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Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-like episodes: a case report and critical reappraisal of treatment options

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Abstract

IMPORTANCE—Stroke-like episodes signal progression and significant disability in the mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes (MELAS) syndrome. Arginine is widely used as a treatment for stroke-like episode, although there is little evidence for this intervention. We discuss the management of a patient with MELAS who presented with a stroke-like episode.

OBSERVATION—During a seizure, which triggers the stroke-like episode, neurons are forced to utilize glycolysis as a source of adenosine triphosphate (ATP). Glycolytic byproducts are damaging to the neuron. Breakdown of the blood-brain barrier leads to vasogenic edema.

CONCLUSION—Treatment of stroke-like episode should include anticonvulsants interictally to prevent seizures and dexamethasone ictally to help repair the blood-brain barrier.

Keywords

Stroke-like episode; glycolysis; arginine; mitochondria; lactic acidosis

INTRODUCTION

MELAS usually presents in childhood with a constellation of different symptoms including migraine headaches, exercise intolerance, hearing loss, stroke-like episodes and lactic acidosis.^{1,2} About 80% of patients with the classical presentation have a point mutation in the mitochondrial genome, m.3243A>G which disrupts the tRNA gene for leucineUUR.³ Other mitochondrial gene mutations also have been identified in the remaining 20% of

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patients.⁴ These mutations compromise the respiratory chain, including complex I and complex IV, impairing oxidative phosphorylation. This cascade causes lactate accumulation, ATP depletion and cerebral energy failure. Clinical manifestations are protean and determined, in part, by the pathogenicity of the mutation, tissue distribution (mitotic segregation), the tissue load (heteroplasmy) and the relative tissue vulnerability to impaired oxidative metabolism. There is no specific treatment for MELAS, but uncontrolled studies suggest some benefit from coenzyme Q10 and L-carnitine.⁵⁻⁷

Patients carrying a MELAS mutation can be divided into three different groups based on proton magnetic resonance spectroscopy: asymptomatic and symptomatic carriers, and patients who fulfill the criteria for MELAS.⁸ MELAS is characterized by elevated ventricular lactate that increases as the disease progresses signifying a progressive shift of the oxidation-reduction (redox) potential.⁹ Stroke-like episodes represent the clinical signature of MELAS, manifested by a mixture of features including altered consciousness, seizures, imaging abnormalities and transient focal deficits. Unlike the sudden nature of an ischemic stroke, these episodes usually progress over days or weeks, and residual neurologic deficits accrue following each episode. Individuals with MELAS have a significantly shorter lifespan relative to asymptomatic carriers with an average survival of only 16.9 years after the clinical onset.¹⁰ We describe a patient presenting with a stroke-like episode, and discuss the pathophysiology of MELAS, and the rationale for various forms of treatment.

CASE REPORT

This 10-year-old right-handed girl presented with headache, vision changes and right arm shaking. She had been born full term to a non-consanguineous Hispanic couple. Early growth and development were normal. At age 8 years, she had the acute onset of binocular blindness with hemiparesis. Imaging was consistent with a stroke-like episode, and genetic studies revealed the common MELAS mutation (m.3243A>G mutation, 72% heteroplasmy). Vision spontaneously returned over 4 days. Wolf Parkinson White (WPW) syndrome was diagnosed on routine electrocardiogram, and later treated with laser ablation. She was discharged on L-arginine, riboflavin and coenzyme Q10 with a persistent left hemiparesis, oppositional defiant behavior at home and bullying at school. Special education has been necessary because of progressive cognitive deficits, including episodes of “speaking nonsense words” and other “incoherent” speech patterns, memory problems and difficulty completing tasks.

3 weeks before presentation, she was started on daily aspirin therapy. 11 days later, she developed headache, nausea, emesis, blurred vision, and slurred speech. A non-contrast head computed tomography (CT) showed multiple chronic infarcts consistent with MELAS. There were no acute changes, but the symptoms worsened and one day before presentation she developed intermittent right arm shaking and worsening headache. In the emergency room, she was awake, alert, tearful, whimpering without discernible words, and not following commands. Examination revealed a sluggishly reactive left pupil, increased tone and brisk tendon reflexes, more so in the right limbs. She moved all extremities spontaneously, more so on the left. There was intermittent right arm and leg trembling and right-sided sensory disturbance. Laboratory abnormalities included a venous pH of 7.33 and

a blood lactate value of 5.5 mmol/L (reference range 0.50–1.60). The non-contrast head CT revealed areas of low attenuation involving multiple regions of the parietal, occipital and temporal lobes bilaterally, and edema spanning the left parietal lobe. Also noted was bilateral basal ganglia calcification and mega cisterna magna.

Initial management included a 10 mg intravenous bolus of dexamethasone followed by 2 mg every 6 hours. Riboflavin, L-arginine and coenzyme Q10 were continued, but aspirin was discontinued. 10% dextrose-containing intravenous fluids were started with intravenous citrulline and arginine bolus and infusion for 24 hours. Her condition improved and she was discharged home on an oral steroid taper and arginine.

DISCUSSION

The term stroke-like episode denotes a complex clinical syndrome that has focal features reminiscent of stroke, epilepsy, and migraine, and a slow progression over days. Stroke-like episodes don't strictly obey cerebrovascular territories; hence, the original use of the term "stroke-like".² Pathologic studies have provided evidence for a small vessel angiopathy: capillary proliferation and increased numbers of abnormal mitochondria in both endothelial and smooth muscle cells of the small arterioles of the brain.^{11,12} Patients with MELAS have low serum arginine and nitric oxide (NO) concentrations.¹³ NO, a potent mediator of cerebral vasodilation, is produced from arginine by the enzymatic activity of nitric oxide synthetase. These observations have led to the hypotheses that abnormal vascular reactivity is a significant contributor to a stroke-like episode, and that vasodilating agents should be therapeutic. In a small open-label study, arginine supplementation seemed to reduce the incidence of stroke-like episode, and intravenous arginine, during an episode, seemed to shorten the duration and severity of the stroke-like episode.^{14,15} However, open-label studies cannot answer questions related to efficacy, and stroke-like episodes are unpredictable from epoch to epoch, making it impossible to determine if an intervention truly influences the temporal incidence. Furthermore, despite having low serum NO levels, patients with MELAS exhibit a robust cerebral hyperemia, which increases as the disease progresses.¹⁶ This raises the question as to whether low NO and arginine levels are the consequence of chronic vascular dilatation. Lastly, the idea of cerebral hypoperfusion during a stroke-like episode is central to the hypothesis of abnormal vasoreactivity. Most investigators have reported a relative hyperemia in the affected brain region.^{17,18} The two studies that have reported decreased regional perfusion during stroke-like episode^{14,19} relied on SPECT scans. Retention of the tracer used in these studies is dependent on the metabolic state of the tissue and the stability of the blood-brain barrier.^{20,21} For instance, technetium 99m hexamethylpropyleneamine oxide (^{99m}Tc-HMPAO) retention is sensitive to the redox potential.²¹ Yeh et al. reported hypoperfusion in a stroke-like episode using ^{99m}Tc-HMPAO SPECT but then showed hyperperfusion using transcranial color-coded sonography.²²

For these reasons, we suspect that abnormal vasoreactivity and tissue ischemia are not central to the pathogenesis of stroke-like episodes. One feature preceding most, if not all, stroke-like episodes is a seizure. In one study, epileptiform discharges were seen in 9 of 11 patients presenting with a stroke-like episode, but some of these EEGs were performed days or weeks after the onset of the episode,²³ suggesting that the rate may be even higher. In

normal brain, seizures lead to a rapid increase in cerebral blood flow, O₂ uptake, and glycolytic flux,²⁴ mediated by the neurovascular unit, a functional grouping of brain endothelial cells, pericytes, astrocytes and neurons. We suspect that the triggering event in every stroke-like episode is a seizure, which leads rapidly to energy depletion in the neurovascular unit, followed by an “exaggerated” post-ictal Todd’s paralysis. Lactate is the preferred energy source for neurons. To support increased synaptic activation, astrocytes increase their production of lactate from glucose. Lactate, produced in astrocytes, is then taken up by neurons and oxidized to pyruvate, where it can be used as the primary substrate for oxidative phosphorylation in the mitochondrion. This metabolic sequence constitutes the astrocyte-neuron lactate shuttle.²⁵ Conditions where oxidative phosphorylation is impaired, such as hypoxia or MELAS, lead to a buildup of lactate. There is also a marked decrease in the nicotinamide adenine dinucleotide oxidized and reduced (NAD⁺/NADH) ratio due to failure of NADH reoxidation by the respiratory chain. This shift in the redox potential prevents the conversion of lactate to pyruvate by lactate dehydrogenase due to the accumulation of NADH. The mass action ratio favors the conversion of pyruvate to lactate and forces the MELAS neurons to compete with astrocytes for glucose and to rely on glycolysis for ATP production. Byproducts of glycolytic metabolism, such as methylglyoxal, can accumulate and, at higher tissue concentrations, become toxic to neurons which, unlike astrocytes, do not have the cellular machinery to detoxify methylglyoxal.²⁶ This speculation, if true, may contribute to the pathophysiology of stroke-like episode and explain the decrease in brain *N*-acetylaspartate seen in the MELAS brain as the disease progresses.⁸

The blood-brain barrier functions to prevent toxic serum factors from entering the brain, and allows for the selective trafficking of essential metabolites. The metabolic work necessary to maintain the blood-brain barrier is thought to be high, explaining the observation that brain endothelial cells have approximately 5–6 times the number of mitochondria compared to endothelial cells in other parts of the body.²⁷ These mitochondria are the first to lose cytochrome oxidase staining in pathologic studies of the MELAS brain.¹² They are likely susceptible to dysfunction in patients with MELAS, and *in vitro* are unable to maintain an adequate blood-brain barrier.²⁸ Brain imaging during a stroke-like episode frequently shows evidence of vasogenic edema, the known consequence of a breakdown of the blood-brain barrier.²⁹

We feel that treatment of stroke-like episodes should focus on available interventions. A prolonged focal seizure starts a cascade of events leading to neuronal injury and breakdown of the blood brain barrier. Treatment should focus on aggressive interictal seizure management with antiepileptic drugs to minimize the stroke-like episode triggering mechanism and ictal management of the acute stroke-like episode with high-dose corticosteroids such as dexamethasone to help stabilize the blood-brain barrier. We favor a treatment intervention with intravenous dexamethasone as the acute management of a stroke-like episode in MELAS patients to help stabilize the blood-brain barrier, reduce tissue edema, and improve perfusion of the compromised brain tissue. In our patient, we elected to stop her aspirin treatment, as aspirin can be toxic to mitochondria by attenuating the proton motive force.³⁰ In fact, we feel that aspirin should not be used in any patient with a

mitochondrial disorder. Our patient was also taking arginine at the time of the episode, and received an arginine bolus during the stroke-like episode. It remains unclear whether arginine is effective, and whether the purported benefit is mediated through a vascular mechanism or some other mechanism. Randomized double blind clinical trials need to be performed to establish whether arginine therapy is truly beneficial. If not, many MELAS patients are being treated needlessly and a meaningful search for an effective agent is being divagated.

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