

Fulminant Form of Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke-Like Episodes: A Diagnostic Challenge

Masayuki Ikeda

Abstract

Since stroke in childhood, although rare, has many potential causes, identification of the underlying disease offers a diagnostic challenge. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is a rare disorder often mistaken for other diseases. Here, we describe the case of a previously healthy 11-year-old girl who initially presented with gastroenteritis-like symptoms after strenuous exercise. Her symptoms, however, rapidly evolved to include diplopia, dysarthria, seizures, and probable status epilepticus, followed by cardiac arrest. Resuscitation was successful, but she went into a persistently vegetative state due to hypoxic brain damage. Hyperlactatemia, hearing loss, and hypertrophic cardiomyopathy were subsequently detected; therefore, a diagnosis of MELAS was established. The fulminant course in the first stroke-like episode posed a challenge in the diagnosis of MELAS.

Keywords: Diagnostic errors; MELAS syndrome; Mitochondrial encephalomyopathies; Stroke

Introduction

Stroke, which is a frequent cause of neurological morbidity and death in children and young adults, poses a diagnostic challenge [1, 2]. Physicians seem to have a limited awareness of childhood stroke, which causes the delay in diagnosis. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is a progressive disorder caused by mitochondrial dysfunction [3-7]. It is characterized by normal early development, followed by episodes of

neurological dysfunction resembling strokes, seizures, and hyperlactatemia. Although virtually all tissues in the body depend to some extent on oxidative metabolism and can therefore be affected in MELAS, metabolically active organs such as the brain and heart are particularly susceptible to the deleterious effect of dysfunctional mitochondria.

MELAS is difficult for doctors to recognize and diagnose because patients with MELAS may exhibit not only stroke-like episodes but also seizures, muscle weakness, digestive problems, heart disease, and many other symptoms [5]. Although mental retardation, muscle weakness, and short stature occurred in approximately half of the patients with MELAS before the onset of stroke-like episodes, such symptoms in these patients were not severe enough to be brought to medical attention [6]. Thus, the first stroke-like episode in a previously healthy child with MELAS poses one of the greatest diagnostic challenges for physicians and pediatricians [5]. The aim of this report is to draw attention to MELAS, which physicians might overlook, and to prevent similar diagnostic errors in the future.

Case Report

An 11-year-old Japanese girl was admitted to the emergency ward of a general hospital because of seizures and impaired consciousness. The patient was born in an uneventful delivery after a full-term gestation. She had been in good health with the exception of short stature. Her height was 140 cm, and she weighed 28.4 kg. She had no family history of stroke or other neurological illness.

On the day of admission, she had performed strenuous exercise in the morning to prepare for a sports meeting in school. She complained of abdominal pain after lunch. In the evening, she vomited repeatedly and passed soft stools, following which she was brought to a local clinic. Physical examination yielded no remarkable chest findings, with no crackles or rhonchi. There was tenderness in the right lower quadrant of the abdomen with no defense. Her body temperature was 36.6 °C, and fosfomycin was administered intravenously as empirical treatment under the suspicion of acute appendicitis. Soon after the infusion, she complained of dip-

Manuscript accepted for publication February 4, 2011

Graduate School of Biomedical Sciences, Nagasaki University, Sakamoto 1-12-4, Nagasaki 852-8523, Japan.
Email: massie.ikeda@gmail.com

doi:10.4021/jmc149w

Table 1. Arterial Blood Gas Values*

| Variable | Value |
|--|-------|
| pH | 7.49 |
| Partial pressure of oxygen (mm Hg) | 151 |
| Partial pressure of carbon dioxide (mm Hg) | 21 |
| Bicarbonate (mmol/L) | 15.8 |
| Base excess (mmol/L) | -6.9 |
| Oxygen saturation (%) | 99.3 |

*Obtained in the emergency room of the hospital while breathing 100% oxygen under artificial ventilation.

lophia and started rapidly blinking and shaking her head. Her speech was dysarthric. Her blood pressure was 180/100 mm Hg, and the pulse was 50 beats/min. Her consciousness rapidly deteriorated with a tonic-clonic convulsion of all 4 extremities, which was worse on the left side than on the right. Within a few minutes, her respiration became weaker and slower with bradycardia, followed by cardiac arrest. After resuscitation, she was transferred to the hospital.

On arrival, she was unresponsive to painful stimuli without spontaneous respiration. Her temperature was 36.4 °C, pulse was 97 beats/min, and blood pressure was 130/58 mm Hg. Pupils were isocoric; the light reflex was initially absent before eventually appearing but was sluggish bilaterally. Her neck was supple, while the tendon reflexes were exaggerated in the lower extremities. Other physical examinations were unremarkable.

A chest radiograph showed no pneumonia or cardiomegaly. An abdominal radiograph and a computed tomographic (CT) scan were both unremarkable. CT of the head did not show any abnormality. The white-cell count was 7300 cells per cubic millimeter. The rest of the complete blood count

was normal. The serum levels of electrolytes and blood ammonia were normal, as were the markers for hepatic and renal functions. Arterial blood gas levels were measured (Table 1). A lumbar puncture was performed on day 2; the results of cerebrospinal fluid analysis are shown in Table 2. Arterial blood lactate levels almost persistently remained high (Table 3) when the hemodynamic status of the patient was stable. Hyperlactatemia secondary to hypoperfusion of the tissue or any drug was subsequently ruled out.

Magnetic resonance imaging (MRI) and CT on day 7 revealed diffuse brain swelling compatible with hypoxic brain damage. Auditory brainstem response tests performed on day 8 elicited a normal response to clicks at 95 dB in the right ear but no response in the left ear, which suggested sensorineural hearing loss in the left, since there was no evidence for conductive hearing loss. On day 17, an electrocardiogram taken during an episode of palpitation revealed supraventricular tachycardia; echocardiography showed left ventricular hypertrophy.

The clinical manifestations and laboratory data, which included hearing loss, hypertrophic cardiomyopathy, and hyperlactatemia, made MELAS the most likely diagnosis. Her guardian, however, did not provide consent for genetic testing, contending that the establishment of a diagnosis would not change the treatment or course of the patient.

Table 2. Findings From Lumbar Puncture

| Variable | Finding |
|------------------------------|------------------|
| Appearance of fluid | Clear, colorless |
| Cells (per cubic millimeter) | 9 |
| Microorganisms | Absent |
| Glucose (mg/dl) | 80 |
| Total protein (mg/dl) | 30 |

Discussion

Our patient had an acute attack on the brain after an episode of abdominal pain and vomiting. The differential diagnosis was broad at the time of initial presentation, including cerebrovascular, infectious, inflammatory, and metabolic processes. An acute cerebrovascular insult was high on the list of diagnostic possibilities due to the absence of a history of

Table 3. Arterial Blood Lactate Levels*

| Day | 4 | 6 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 |
|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lactate | 4.3 | 3.8 | 1.0 | 3.1 | 3.3 | 3.0 | 1.8 | 4.6 | 3.7 | 2.7 | 3.7 | 6.7 |

*Normal range: 0.6 - 1.7 mmol/L

a prodrome (such as headache, subtle neurologic symptoms, and systemic illness) or predisposing conditions. Seizures, a key feature in the present case, are observed in only 2% - 33% of ischemic strokes [8] but a common presenting feature of other cerebrovascular diseases. Subsequent investigation revealed hearing loss, hypertrophic cardiomyopathy, and hyperlactatemia. Few conditions can completely account for this symptom complex. Her symptoms and signs allowed for the diagnosis of mitochondrial disorders, in which organs with high rate of oxidative metabolism, e.g., the gut, heart, brain, and peripheral nerves, are affected. Of the variety of clinical syndromes associated with mitochondrial dysfunction, the patient's illness is best characterized as MELAS [3-7], which presents with a wide range of clinical symptoms and signs, including abdominal pain and vomiting, seizure-like episodes, sensorineural hearing loss, cardiomyopathy, and hyperlactatemia.

Since stroke in childhood, although rare, has many potential causes in contrast to adult stroke [1], identification of the underlying disease is a diagnostic challenge. For a number of reasons, MELAS is one of the last possibilities that come to mind when the probable causes of pediatric stroke are considered. First, people with MELAS exhibit diverse manifestations that depend on the tissues that are affected. Second, a stroke-like episode often occurs with signs and symptoms atypical for a common ischemic stroke. Third, common laboratory tests, i.e., hematologic, blood chemical and urinary values, often present negative results. Even if some routine laboratory tests yield abnormal results, they do not provide compelling evidence for MELAS. Fourth, neuroimaging shows only nonspecific changes, although SPECT [9] shows some sensitivity to MELAS. Therefore, the first stroke-like episode in a previously healthy child with MELAS, as with this patient, poses one of the greatest diagnostic challenges for physicians and pediatricians.

A high index of clinical suspicion is a key factor in the diagnosis of MELAS [5]. Of great importance for diagnosis in the present case was the intent to evaluate MELAS at the time of the first stroke-like episode. The correct diagnosis in this case might have been impossible without the detection of hyperlactatemia, hearing loss, or hypertrophic cardiomyopathy. Patients with MELAS tend to evince neurological deterioration related to their stroke-like episode and recurrent seizures. Mortality in mitochondrial diseases is associated with cardiopulmonary failure and status epilepticus

[10], both of which were associated in the present case. In a pediatric cohort, younger age at onset is an independent predictor of death [11]. Unfortunately, the patient remains in a persistently vegetative state. Given that MELAS is not treatable except in a palliative sense, even timely recognition of MELAS could not have prevented the grave morbidity.

Conflict of Interest

The author declares no conflict of interests in this manuscript.

References

1. Roach ES, Golomb MR, Adams R, Biller J, Daniels S, Deveber G, Ferriero D, et al. Management of stroke in infants and children: a scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. *Stroke* 2008;39(9):2644-2691.
2. deVeber GA. Delays in the timely diagnosis of stroke in children. *Nat Rev Neurol* 2010;6(2):64-66.
3. Hirano M, Ricci E, Koenigsberger MR, Defendini R, Pavlakis SG, DeVivo DC, DiMauro S, et al. MELAS: an original case and clinical criteria for diagnosis. *Neuromuscul Disord* 1992;2(2):125-135.
4. Sproule DM, Kaufmann P. Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes: basic concepts, clinical phenotype, and therapeutic management of MELAS syndrome. *Ann N Y Acad Sci* 2008;1142:133-158.
5. Testai FD, Gorelick PB. Inherited metabolic disorders and stroke part 1: Fabry disease and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes. *Arch Neurol* 2010;67(1):19-24.
6. Goto Y, Horai S, Matsuoka T, Koga Y, Nihei K, Kobayashi M, Nonaka I. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS): a correlative study of the clinical features and mitochondrial DNA mutation. *Neurology* 1992;42(3 Pt 1):545-550.
7. Hom XB, Lavine JE. Gastrointestinal complications of mitochondrial disease. *Mitochondrion* 2004;4(5-6):601-

- 607.
8. Camilo O, Goldstein LB. Seizures and epilepsy after ischemic stroke. *Stroke* 2004;35(7):1769-1775.
 9. Miyamoto A, Oki J, Takahashi S, Itoh J, Kusunoki Y, Cho K. Serial imaging in MELAS. *Neuroradiology* 1997;39(6):427-430.
 10. Klopstock T, Jaksch M, Gasser T. Age and cause of death in mitochondrial diseases. *Neurology* 1999;53(4):855-857.
 11. Debray FG, Lambert M, Chevalier I, Robitaille Y, Decarie JC, Shoubridge EA, Robinson BH, et al. Long-term outcome and clinical spectrum of 73 pediatric patients with mitochondrial diseases. *Pediatrics* 2007;119(4):722-733.