Mitochondrial Encephalomyopathy, Lactic Acidosis, Stroke-Like Episodes: A Unique Late Onset Presentation and Subsequent Management on a Symptomatic Basis

Praneeth Katrapati, MS1; Imran Ali, MD2,3
1University of Toledo College of Medicine and Life Sciences, Toledo, OH
2Department of Neurology, University of Toledo College of Medicine and Life Sciences, Toledo, OH
3Department of Academic Affairs, University of Toledo College of Medicine and Life Sciences, Toledo, OH

ABSTRACT

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome is a mitochondrial cytopathy that affects many of the body's systems, particularly the nervous and musculoskeletal systems. In most cases, the signs and symptoms of this disorder appear in childhood generally between ages 3-15. Early symptoms may include muscle weakness and pain, recurrent headaches, loss of appetite, vomiting, and seizures. Here, we present a unique case of late onset of symptoms and the resulting disease course following admission.

A 64-year-old female was initially admitted due to altered mental status and seizure-like episodes thought to be secondary to an episode of generalized tonic-clonic seizures. Patient had subsequent admission for abdominal pain. Laboratory data showed elevated lactate levels. Brain magnetic resonance imaging (MRI) using diffusion-weighted imaging revealed a hyperintense lesion in the left temporal lobe on initial admission and subacute infarcts in the right temporal lobe on subsequent admission. Mitochondrial workup was performed, and biopsy tested positive for ragged-red fibers. The patient's symptoms and family history led to the diagnosis of MELAS. She has been treated on a symptomatic basis and is currently seen as an outpatient to monitor status and rehabilitation.

MELAS is a rare mitochondrial cytopathy that is presented here as uncharacteristically appearing at an advanced age. Disease course can vary but is similar in our patient as to what has been traditionally described in the literature. Initial presenting symptoms include muscle weakness and pain, usually followed by headaches/neurological symptoms and then gastrointestinal symptoms such as nausea and vomiting. Stroke-like episodes are usually the last to appear. Treatment has focused on each symptom as it appears, and closely monitoring this patient’s condition is vital. Outpatient check-ups should be maintained; a thorough history should be required at each visit to assess disease progression. Literature search was performed and other cases of late onset MELAS have not been discovered.

Corresponding Author: Praneeth Katrapati, MS, University of Toledo College of Medicine and Life Sciences, 2801 W. Bancroft, Toledo, OH 43606.
Email: Praneeth.Katrapati@utoledo.edu
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CASE PRESENTATION

A 64-year-old female presented to the emergency department in 2011 with a chief complaint of left temporal headache and altered mental status including confusion and expressive aphasia. According to family members, the patient originally had a left temporal headache 2-3 days prior. Patient then developed confusion at dinner, forgetting her children’s names. Patient denied any fever, chills, trouble with vision, chest pain, palpitations, ataxia, loss of consciousness, nausea/vomiting/diarrhea, and any numbness/tingling/weakness in the extremities. Patient had a history significant for hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, insulin-dependent diabetes mellitus, anxiety, and depression. In-depth questioning of the patient’s past medical history revealed no prior episodes or related neurologic symptoms. She had not taken anything to attempt to alleviate her symptoms. Family history was deemed unremarkable at the time of admission. Past surgical history included a hysterectomy. Patient denied use of alcohol, tobacco, or other drugs. Medications at the time of visit included trazadone 50 mg oral (PO) daily, albuterol 90 mcg 2 puffs daily, budesonide 160 mcg 2 puffs daily, simvastatin 20 mg PO daily, citalopram 30 mg PO daily, isosorbide mononitrate 30 mg PO daily, and insulin glargine 15 units subcutaneously as needed. No known allergies were noted. Physical exam on arrival revealed an anxious and alert 64-year-old woman with difficulty expressing words and a left-sided headache. Pupils were equal and reactive to light. Neurologic exam revealed all cranial nerves intact. Full range of motion and sensation were intact in bilateral extremities. Heart had a regular rate and rhythm, and lungs were clear to auscultation.

Brain MRI revealed left temporal lobe signal abnormality, most consistent with encephalitis or an area of subacute infarct. Specifically, left temporal cortical high signal intensity in the middle cerebral artery (MCA) territory on T2 weighted imaging was noted (Figure 1).

Figure 1. MRI T2 showing cortical high intensity left-sided lesion suggestive of encephalitis in 2011, two years prior to the diagnosis of MELAS.

Immunologic antibody titers for herpes encephalitidis and arboviruses were negative. Further questioning revealed recently associated episodes of seizure-like activity, characterized as complex partial seizures of variable onset and associated loss of consciousness. Electroencephalogram (EEG) monitoring confirmed this diagnosis, and the patient was started on phenytoin 100 mg PO daily, lacosamide (100mg PO daily for three days, then increased to 200mg PO daily) and levetiracetam 500 mg PO daily. An infectious disease specialist was consulted and suggested performing a brain biopsy, which showed normal brain tissue with no acute vasculitis and an increase in glial cellularity. Patient was monitored until EEG revealed resolution of seizure activity for 24 hours and was then discharged with instructions to continue current regimen of seizure medications. She was subsequently seen in the neurology outpatient clinic for management of seizures. Her language deficits were steadily improving, and her only complaints on outpatient visits were pain around the area of biopsy and worsening hearing on the left side. During outpatient visits, paraneoplastic workup was performed to rule out the possibility of a neoplastic or cancerous mass causing these symptoms; results were negative. Anti-glutamate receptor antibody workup, performed to rule out autoimmune pathology causing pos-
possible encephalitis or epilepsy, was negative. Follow-up MRI two months later revealed resolution of the high signal abnormalities with slight focal atrophy noted (Figure 2).

![Figure 2. MRI T2 from 2011 indicating resolution of the left-sided lesion from two months prior.](image)

Patient’s course was unremarkable until 2013 when she presented to a local emergency department with complaints of diffuse abdominal pain, nausea, and vomiting. *Clostridium difficile* testing was positive for toxin in the stool, and patient was started on metronidazole 500 mg PO daily for 14 days and discharged. Risk factors for *Clostridium difficile* such as previous antibiotic use were not present.

According to the patient, metronidazole did not improve her diarrhea, and she continued to have up to 8-10 loose bowel movements per day, leading to her return to the emergency department. Patient denied a history of blood in the stool but complained of acute, sharp, and intermittent abdominal pain localized to the right lower quadrant. She also had nausea and two episodes of vomiting. Patient’s lab work on admission, including urinalysis, was unremarkable except for an elevated serum lactate level of 3.1 mmol/L (N=0.5-2.2). Patient was started on intravenous hydration and pain medication. Nausea and vomiting did not improve, so a gastroenterology specialist restarted metronidazole medication. Repeat *Clostridium difficile* testing was negative, and metronidazole was discontinued. Colonoscopy was performed to rule out inflammatory bowel disease; the procedure revealed a normal colon with no masses, polyps, or features of colitis. After a few more days, patient’s symptoms resolved, and she was discharged with instructions to follow up with the gastroenterology department (if pain came back) and with her primary care physician.

On outpatient visit with her primary care physician a month later, patient noted continuing abdominal pain of less severity consisting of transient vague periumbilical pain throughout the day. Patient denied any nausea, vomiting, hemoptysis, hematochezia, dyspnea, or tachycardia. Chest and abdominal computed tomography (CT) were ordered and revealed evidence of pulmonary emboli in the left lung, suggestive of a hypercoagulable state.

Patient’s family members also noted some confusion, speech problems, and continued hearing loss around this time. However, the patient denied any significant weakness, numbness, or dizziness/vertigo. It was also ascertained at this time that the patient’s family history was significant for deafness and muscle weakness in her sisters and other female relatives. Patient was then admitted to the inpatient service with the working diagnosis of right MCA infarct. She was started on low-dose heparin (5000 units continuous IV). CT and MRI were performed the following day to rule out embolic stroke and revealed swelling in the right temporal lobe with areas of restricted diffusion (Figure 3), which interestingly did not correlate with areas of restricted diffusion on diffusion-weighted imaging; these findings led the stroke team to rule out a classic embolic stroke affecting a large arterial territory and to consider a subacute lesion caused by some underlying disease process.

A repeat CT was ordered five days later to rule out any progression of neurological disease and showed a subacute infarct involving a large part of the right MCA territory. The course of stay was complicated by a witnessed grand mal seizure with post-ictal confusion.
At this point, the diagnosis of mitochondrial disorder was considered, particularly since the patient’s family history was significant for deafness in her sisters. Workup included N-methyl-D-aspartate (NMDA) receptor antibody, limbic encephalitis panel, hypercoagulable profile, and vasculitis profile—all of which were negative. C3, C4, anti-DNA antibody, and anti-nuclear antibody testing was performed to rule out underlying autoimmune pathology; the tests were normal. Lactate was slightly elevated at 2.3 mmol/L. Cortisol and thyroid stimulating hormone levels were normal. Patient was started on L-arginine (4 gm IV every 8 hours) and coenzyme Q (200 mg PO three times daily), both of which have shown to be effective supplements for MELAS patients. Thiamine (1 tablet PO daily) was given to prevent neuronal death, and levetiracetam was increased to 1000 mg PO daily. Mitochondrial workup consisted of a muscle biopsy of the right vastus lateralis, revealing the presence of ragged-red fibers using hematoxylin and eosin (H&E) and trichrome stains. Electron microscopy showed enlarged mitochondria with abnormal paracrystalline inclusions in the subsarcolemmal area. This finding was consistent with ragged red fibers observed by light microscopy, confirming the presence of a mitochondrial disease process. Due to the patient’s history of seizures, stroke-like episodes, various abdominal symptoms, and an elevated lactate level, the diagnosis of MELAS was made. Patient’s symptoms slowly improved, and she was discharged on hospital day 12.

Since her last admission, the patient has been seen on an outpatient basis and reports increasingly unstable gait. Her family members report sudden and repeated episodes of seizure-like activity. Levetiracetam was increased to 500 mg PO TID, and patient has been advised to continue physical therapy treatment.

**DISCUSSION**

This case describes a unique presentation of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome. There is no established pathological correlation between the mitochondrial pathology and the disease presentation. No distinct brain pathology exists; rather, the culmination of symptoms with the underlying mitochondrial defect is used to classify this disease. The stroke-like episodes have been attributed to mitochondrial accumulation within vascular endothelial and smooth muscle cells in cerebral small arteries and arterioles. An important characteristic in this patient is the advanced age of onset with which the symptoms presented. Most patients with this condition are diagnosed in childhood due to the early appearance of symptoms with some evidence that the stroke-like episodes occur before approximately age 40. At the time of symptom onset, this patient was 61 years old. There has been no established order to the appearance of the symptoms described in the literature, although a general trend does exist with initial symptoms presenting in early childhood. However, with each subsequent symptom, it is important to rule out other causes. Ta-

![Figure 3. CT and MRI showing right MCA infarct in 2013 following onset of abdominal pain and altered mental status.](image-url)
ble 1 lists various differential diagnoses and the tests used to rule them in or out.

The initial presentation of headache and encephalitis required workup for other possibilities, mainly infection. The stroke-like episodes were confirmed via imaging. The stroke team decided that a true stroke was not the etiology, but rather an underlying condition that had caused the infarct. Additionally, the abdominal CT, which revealed multiple pulmonary emboli, further highlights the logic that this patient had a predilection for a hypercoagulable state due to her underlying mitochondrial condition. This increased state of coagulability can be attributed to the idea that mitochondrial angiopathy leads to vascular injury, causing the recurrent strokes seen in our patient. Unfortunately, no reasoning has been established as to why our patient’s symptoms were triggered at such a relatively old age compared to established reports. We can only surmise that some underlying mechanism brought about the onset of disease at the late age at which the patient presented.

Seizures and abdominal pain are two hallmark characteristics of MELAS. The seizures may be a result of cortical compromise due to the episodes of encephalitis or subacute infarcts. Abdominal pain has usually been thought of as related to the buildup of lactic acid. It is uncertain whether the associated diarrhea in this case is due primarily to the lactic acid or the *Clostridium difficile* infection. Ataxia is a less common

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<td>Anti-NMDA receptor antibody – NEG</td>
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*Table 1.* Various diagnoses considered and corresponding tests used to rule in or rule out the pathology. NEG indicates a negative finding for that diagnosis in a patient with MELAS; POS indicates that a particular finding is most likely present in a MELAS patient.
symptom associated with this condition; however, as seen in our patient, this presented later in the disease course. It is also important to note the family history component; namely, the presence of deafness and muscle weakness in the patient’s sisters and female relatives suggests the presence of this cytopathy in previous generations. Other mitochondrial cytopathies such as myoclonic epilepsy with ragged red fibers (MERRF), which has a similar presentation, were ruled out. Seizures in MELAS are a result of cortical compromise due to the recurrent stroke-like episodes. MERRF is a mitochondrial disorder in which the seizures are a primary characteristic of the underlying pathology themselves. The two disorders are differentiated by their clinical presentation. MERRF is associated more with ataxia and myoclonus than MELAS. Furthermore, imaging studies usually do not show evidence of cerebral infarcts in MERRF as they do in MELAS. If clinical suspicion is not enough, genetic studies can be performed; both disorders have been linked to certain specific mitochondrial gene mutations.

To date, there has unfortunately been no known treatment for the underlying mitochondrial disease, which is progressive and fatal. Patients have traditionally been managed symptomatically. In this case, anti-epileptics were given to manage the seizures. The patient was also started on warfarin as prophylaxis for future embolic events. Although there have been no controlled trials on long-term benefits of dietary manipulations, certain supplements have shown promise and given hope to MELAS patients; coenzyme Q10 has been helpful for some MELAS patients in reducing serum lactate levels and decreasing muscle weakness. Our patient is being followed for any improvements and has noticeably improved muscle strength. The administration of L-arginine during the acute and interictal periods may represent a potential therapy for this syndrome in reducing brain damage by increasing nitric oxide concentration and ultimately increasing vasodilation of cerebral vasculature.

There have been no studies reporting increased risk of embolic events with this treatment option. Our treatment, focusing on symptomatic management, is currently effective in that it allows the patient to achieve a certain quality of life with relative symptom control. Furthermore, administration of dietary supplements will hopefully slow the disease progression. Without a more concrete treatment, we suggest symptomatic management as the current standard of therapy.

The late onset presentation in our patient is unusual; however, it should be mentioned that there could be many more cases of MELAS that go undiagnosed in the elderly population because of a lack of documented instances. Therefore, we recommend that a thorough history be taken for all stroke patients, focusing on any abdominal or gastrointestinal symptoms. If these are positive, a serum lactate level should be obtained, which may shed some light on underlying disease pathology.

A limitation of this case report is the limited history available for this patient. Although the symptoms presented at a late age, earlier episodes of seizure activity and altered mental status may have occurred to a lesser degree but went unnoticed by the patient and surrounding family members.

**LEARNING POINTS**

- MELAS is a rare mitochondrial cytopathy with variable presentation as evidenced by this late-age onset of symptoms.
- Treatment should be focused on alleviating each symptom as it presents, ideally via...
prophylactic administration of proper medical therapy.

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REFERENCES


