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New Diagnosis of Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes Following First Live Birth in a Woman With an MT-TL1 m.3260A>T Mutation

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Abstract

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is a rare mitochondrial disorder characterized by multisystem involvement. Clinical manifestations are usually present in childhood. Here, we present the case of a 23-year-old woman who was newly diagnosed with MELAS approximately eight months following her first live birth. Serial laboratory evaluation demonstrated fluctuations in serum lactate, with generally higher values during the daytime and lower values overnight and in the early morning, despite maintenance of a normal pH with sodium bicarbonate supplementation. During the transition from intravenous to oral sodium bicarbonate, management was focused on normal acid-base status rather than normalization of lactate, which continued to fluctuate. Once the patient was stabilized on an oral regimen of sodium bicarbonate, she was discharged home. This case highlights an uncommon diagnosis of MELAS following a first live birth. Additionally, observed cyclic changes and persistent elevation of lactate despite clinical improvement suggest that acid-base status and overall clinical condition may serve as useful adjunctive measures in assessing metabolic stabilization in patients with MELAS.

Categories: Obstetrics/Gynecology, Neurology, Internal Medicine
Keywords: lactic acidosis, melas, mitochondrial disease, mitochondrial encephalomyopathy, mt-tl1, postpartum, pregnancy

Introduction

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is an uncommon mitochondrial disorder characterized by maternal inheritance of mitochondrial genetic variants, most commonly the m.3243A>G mutation in the MT-TL1 gene [1]. While widely heterogeneous in presentation, early manifestations often include sensorineural hearing loss, stroke-like episodes, seizures, headaches, diabetes mellitus, and exercise intolerance. Historically, diagnostic criteria have included evidence of stroke-like episodes prior to age 40, encephalopathy, and mitochondrial myopathy [2]. Notably, it is a diagnosis that is often made in childhood. One Japanese study estimated that 75% of diagnoses were established before age 15 [3]. Because MELAS is often diagnosed in childhood, most affected women receive the diagnosis prior to their first pregnancy. Our literature review identified three cases reported of women diagnosed with MELAS during their first pregnancy [4-6] and one case in which a woman was diagnosed after multiple pregnancies [7]. Given the substantial metabolic demands of pregnancy, postpartum diagnosis of MELAS appears to be relatively uncommon.

Here, we present a case of a patient diagnosed with MELAS eight months after the patient's first live birth. This case is notable for a diagnosis in early adulthood, profound recurrent lactic acidosis, and a rare MT-TL1 m.3260A>T variant, whose association with the MELAS phenotype has not been well characterized.

Case Presentation

Clinical presentation and history

The patient was a 23-year-old woman with a history of cannabinoid use disorder and severe malnutrition who was transferred from an outside hospital for evaluation of persistent, severe lactic acidosis and concern for an underlying genetic disorder.

Approximately two weeks before transfer, she presented to the outside hospital with a one-week history of nausea and vomiting and was found to have profound lactic acidosis, with a lactate level of 31.5 mmol/L, pH of 6.84, and bicarbonate of 1.9 mmol/L. At presentation, she was lethargic and minimally responsive to questions. She required emergent continuous renal replacement therapy. Following initiation of renal replacement therapy, intravenous fluids, and sodium bicarbonate, her lactate improved but remained

persistently elevated at approximately 9-11 mmol/L. Attempts to discontinue intravenous fluids resulted in recurrent worsening of the lactic acidosis.

The patient had experienced similar episodes previously, including multiple hospitalizations for emesis associated with lactate levels as high as 12 mmol/L. Her most recent hospitalization until that time had been following her first live birth approximately eight months prior. Her episodes of nausea and vomiting began at approximately 18 years of age and had previously prompted gastroenterological evaluation. Over time, she noted that these episodes were frequently precipitated by stress, physical exhaustion, and heat. She also reported longstanding exercise intolerance and myalgias.

During the current hospitalization, she developed transient focal neurologic symptoms concerning a stroke-like episode, including unilateral numbness, tingling, and weakness involving the left hand and foot. The duration of the left hand and foot weakness could not be determined from the available outside hospital documentation, and detailed neurologic examination findings from that period were not available. By the time of transfer to our facility, the symptoms involving the left hand had resolved, while numbness and tingling of the left foot persisted through discharge and were still present at outpatient follow-up. She additionally described intermittent, transient visual disturbances during which she felt that her eyes were "crossed." A review of her history revealed additional manifestations concerning a multisystem mitochondrial disorder, including ptosis beginning in high school, peripheral neuropathy, rhabdomyolysis, recurrent/cyclic emesis, transaminitis, exercise intolerance, myalgias, and severe malnutrition with difficulty gaining weight.

A lactate-to-pyruvate ratio greater than 20, together with a creatine kinase level greater than 6,000 U/L, further raised concern for mitochondrial dysfunction.

Laboratory and imaging evaluation

An extensive evaluation was performed to exclude alternative causes of her clinical and laboratory abnormalities. Testing for viral hepatitis, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, and human immunodeficiency virus was negative. Serum immunoglobulin levels were within normal limits. F-actin antibody and antimitochondrial antibody testing were negative, arguing against autoimmune hepatitis and primary biliary cholangitis, respectively.

At presentation, her body mass index was 16.6 kg/m², and she reported a longstanding inability to gain weight. Nutritional evaluation demonstrated normal levels of vitamins B12, B9, A, and E, as well as zinc and copper. Thiamine was elevated at 192 nmol/L, vitamin B2 was elevated at 20 mcg/L, and 25-hydroxyvitamin D was decreased at 9.2 ng/mL. Acylcarnitine levels were within normal limits, making a fatty acid oxidation disorder less likely.

Brain magnetic resonance imaging was performed after the patient was transferred to our facility, at which time the patient was no longer experiencing focal neurologic symptoms aside from persistent left foot tingling. MRI demonstrated no structural abnormalities. Magnetic resonance spectroscopy showed a normal spectral pattern without a detectable lactate peak (Figure *1*). Although a cerebral lactate peak on magnetic resonance spectroscopy can be suggestive of impaired oxidative phosphorylation, it does not exclude mitochondrial dysfunction, as lactate elevations can be transient and regionally dependent. Transthoracic echocardiography showed no evidence of cardiomyopathy. Electroencephalography was not performed during this hospitalization.

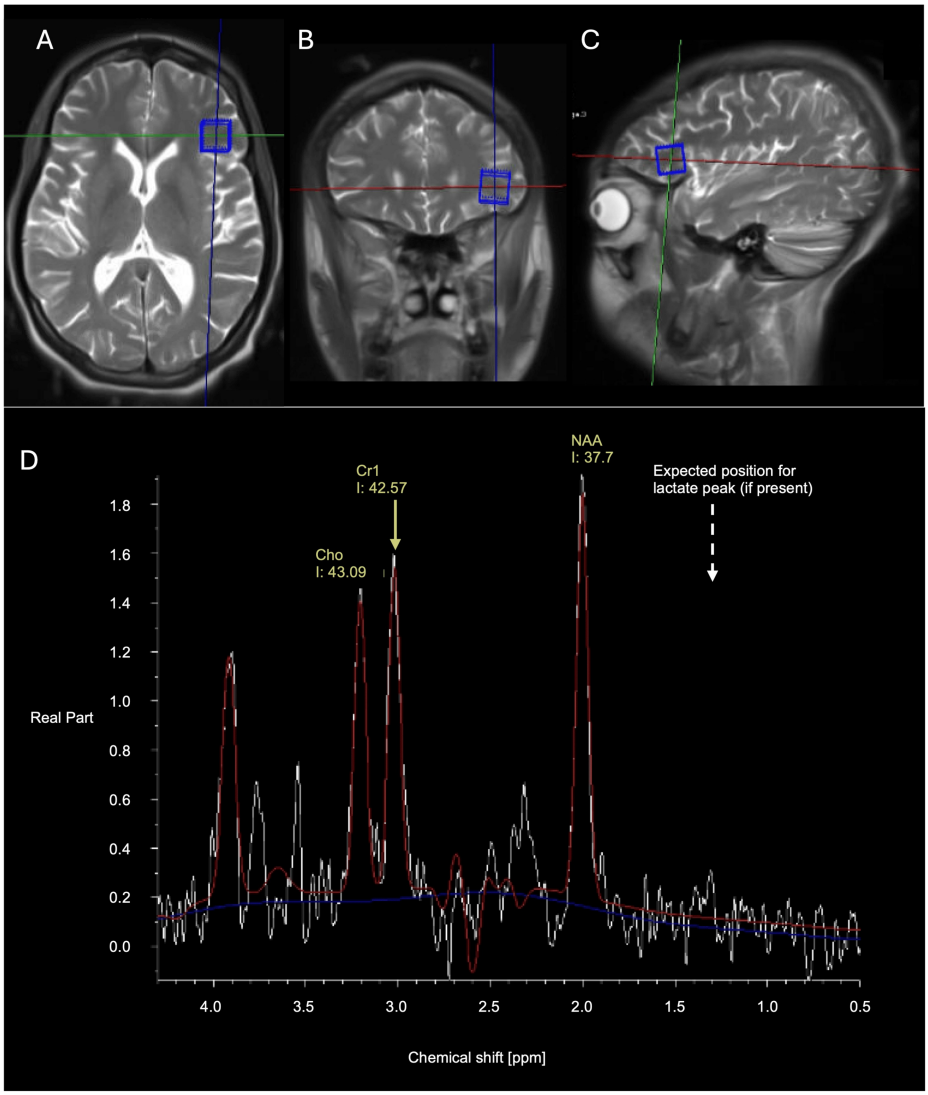


FIGURE 1: Magnetic resonance spectroscopy demonstrates no detectable lactate peak

A: axial; B: coronal; C: sagittal T2-weighted magnetic resonance images demonstrate placement of the spectroscopy voxel within the left frontal lobe; D: magnetic resonance spectroscopy demonstrates expected metabolite resonances, including choline (Cho) at approximately 3.2 ppm, creatine (Cr) at approximately 3.0 ppm, and N-acetylaspartate (NAA) at approximately 2.0 ppm. No definite lactate peak is identified at the expected chemical shift of approximately 1.3 ppm.

Clinical and molecular diagnosis

Given the patient's persistent severe lactic acidosis, elevated lactate-to-pyruvate ratio, rhabdomyolysis, neurologic symptoms, ptosis, recurrent emesis, exercise intolerance, and severe malnutrition, a primary mitochondrial disorder, particularly MELAS, was strongly suspected.

Although the patient did not meet all classic Hirano criteria for MELAS [2], she showed several key features of the syndrome. She had marked lactic acidosis consistent with mitochondrial dysfunction and developed focal neurologic deficits before the age of 40 that were clinically concerning for a stroke-like episode. No corresponding abnormalities were identified on brain MRI; however, imaging was obtained after the acute focal hand symptoms resolved, which may have limited detection of a transient abnormality. She also had additional supportive features, including recurrent headaches and emesis. Although she was lethargic and minimally responsive during her initial presentation with profound metabolic acidosis, she did not have a clearly documented encephalopathic syndrome characterized by seizures or dementia.

Whole-genome sequencing with mitochondrial DNA analysis identified a likely pathogenic MT-TL1 m.3260A>T variant at 58% heteroplasmy in blood and 86% in urine. The testing laboratory classified the variant as likely pathogenic and noted that, at the observed levels of heteroplasmy, it was expected to be

associated with a mitochondrial disorder. Notably, growth differentiation factor 15 (GDF15), a biomarker associated with mitochondrial myopathy, was markedly elevated >6,000 pg/mL. Although muscle biopsy can provide additional diagnostic support in mitochondrial disease when clinical phenotype and molecular results are inconclusive, in this case, a muscle biopsy was not performed as the treating genetics team felt the molecular and clinical evidence to be sufficient for diagnosis.

Although the MT-TL1 m.3260A>T variant is not among the variants most commonly associated with MELAS and its association with the MELAS phenotype has not been well characterized, the genetics team interpreted this molecular finding in the context of the patient's profound recurrent lactic acidosis, elevated GDF15, transient focal neurologic symptoms, and multisystem manifestations as sufficient to establish a diagnosis of MELAS.

Treatment and clinical course

Despite persistently elevated serum lactate levels, serial venous blood gas measurements showed that blood pH remained within a relatively normal range. Lactate levels appeared to exhibit a diurnal pattern, tending toward higher values during the day and lower values overnight and in the early morning. Differences in metabolic demand, dietary intake, and overnight fasting may have contributed; however, activity, nutrition, intravenous fluid administration, and oral sodium bicarbonate supplementation changed concurrently. A strict low-carbohydrate diet was trialed, during which a modest decrease in serum lactate levels was observed. However, the contribution of the dietary modification could not be distinguished from these other concurrent changes in management.

As had occurred at the outside hospital, attempts to wean intravenous fluids and sodium bicarbonate were associated with an increase in serum lactate; however, blood pH remained stable (Figure *2*). Clinically, the patient improved, with resolution of nausea and vomiting, and was subsequently transitioned to oral sodium bicarbonate 650 mg three times daily, with continued maintenance of a normal pH. She was discharged on sodium bicarbonate 1,950 mg twice daily.



FIGURE 2: Serial serum lactate and venous blood pH during hospitalization

A: serum lactate concentrations from hospital days 16–21 plotted according to actual sampling time; B: corresponding venous blood pH measurements. Major changes in intravenous sodium bicarbonate administration, initiation of a low-carbohydrate diet, transition to oral sodium bicarbonate, and discharge are indicated along the timeline. Because dietary intake, activity, intravenous fluids, and bicarbonate administration changed concurrently, observed lactate fluctuations cannot be attributed to any individual intervention.

Two weeks after discharge, the patient was evaluated in the Pediatric Genetics clinic to review the results of her genetic testing. Although her lactate levels remained elevated, she continued to demonstrate clinical improvement and denied any recurrent episodes of nausea or vomiting.

Discussion

MELAS is a clinically heterogeneous mitochondrial disorder that requires the integration of characteristic clinical manifestations and molecular findings [1,2]. Other mitochondrial disorders with neurological manifestations include myoclonic epilepsy with ragged red fibers (MERRF), progressive external ophthalmoplegia (PEO), and mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). MERRF is typically characterized by myoclonus, followed by generalized epilepsy and myopathy [8]. PEO is described by ptosis and impaired extraocular movements [9]. MNGIE is characterized by gastrointestinal dysmotility in addition to ptosis, external ophthalmoplegia, cachexia, and sensorimotor neuropathy [10]. Although mitochondrial disorders have phenotypic overlap, our patient's presentation was considered most consistent with MELAS given the absence of myoclonus or epilepsy characteristic of MERRF, the progressive ophthalmoplegia of PEO, and the typical gastrointestinal dysmotility of MNGIE.

There are no curative therapies for MELAS, and management is largely supportive and directed at disease manifestations. During acute stroke-like episodes, arginine and citrulline supplementation have been used with the goal of increasing nitric oxide availability and promoting cerebral vasodilation. Other treatments consist of coenzyme Q10, vitamin K1, vitamin K3, and ascorbate, which serve as electron donors to cytochrome C and are thought to promote mitochondrial function [11]. Notably, idebenone, a synthetic analog of coenzyme Q10, has been studied in a Phase IIa trial in patients with MELAS (ClinicalTrials.gov Identifier: NCT00887562).

One published review of mitochondrial disorders in pregnancy included four MELAS patients with varied genetic mutations [12]. Those patients were all able to successfully carry a pregnancy. Unfortunately, all reported cases suffered complications of pregnancy ranging from gestational diabetes and threatened preterm labor to preeclampsia requiring emergency cesarean delivery. Our patient had a history of two prior pregnancies, with one ending in spontaneous abortion at six weeks. Her most recent pregnancy was complicated by preeclampsia with severe features, including epigastric pain and elevated blood pressures, requiring a cesarean delivery at 34 weeks and three days. The infant was successfully delivered. Her postpartum period was complicated by metabolic acidosis, with her lactate peaking at 13.6 mmol/L on the day of her delivery. Two days later, her lactate decreased substantially to 2.5 mmol/L without specific intervention. These metabolic irregularities were attributed to hyperemesis gravidarum, and she was discharged two days later.

Our patient demonstrated several features atypical for a MELAS presentation. She presented with a history of recurrent cyclic emesis, starting at the age of 18, toward the later end of the typical age range for MELAS onset. Nevertheless, her history revealed other findings suggestive of longstanding mitochondrial dysfunction, including chronic exercise intolerance and inability to gain weight. Notably, she had no known history of stroke-like episodes and had not previously developed lactic acidosis approaching the severity observed during this hospitalization, when her serum lactate reached 31.5 mmol/L.

The severity of her metabolic derangement was also notable in comparison with a prior hospitalization in the immediate postpartum period. Despite the metabolic demands of pregnancy and postpartum, her most profound known episode of lactic acidosis occurred outside the postpartum period. Although the patient was able to identify stress, heat, and physical exhaustion as triggers for previous episodes, she could not identify a clear precipitating event for this hospitalization. This highlights the clinical heterogeneity of MELAS and the potential unpredictability of metabolic decompensation.

Another notable aspect of this case was the persistence of markedly elevated serum lactate despite clinical improvement. Lactate levels seemed to demonstrate a diurnal trend, with higher values observed during daytime and low values observed overnight and early morning. This pattern could reflect fluctuating energy demands in the setting of impaired oxidative phosphorylation, although this could not be determined from the available data. Additionally, the diurnal trend may have been influenced by dietary intake during the day versus overnight fasting. As such, we trialed a strict low-carbohydrate diet, during which there was a modest decrease in serum lactate levels. However, the contribution of this dietary modification could not be isolated from other concurrent adjustments in intravenous fluid administration and oral sodium bicarbonate dosing. Interestingly, a recent controlled study of 33 participants with mitochondrial disorders, including patients with MELAS, found a trend toward greater than 50% reduction in seizure frequency in patients receiving a ketogenic diet [13]. Importantly, this study evaluated seizure control and did not address hyperlactemia. Further studies are warranted to evaluate the efficacy of a ketogenic diet in controlling myopathic and metabolic symptoms in MELAS patients.

Her persistently elevated lactate levels became increasingly discordant with her clinical stability and acid-base status, whereas maintenance of normal pH seemed to better correlate with her clinical symptoms. Given this observation, the management was directed toward maintaining normal acid-base balance and sustained clinical improvement rather than normalizing serum lactate concentration. Eventually, the patient was able to be transitioned from an intravenous to an oral regimen of sodium bicarbonate without recurrent emesis or metabolic decompensation requiring rehospitalization.

Conclusions

This case illustrates the variability in presentation and time to diagnosis in MELAS. It also underscores the potential discordance between serum lactate concentration and acid-base status. In this patient, normal acid-base homeostasis was able to be achieved despite persistent hyperlactatemia. Therefore, clinical stability and pH normalization may be useful in assessing metabolic recovery in MELAS patients.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Taylor S. Hulahan, Leonidas Walthall

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Drafting of the manuscript: Taylor S. Hulahan

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Supervision: Leonidas Walthall

Disclosures

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