in another hospital failed to provide an etiology. Brain magnetic resonance imaging 6 months later showed no evidence of the previous lesion and identified an asymptomatic right temporal lesion, suggestive of low-grade astrocytoma. The right temporal lesion was not apparent on magnetic resonance imaging 6 months later. Years later, he presented with sudden-onset aphasia, visual deficit, and behavior changes, and there was a new left parieto-temporo-occipital lesion on magnetic resonance imaging. Magnetic resonance angiography was normal.

When he first came to our attention, there was severe executive dysfunction with multiple higher mental function changes and urinary incontinence. He was taking risperidone, memantine, valproate, aspirin, and dipyridamole.

Echocardiography and cervical and transcranial Doppler ultrasonography were normal, and metabolic causes of reversible dementia were excluded. Brain magnetic resonance imaging 6 months later showed no evidence of the previous lesion and identified a new right parieto-temporo-occipital lesion on magnetic resonance imaging. The patient shows cortical diffusion restriction with subcortical diffusion facilitation on diffusion-weighted imaging (D) and apparent diffusion coefficient map (E) with only scarce cortical gadolinium enhancement (not shown).
imaging was obtained at this point (Figure 1) and showed features highly suggestive of a metabolic disorder. Laboratory workup results subsequently found lactacidemia (lactic acid level, 35.01 mg/dL; normal range <19.8 mg/dL [to convert to micromoles per liter, multiply by 0.111]) and raised cerebrospinal fluid lactate (48.29 mg/dL; normal range, <27 mg/dL [to convert to micromoles per liter, multiply by 0.111]). Electroencephalogram recordings showed frequent epileptiform discharges in the posterior regions.

The diagnosis of mitochondrial disease was confirmed with a deltoid muscle biopsy showing ragged-red fibers on modified Gomori trichrome stain, strongly succinate dehydrogenase–positive blood vessels, and some citocrome c oxidase–negative fibers. We further studied the MTTL1 mitochondrial gene and identified the point mutation m3242 A>G (in heteroplasmy as described in Figure 2).

We prescribed aspirin, 100 mg/day, and arginine, 60 mg/day, and we minimized the iatrogenic cognitive symptoms, discontinuing valproate, memantine, and risperidone and replaced them with low-dose quetiapine.

Discussion | The diagnosis of mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes (MELAS) syndrome is sometimes elusive owing to the phenomenon of heteroplasmy.1 We could hypothesize that the low level of mutated mitochondrial DNA in blood leukocytes of our patient justifies its late presentation and oligosymptomatic picture, but we have no knowledge of the percentage of mutated mitochondrial DNA in the symptomatic tissue in this patient, namely central nervous system neurons and possibly central nervous system blood vessels.2

The greatest difficulty in diagnosing MELAS syndrome in this patient was the low level of suspicion. However, the absence of a satisfying etiology for strokelike episodes in a relatively young man with barely any vascular risk factors should have encouraged further study. Ultimately, it was the neuroimaging characteristics of evanescent lesions, highly suggestive of a metabolic disorder, that put us on the right track.3

The pathophysiology of strokelike episodes remains to be clarified. A previous group,4 reporting a case of MELAS syndrome with elderly-onset strokelike episodes, hypothesized that it could be the absence of strongly succinate dehydrogenase–positive blood vessels and evidence of vascular affection that justified the delay in symptoms. Our case does not support this hypothesis, given that there were strongly succinate dehydrogenase–positive blood vessels in this patient’s muscle biopsy, despite the late onset of the strokelike episodes.

The diagnostic criteria for MELAS syndrome require strokelike episodes before 40 years of age, encephalopathy (seizures or dementia), and either blood lactic acidosis or the presence of ragged-red fibers in skeletal muscle biopsy. However, the amount of publications reporting cases that do not conform to such criteria keeps growing, as previously noted.5 Our patient is proof of the need for a new level of suspicion in what concerns mitochondrial diseases, given that he spent 5 years without a proper diagnosis and was exposed to the iatrogenic effects of probably unnecessary medications.
S. Ali Nabavizadeh, MD
Arastoo Vossough, MD, PhD

Author Affiliations: Division of Neuroradiology, Hospital of the University of Pennsylvania, Philadelphia (Nabavizadeh); Perelman School of Medicine, University of Pennsylvania, Philadelphia (Nabavizadeh); Division of Neuroradiology, Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania (Vossough).

Corresponding Author: S. Ali Nabavizadeh, MD, Division of Neuroradiology, Hospital of the University of Pennsylvania, Perelman School of Medicine of the University of Pennsylvania, 3400 Spruce St, Philadelphia, PA 19104 (seyedali.nabavizadeh@uphs.upenn.edu).

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In Reply I appreciate the letter from Nabavizadeh and Vossough regarding the case of reversible cerebral vasocconstriction syndrome (RCVS) I reported1 and their suggestion of posterior reversible encephalopathy syndrome (PRES) instead of RCVS as the diagnosis. The diagnostic criteria for RCVS were not fulfilled owing to incompleteness of the clinical presentation and medical history. After a second review of the medical record, it was seen that the patient initially presented to the emergency department for a severe headache after synthetic cannabinoid use. She developed the seizure on the way to the hospital, which resulted in a change in her presenting symptom. This does not clinically change the diagnosis because PRES can present with headache.3 The patient was normotensive on presentation to the emergency department and did not require any antihypertensive treatment during or after hospitalization, which is atypical for PRES but not exclusive.3

She had history of an ischemic stroke and myocardial infarction 4 months prior following synthetic cannabinoid use and presented with a severe headache and left upper extremity weakness. The previous hospitalization’s neurologic deficits persisted for weeks, with eventual resolution prior to the second event, which aligns more with RCVS but no repeated imaging was obtained.2 These clinical features influenced our neurologist to presume the diagnosis of RCVS. The magnetic resonance imaging scan did exhibit a pattern similar to PRES3 and the reading included both PRES and RCVS in the differential diagnosis. The patient’s clinical course was deficient in appropriate vascular studies, cerebrospinal fluid testing, and clinic visits to complete diagnostic criteria for RCVS. The deficit was owing to the patient and family declining additional workup on both hospitalizations.

It would be interesting to have had more data to solidify the diagnosis of RCVS. In retrospect, PRES is probably the correct diagnosis owing to lack of diagnostic criteria for RCVS and...