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 stroke-like 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 risperdone, 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 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.

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The report of previous evanescent lesions coupled with these images was highly suggestive of a metabolic disorder. The overall distribution of lesions on T2-weighted fluid-attenuated inversion recovery images (shown through cross-sections in A, B, and C), predominantly posterior, with no clear definition of a vascular territory, contributes to the diagnosis. 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 stroke-like episodes (MELAS) syndrome is sometimes elusive owing to the phenomenon of heteroplasmy. 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.

The greatest difficulty in diagnosing MELAS syndrome in this patient was the low level of suspicion. However, the absence of a satisfying etiology for stroke-like 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.

The pathophysiology of stroke-like episodes remains to be clarified. A previous group, reporting a case of MELAS syndrome with elderly-onset stroke-like 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 stroke-like episodes.

The diagnostic criteria for MELAS syndrome require stroke-like 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. 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.

**Acknowledgments** | We acknowledge Laura Vilarinho, PhD, from the Newborn Screening Unit at the Medical Genetics Institute of the Portuguese National Institute of Health, who performed the genetic analysis and provided the corresponding images, and Maria Matos, MSc, Business Administration at...
the Católica-Lisbon School of Business and Economics, for postprocessing all images included in the manuscript. They did not receive compensation for their work.


**COMMENT & RESPONSE**

**Reversible Cerebral Vasocclusion Syndrome vs Posterior Reversible Encephalopathy Syndrome**

**To the Editor** We read with interest a recent Images in Neurology article, which presented an example of reversible cerebral vasocclusion syndrome (RCVS).¹ Sorensen² described a woman who presented with tonic-clonic seizure following synthetic cannabis use, with improvement after 24 hours. The only presented images are T2-weighted sequences that demonstrate bilateral hyperintensities involving cortical and subcortical regions.

The clinical presentation is somewhat atypical for and the neuroimaging does not correspond to pure RCVS. On the other hand, the clinical presentation, course, and neuroimaging are prototypical manifestations of posterior reversible encephalopathy syndrome (PRES). The primary hallmarks of RCVS are acute severe (often thunderclap) headache and demonstration of segmental vasocclusion of cerebral arteries that resolve by 3 months.²,³ Neither of these was present or reported in this case. The most common presentation of PRES is acute encephalopathy with seizures and there is usually rapid reversal of clinical symptoms. The images shown are also the classic neuroimaging manifestations of PRES, with focal regions of edema involving cortex and subcortical regions of bilateral cerebral hemispheres more commonly involving parietal and occipital lobes followed by the frontal lobes,⁴ matching the imaging shown by Sorensen.¹ There has been a widespread recent surge of potent synthetic cannabinoid use around the country, and case reports of complications, including PRES, are emerging.⁵

It should be noted RCVS can be complicated in a minority of cases by PRES, particularly if a hypertensive episode is present.¹ The notion that this case represents secondary PRES in the context of RCVS would be speculative and not supported by appropriate vascular studies and adequate follow-up. This Images in Neurology² report would have been best presented as a case of PRES.

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**In Reply** I appreciate the letter from Nabavizadeh and Vossough regarding the case of reversible cerebral vasocclusion syndrome (RCVS) I reported¹ and their suggestion of posterior reversible encephalopathy syndrome (PRES) instead of RCVS as the diagnosis. The diagnostic criteria for RCVS⁴ 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...