Familial Occurrence of Intestinal Obstruction in Children With the Syndrome of Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes (MELAS)

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The syndrome of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is an uncommon neuromuscular disorder caused by mitochondrial dysfunctions that result in headaches, seizures, and progressive dementia. The authors describe a clinical case study of gastrointestinal manifestations in a pedigree with MELAS, in which all three children, ages 11, 8, and 6, demonstrated acute onset of intestinal obstruction. They unexpectedly showed severe abdominal distension and vomiting. Their parents had no clinical manifestation. The first female sibling underwent an emergent laparotomy because she was diagnosed to have intestinal strangulation. She had postoperative complications caused by progressive lactic acidosis and died the next day. The second and third sisters had similar onsets of the disease and were treated with gastrointestinal

THE SYNDROME of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is an uncommon neuromuscular disorder that usually is associated with a sudden onset of headache, convulsions, and hemiplegia or hemianopsia in previously healthy children and young adults.^{1,2} This syndrome causes systemic metabolic disorders and involves multiorganic symptoms including the alimentary tract. Chronic diarrhea is known to occur in 65% to 70% of patients with MELAS.³

In this report, we describe a clinical case study of gastrointestinal manifestation of a MELAS pedigree, in which all three sisters manifested the disease with sudden onset of intestinal obstruction in childhood.

CASE REPORT

An 8-year-old girl, the second of three female siblings, was referred to our institution because of abdominal distension and vomiting. Previously she had normal early development, although she showed slightly short stature (height, 130.5 cm; weight, 26.0 kg). No anemia or jaundice was found. Bowel sounds were hypoactive. Abdominal plain x-ray film showed increased jejunoileal gas with air-fluid levels (Fig 1).

Three years before, her older sister underwent an emergent laparotomy at another medical institution at the age of 11 years because she exhibited acute onset of intestinal obstruction. She was diagnosed with intestinal strangulation. Surgery resulted in death caused by progressive lactic acidosis the next day. Postmortem examination was not performed, but it was speculated that she had a metabolic crisis caused by mitochondrial encephalomyopathy because the preoperative physical examination suggested myoclonus and tremulous movements of the extremities and trunk. decompression and intravenous administration of lactatefree fluid and coenzyme Q10. Genetic testing using blood samples showed an A-to-G point mutation at nucleotide position 3243 in the tRNA^{Leu(UUR)} region in the mitochondrial DNA. In MELAS children who demonstrate acute onset of gastrointestinal manifestations, a careful review of family history and an elevation of serum lactate and pyruvate levels may enable a differential diagnosis to be made of acute abdomen to avoid unnecessary surgical intervention. *J Pediatr Surg 33:1837-1839. Copyright* © *1998 by W.B. Saunders Company.*

INDEX WORDS: Mitochondrial encephalomyopathy, ileus, MELAS.

On admission to our hospital, the patient had a mild headache but no other neurological abnormality. The parents had no clinical manifestation. Laboratory data indicated a white blood cell count of 14,900/µL; hemoglobin, 13.7 g/dL; hematocrit, 39.9%; platelet count, 255,000/µL; lactate dehydrogenase, 1,307 U/L; (234 to 471, normal range); asparate aminotransferase, 39 U/L; alanine aminotransferase, 39 U/L; total bilirubin, 0.44 mg/dL; creatinine kinase, 1,020 U/L (range, 33 to 158); urea nitrogen, 13 mg/dL; creatinine, 0.2 mg/dL; sodium, 137 mmol/L; potassium, 4.1 mmol/L; chloride, 99 mmol/L; c-reactive protein (CRP), 5.1 mg/dL (<1.0). Blood gas data showed Pao₂ of 96.7 mm Hg; Paco₂, 26.2 mm Hg; pH, 7.470; base excess, -3.0 mmol/L; bicarbonate, 18.8 mmol/L. Serum lactate and pyruvate levels were 43.1 mg/dL (2.6 to 16.1) and 2.27 (0.1 to 0.9), respectively. Based on her family history and laboratory data, metabolic disorder complicated with paralytic ileus was diagnosed, which was derived from possible mitochondrial encephalomyopathy. A nasoenteric tube was inserted to lead gastrointestinal decompression, and lactate-free fluid and coenzyme Q10 were administered intravenously. She recovered gradually in the next 5 days, and metabolic parameters were normalized. She was discharged from our hospital 2 weeks later. Further examinations to detect neurological abnormalities including brain computed tomography (CT), magnetic resonance imaging (MRI), and electroencephalogram were started in the division of pediatric neurology.

Genetic testing was performed to detect possible germline mutations specific for mitochondrial encephalomyopathy. Total DNA was isolated

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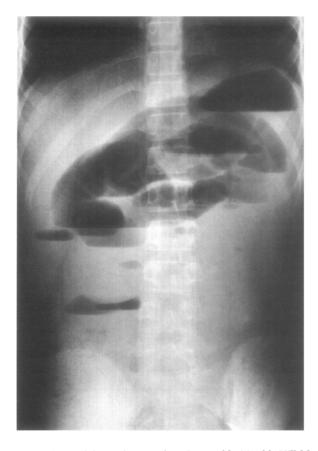


Fig 1. Plain abdominal x-ray of an 8-year-old girl with MELAS syndrome shows intestinal obstruction. The patient's older sister had a similar onset of the disease at the age of 11 years, and underwent an emergent laparotomy that resulted in death caused by progressive lactic acidosis 3 years before. Her younger sister also manifested MELAS syndrome at the age of 6 years. The second and third sisters were treated by gastrointestinal decompression and coenzyme Q10 administration.

from peripheral blood lymphocytes and prepared for genetic amplification of the mitochondrial DNA region, which includes the tRNA^{Leu(UUR)} gene, by polymerase chain reaction (PCR). The analysis identified an A-to-G base substitution in the tRNA^{Leucine} gene in the mitochondrial gene (MELAS 3243 mutation).⁴ The patient's younger sister, the third of the three sisters, also was examined to detect a possible genetic abnormality, and the same mutation was found.

Two years later, the third female sibling manifested the disease with headache, vomiting, and seizures at the age of 6. MELAS was diagnosed based on clinical manifestations and genomic analysis. She started a series of regimens to control myoclonus and tremolous movements of the extremities and trunk. She required gastrointestinal decompression and coenzyme Q administration to relieve the paralytic ileus three times thereafter.

DISCUSSION

Pediatric surgeons rarely face intestinal obstructions caused by metabolic disorders in children with MELAS syndrome. A neurological abnormality usually is recognized before gastrointestinal manifestations in such patients.^{5,6} This syndrome demonstrates a maternal inheritance, but the onset, severity, and course of the disease cannot be accurately predicted because of the effects of heteroplasmy and differing threshold values in varving organs and individuals.7 In the present pedigree, the first sibling manifested the disease, whereas no other family member had clinical symptoms. The diagnosis of mitochondrial encephalomyopathy sometimes is made based on limited data. The presence of such patients with metabolic crises may become a pitfall in diagnostic and therapeutic decision making for children with intestinal obstructions.

The mechanisms of metabolic disorders and paralytic ileus in MELAS patients remain unclear. Recent studies in molecular biology showed an A-to-G point mutation at nucleotide position 3243 in the transfer RNA^{Leu(UUR)} region in mitochondrial DNA (MELAS 3243 mutation).^{4,8} We found the same mutation in the present pedigree. The affected mitochondrial energy metabolism results in decreased aerobic ATP production and impairment of energy-requiring cellular function. These defects seem to cause muscle weakness, angiopathy, or metabolic abnormalities in a wide range of multisystem symptoms.⁹ Serum lactate and pyruvate levels reflect the severity of metabolic disorders and clinical symptoms, and can be used as metabolic parameters in MELAS patients.^{3,5}

DNA diagnosis to detect a possible MELAS 3243 mutation can be performed with greater than 99% accuracy.⁸ Genetic counseling to identify family members at high risk of carrying this mutation is recommended to introduce adequate treatments. A careful review of a patient's family history, including genetic analysis results and measurement of metabolic parameters, may provide clues to make an adequate diagnosis and therapeutic decision in MELAS children who demonstrate acute onset of intestinal obstruction.

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