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Pediatric Neurology

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Clinical Observations

Mitochondrial Encephalopathy With Lactic Acidosis and Stroke-like Episodes (MELAS) May Respond to Adjunctive Ketogenic Diet

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ABSTRACT

BACKGROUND: Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome can present management challenges. Refractory seizures and stroke-like episodes leading to disability are common. **PATIENT:** We analyzed the clinical, electrophysiologic, and radiologic data of a 22-year-old woman with multiple episodes of generalized and focal status epilepticus and migratory cortical stroke-like lesions who underwent muscle biopsy for mitochondrial genome sequencing. **RESULTS:** Although initial mitochondrial genetic testing was negative, muscle biopsy demonstrated a mitochondrial DNA disease-causing mutation (m.3260A > G). New antiepileptic medications were added with each episode of focal status epilepticus with only temporary improvement, until a modified ketogenic diet and magnesium were introduced, leading to seizure freedom despite development of a new stroke-like lesion, and subsequent decrease in frequency of stroke-like episodes. We propose a metabolic model in which the ketogenic diet may lead to improvement of the function of respiratory chain complexes. **CONCLUSIONS:** The ketogenic diet may lead to improvement of mitochondrial dysfunction in MELAS, which in turn may promote better seizure control and less frequent stroke-like episodes.

Keywords: MELAS, status epilepticus, ketogenic diet, magnesium, refractory seizures, respiratory chain complexes

Pediatr Neurol 2014; 50: 498–502

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Introduction

We describe a 22-year-old woman with the clinical syndrome mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) and a pathogenic mitochondrial mutation. Until a ketogenic diet and magnesium were introduced, she had repeated episodes of both generalized and focal status epilepticus despite taking multiple antiepileptic medications. We propose a model by which a ketogenic diet

may have improved mitochondrial function and led to clinical improvement.

Case Report

This woman of Chinese origin first presented at age 18 years with generalized convulsive status epilepticus after a headache with visual aura. This led to a stay in the intensive care unit, and she was discharged without antiepileptic treatment. Findings of a magnetic resonance imaging (MRI) scan of the brain and cerebrospinal fluid (CSF) analyses were normal. She remained well, with the exception of occasional migraines, until age 22, when she had generalized convulsive status epilepticus after a migraine, leading to another stay in the intensive care unit, where she was administered phenytoin, which stopped her seizures. Repeat MRI imaging and CSF analyses were again noncontributory to her diagnosis. She was discharged on lamotrigine and phenytoin.

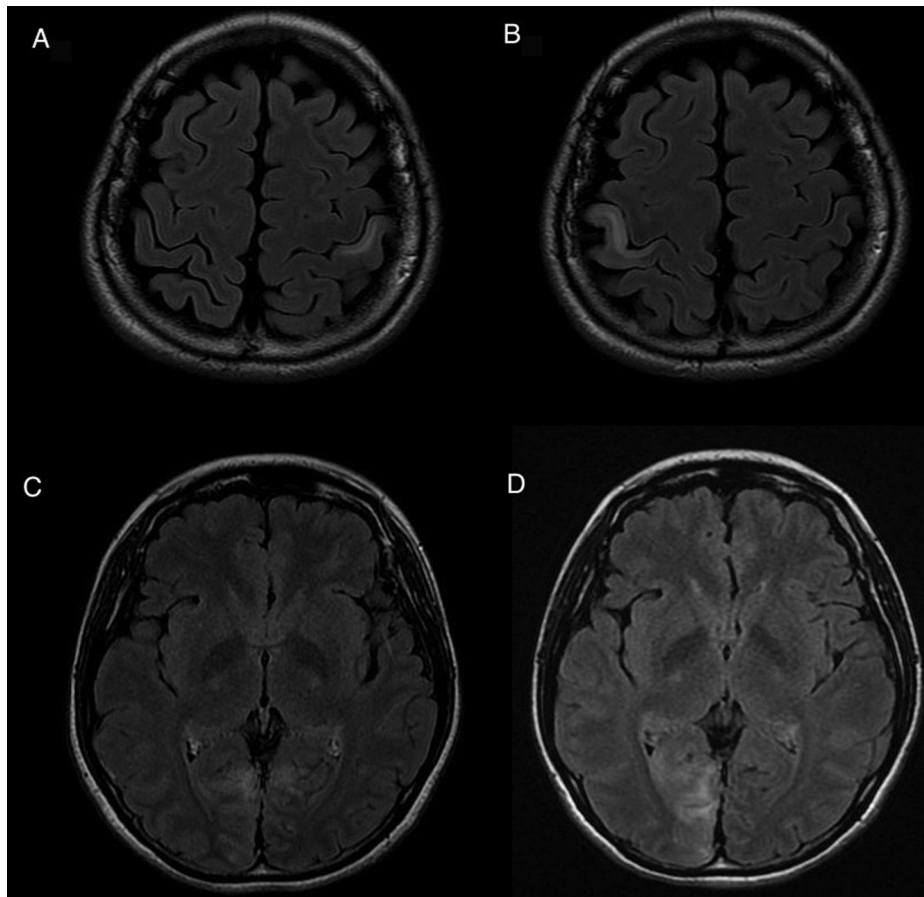
One month later, she returned with nonrhythmic, episodic twitching movements of her right hand accompanied by sensory symptoms. MRI revealed a left postcentral gyrus hyperintensity (Fig 1A), but

Article History:

Received October 24, 2013; Accepted in final form January 1, 2014

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**FIGURE 1.**

MRI images showing 3-T and 1.5-T fluid-attenuated inversion recovery magnetic resonance imaging sequences over the course of the patient's illness. (A) Left postcentral gyrus cortical hyperintensity. On diffusion-weighted images, this showed diffusion restriction. (B) Right postcentral gyrus cortical hyperintensity, which again showed diffusion restriction. Note complete resolution of previous lesion. (C) Bilateral medial occipital lobe cortical hyperintensities, and with associated mild gyral swelling. (D) Resolution of left occipital lobe lesion with worsening of right occipital lobe hyperintensity, and with associated mild gyral swelling.

electroencephalogram (EEG) did not show epileptiform activity. Imaging findings were thought at the time to be most likely secondary to seizure activity not captured on EEG. Her dose of lamotrigine was increased, and her symptoms resolved after 1 week.

She then developed semirhythmic, choreo-athetotic movements in the opposite hand, prompting repeat imaging. A new right postcentral gyrus hyperintensity was noted, with resolution of the previous cortical abnormality (Fig 1B). This time, there were right hemispheric electrographic seizures recorded on EEG. CSF showed 1 white blood cells, 0 red blood cells, glucose 3.0 mM, protein 0.28 g/L, lactate 1.8 mM, ($N < 2.8$). Levetiracetam 1500 mg twice daily (bid) was added to her anticonvulsant regimen and after 1 week, her symptoms resolved.

At that point, investigations were broadened and included antinuclear antibody, antineutrophil cytoplasmic antibody, antithyroid peroxidase and antithyroid peroxidase antibodies, serum NMDA NR1, AMPA, GABA(B), mGluR1 and mGluR5, and voltage-gated potassium channel (LG11 and CASPR2) antibodies, all negative. A mitochondrial workup from blood-derived DNA was normal and included restriction fragment length polymorphism for MELAS 3243, 3252, 3256, 3271, and 3291 in the MT-TL1 gene and MELAS 13513 of the MT-ND6 gene, along with NARP 8993 in the MT-ATP6 gene, and MERRF 8344, 8356, 8363, and 8296 in the MT-TK gene as well as polymerase gamma DNA sequencing. The findings of metabolic workup that included homocysteine, organic acids, acylcarnitine, carnitine, amino acids, lactate, pyruvate, and urate levels were normal. MR spectroscopy did not show a lactate peak. MR angiography demonstrated normal vessels.

The patient returned 1 month later with cortical blindness and bilateral hand twitching, with preserved consciousness. Repeat MRI showed bilateral occipital lobe cortical hyperintensities and resolution of previous lesions (Fig 1C), and EEG showed occipital status epilepticus with independent left and right occipital onset seizures (Fig 2). Clobazam was added to phenytoin, lamotrigine, and levetiracetam. At that point, MELAS was the leading diagnostic consideration despite the negative serum screening genetic testing; therefore, the patient was started on a cocktail of CoQ10 200 mg bid, L-carnitine 330 mg tid, folic acid 5 mg once daily (od), vitamin D 1000IU od, and vitamin B complex, and she was referred for muscle biopsy for MELAS. Her symptoms resolved after 1 week.

Subsequently, levetiracetam dosing was decreased because of cognitive complaints and its apparent inefficacy in preventing the prior episode of status epilepticus. Three months after her last episode of focal status epilepticus, she developed a right temporal visual field disturbance, headache, and seizures involving the right arm. MRI showed progression of previous left occipital cortical lesion, with interval improvement in the right occipital lesion. Levetiracetam 1500 mg bid was resumed, and magnesium citrate 1500 mg daily also was introduced. After those changes, seizure activity stopped. In addition, she was placed on a modified ketogenic diet, consisting of a high-fat, low-carbohydrate intake.

Approximately 10 days after the introduction of the ketogenic diet, she developed a new right occipital lesion (Fig 1D) causing a left visual field defect. Unlike previous episodes, the patient had no associated seizure activity and did not require hospitalization. The visual field defect resolved completely within 1 week.



FIGURE 2.

Anteroposterior-bipolar montage electroencephalogram. Upper panel shows part of a right posterior hemispheric electrographic seizure. Lower panel reveals an independent left posterior hemispheric seizure. (Color version of figure is available in the online edition)

The patient was referred for a neurometabolic consultation, and a muscle biopsy was obtained as described previously.¹ The muscle biopsy was normal at the light microscopic level aside from minimal type II fiber atrophy (ie, no ragged red fibers and no COX-ve fibers), with only a few paracrystalline inclusions seen on electron microscopy. Given the high clinical pretest likelihood of a mitochondrial disorder, mtDNA sequencing was obtained from muscle derived DNA and revealed an m.3260 A > G transition mutation in the MT-TL1 gene at 85% mutant heteroplasmy. The mitochondrial cocktail she had been started on was augmented with creatine monohydrate 3 g bid, alpha-lipoic acid 300 mg bid, and vitamin E 800IU od.²

She was maintained on the ketogenic diet for 1 year and has continued to remain seizure free with no further stroke-like episodes. Her sister later developed a stroke-like episode (ascending numbness in left arm) followed by status epilepticus requiring intubation, after a metabolic stressor (hot yoga). On admission to the hospital, her lactate was 21 mmol/L (normal range <2.2), and she was treated with phenytoin and discharged on levetiracetam with a high-normal discharge serum lactate of 2.1 mmol/L. She also underwent skeletal muscle biopsy and was confirmed to have 38% heteroplasmy for the same m.3260 A > G transition mutation. Their mother was asymptomatic and had ~5% heteroplasmy for m.3260A > G in blood derived mtDNA.

Discussion

Although the initial evaluation for mitochondrial disease was negative, the clinical suspicion for mitochondrial

disorder remained high and sequencing of mitochondrial DNA from muscle revealed a disease-causing mutation. Indeed, our patient carried two main features of MELAS syndrome—stroke-like episodes and seizures—as well as two supportive features, normal early development and recurrent headaches.³ Our patient lacked other known clinical manifestations of MELAS syndrome, which include lactic acidosis, myopathic weakness, exercise intolerance, ataxia, myoclonus, hearing loss, short stature, and early dementia.⁴ The mutation carried by our patient traditionally has been associated with maternal myopathy and cardiomyopathy⁵; however, it has been reported to generate a MELAS phenotype in two other families. In one Japanese family, the proband presented at a young age with complex partial seizures, followed by myoclonic epilepsy and episodic blindness suggestive of stroke-like episodes. Lactic acidosis and presence of ragged-red fibers on muscle biopsy supported the diagnosis of MELAS.⁶ In another family of white race, one woman presented at a young age with short stature, ptosis, cardiomyopathy, myopathy, and increased CSF lactate while later developing stroke-like episodes and partial seizures. Her mother had a history of exercise intolerance, hearing loss, and increased baseline serum lactate; she later presented with a large parieto-occipital cortical stroke, and subsequent seizures. Her

brother also had a history of exercise intolerance, migraine, and developed two stroke-like episodes. Other members of the family had isolated signs and symptoms of MELAS, namely increased serum lactates, migraines, exercise intolerance, but also cardiomyopathy and autism, thus illustrating the wide phenotypic variability observed with mitochondrial DNA mutations.⁷ This may be partially related to the percentage of mutant heteroplasmy in various tissues.⁴ In addition, the MELAS-like presentation of our patient's sister, who also carries the mutation, albeit with lower heteroplasmy, argues for the pathogenicity of the mutation in our patient.

A combination of different types of focal seizures, epilepsy partialis continua, secondarily generalized seizures, segmental, and generalized myoclonic seizures are considered typical for MELAS.⁴ Status epilepticus is not commonly an initial presentation as it was in our patient, although ultimately develops in 19% of patients.⁴

The treatment of mitochondrial epilepsy frequently requires multiple antiepileptic medications, as previously reported in patients with MELAS. With our patient, three months of exposure to a partial mitochondrial cocktail and four anticonvulsants were unable to prevent a recurrent stroke-like episode and seizures, yet within 10 days of introduction of the ketogenic diet and magnesium citrate, another stroke-like episode occurred without occurrence of seizures or need for hospitalization, suggesting one or both may have provided significant benefit in treating the seizures in this syndrome. Indeed, there has been a recent reemergence of interest in the ketogenic diet, with multiple randomized trials showing benefit in children with intractable seizures despite multiple antiepileptic medications.⁸ Although there has not yet been a randomized trial of the ketogenic diet in adults with epilepsy, there are accumulating prospective studies showing potential efficacy of the ketogenic diet in adults with refractory seizures.⁹ Specifically, benefit has been shown in children with mitochondrial epilepsy suffering from intractable seizures despite at least two antiepileptic medications.¹⁰ Data on efficacy in adults with mitochondrial epilepsy is lacking, with only one report of seizure control in an adult with POLG-1 mutation related epilepsy.¹¹

Furthermore, the frequency of stroke-like episodes diminished after the introduction of the ketogenic diet, which then raises the possibility of the ketogenic diet improving the mitochondrial dysfunction of MELAS itself. Of note, a ketogenic environment has been shown to lead to intracellular selection and reduction in proportion of mutated mtDNA and improved respiratory chain complex function in cells with mutated mtDNA heteroplasmy.¹² Although we recognize the difficulty of extrapolating findings from one patient to a disease that is intrinsically variable, we propose the following model by which the ketogenic diet may benefit patients with MELAS. First, complex I deficiency has been demonstrated in patients with MELAS due to mutation of the tRNA-Leu^(UUR) gene (involved in our patient's mutation) both in skeletal muscle and frontal cortex of affected patients,¹³ trans-mitochondrial cybrids,⁵ and most recently, human induced pluripotent stem cell-derived disease models.¹⁴ Second, it has been hypothesized that bypassing complex I by providing more reducing equivalents to complex II (downstream from

complex I) may be beneficial in mitochondrial diseases due to complex I deficiency.¹⁵ Specifically, a ketogenic diet would increase fatty acid beta oxidation and provide a NADH + H⁺:FADH₂ ratio of 1:1, compared with the carbohydrate driven tricarboxylic acid cycle, which would yield a NADH + H⁺:FADH₂ ratio of 3:1. Although NADH provides reducing equivalents to complex I, FADH₂ feeds into complex II. It then follows that a greater proportion of FADH₂ would shift reducing equivalents to complex II, thereby bypassing a deficient complex I. This concept has been shown to lead to clinical and biochemical improvement in patients with mitochondrial myopathy due to complex I deficiency.¹⁵ Interestingly, one group has tried the opposite approach and treated MELAS with oral nicotinamide, thus attempting to saturate a deficient complex I. Biochemical improvements, with reduction in lactate were noted, but no clinical information was provided.¹⁶ A limitation of our model is that it does not take into consideration the known complex IV deficiency which has been noted in patient tissues.¹³

In summary, we hypothesize that the ketogenic diet may shift energy production to complex II, thereby bypassing a deficient complex I, and may result in clinical improvement, as it did in our patient.

The authors thank the patient and her family for agreeing to have her information published. They also thank Dr. Gregory Day for his valuable help in this patient's care. Conflict of Interest disclosures: Mark A. Tarnopolsky has consulted for Biomarin, Amicus Therapeutics, and Genzyme.

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