

What condition caused the cyclical decompensation in this child?

Mitochondrial cytopathy refers to a group of disorders caused by a genetic defect that affects cell metabolism. A lack of unique symptoms makes the diagnosis difficult.

Tracy M. Deutsch, MS, PA-C

CASE

The parents of an 8-week-old white male brought the infant to the hospital after noticing him making apparent abnormal hand movements. At birth, the infant was full term; weight, 8 lb 12 oz; length, 21 inches; Apgar scores, 7 and 9. No abnormal movements were noted. The parents reported that at age 2 weeks, the infant had begun to cry frequently and intensely. The patient's physical examination at the hospital was unremarkable, but an EEG indicated irregular waves in the temporal lobes. The patient was sent home with his parents with no follow-up appointment.

At age 6 months, the baby lagged in reaching developmental milestones. By age 1 year, he had experienced numerous questionable seizures consisting of eye closing, staring, and small body movements. A potential diagnosis of cerebral palsy was made. At age 2 years, the child was able to stand with the help of a stander, perform the commando crawl, and walk with support. The child was also able to support his head until he became tired, which was after about 15 to 20 minutes. At age 3 years, a 1-week EEG revealed no seizures; however, abnormal brain activity was noted. The possibility of a metabolic disorder was considered. A muscle biopsy confirmed a diagnosis of mitochondrial myopathy complex I deficiency.

DISCUSSION

Mitochondrial cytopathy is a group of heterogeneous disorders caused by a genetic defect in the mitochondria or cellular DNA (mtDNA). The defect results in a biochemical abnormality that affects metabolism, or energy production, in cells. More than 90% of the body's energy is generated by the mitochondria, which are referred to as the powerhouses of cells.¹ Mitochondria are found in all human cells except erythrocytes (see Figure 1); therefore, mitochondrial cytopathy can be multisystemic.² When the mitochondria do not function properly, energy production is decreased, and free radicals, metabolites, and lactic acid are produced in excess, causing secondary damage to neurons and other

susceptible cells.³ High-energy organs, such as the brain, liver, and kidneys; eyes and ears; muscles; and nerves are most often affected by these disorders.²

A mitochondrion contains 37 mtDNA genes and more than 1,000 proteins. Only 13 of the proteins are encoded by mtDNA; the rest are encoded by nuclear DNA.⁴ Mitochondrial gene defects are possible only by maternal inheritance. Each ovum cell contains one nucleus and hundreds of mitochondria. A single cell is a *heteroplasm*, defined as containing both mutant and normal (wild-type) mitochondria.⁵ The balance of the two types of mitochondria determine the health of the cell. Mitochondria concentrations differ in each type of cell; therefore, the term *mitochondrial diseases* refers to the state of the organelle rather than a specific organ.

Mitochondrial cytopathy does not have any identifying features or hallmark symptoms, making the disorder difficult to diagnose.⁶ However, manifestations are specific to certain organs and systems (see Table 1, page 29). Mitochondrial cytopathy is usually suspected when a common disorder such as a migraine, a seizure, or a respiratory tract

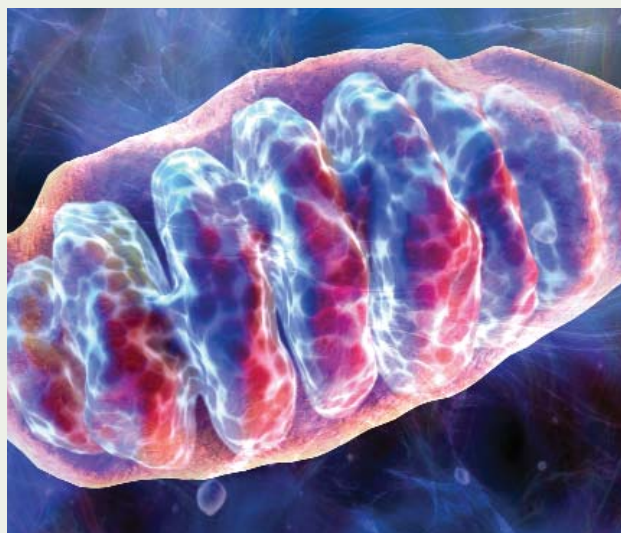


FIGURE 1. Computer illustration of a mitochondrion

TABLE 1. Manifestations of mitochondrial cytopathy

EARS	• Intestinal obstruction	• Exercise intolerance	• Peripheral neuropathy
• Hearing loss	• Irritable bowel syndrome	• Hypotonia	• Seizures
• Poor balance	• Poor appetite	• Myoclonus	• Spasms
EYES	• Vomiting	• Pain	PANCREAS
• Cataracts	HEART	• Rhabdomyolysis	• Diabetes
• External ophthalmoplegia	• Cardiomyopathy	• Weakness	• Exocrine pancreatic failure
• Optic atrophy	• Conduction block	NERVOUS SYSTEM	SYSTEMIC DISORDERS
• Ptosis	• Heart defects	• Absent reflexes	• Fatigue
• Visual defects	KIDNEYS	• Atypical cerebral palsy	• Respiratory tract problems
GI TRACT	• Fanconi syndrome	• Delays in motor skill, speech/learning, and mental development	URINARY BLADDER
• Abdominal pain	• Myoglobinuria	• Dementia	• Double voiding
• Bloating	• Renal calculi	• Encephalopathy	• Urinary calculi
• Constipation	LIVER	• Migraines	• Urine retention
• Delayed gastric emptying	• Hepatic failure	• Movement disorders	VASCULAR SYSTEM
• Diarrhea	• Hypoglycemia	• Neuropsychiatric disturbances	• Stroke
• Failure to thrive	MUSCLES		
• Gastroesophageal reflux disease	• Cramps		

Data from United Mitochondrial Disease Foundation. About Mitochondrial Disease. United Mitochondrial Disease Foundation Web site. http://www.umdf.org/site/c.dnJEKLNqFoG/b.3042169/k.7A8C/About_Mitochondrial_Disease.htm. Accessed January 6, 2009; and Goldstein A. Neurological manifestation of mitochondrial disease. Paper presented at: Mastering the Mitochondrial Maze Conference; June 2006; Atlanta, Ga.

infection manifests with unusual features; when three or more organ systems are involved; and when recurrent infections are seen in a chronic disease.

The disorder primarily affects children, but adult onset can occur. Newborns typically present with nonspecific symptoms such as lethargy, irritability, hyperactivity, cyanosis, failure to adequately feed, seizures, and jaundice.¹ Mitochondrial cytopathy is often initially misdiagnosed as cerebral palsy.⁷ Adult onset typically manifests as new muscle weakness, cramping, fatigue, migraine, stroke, and early cardiomyopathy or a cardiac conduction defect.¹

Each organ system is affected differently because of different gene mutation threshold levels. The threshold level pertains to the amount of mutant mitochondria needed for the disorder to be clinically evident within the organ system; for example, muscle weakness is most prominent in the eye muscles.⁶ Mitochondrial cytopathy can also affect the autonomic system, causing changes in heart rate, BP, and temperature.⁸

Diagnostic criteria are not universally accepted; therefore, a detailed history and complete physical examination are crucial for an accurate diagnosis. Different blood and CSF

TEACHING POINTS

- Mitochondrial cytopathy is a group of heterogenous disorders caused by a genetic defect in the mitochondria or cellular DNA. The defect results in a biochemical abnormality that affects metabolism, or energy production, in cells. More than 90% of the body's energy is generated by the mitochondria, which are referred to as the powerhouses of cells.
- Mitochondrial gene defects are possible only by maternal inheritance. Each ovum cell contains one nucleus and hundreds of mitochondria. Mitochondria concentrations differ in each type of cell; therefore, the term *mitochondrial diseases* refers to the state of the organelle rather than a specific organ.
- Mitochondrial cytopathy does not have any identifying features or hallmark symptoms. The disorder is usually suspected when a common disorder such as a migraine, a seizure, or a respiratory tract infection manifests with unusual features; when three or more organ systems are involved; and when recurrent infections are seen in a chronic disease.
- Multidisciplinary routine health maintenance is critical for maintaining the patient's level of function. Specialists who may be on the patient's health care team include a neuro-ophthamlogist, a dietitian, physical and occupational therapists, and speech and language therapists. Some patients may need a pulmonologist or a gastroenterologist as well.

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tests can be used to detect unused fuel molecules such as bicarbonate, ammonia, lactate, ketones, pyruvate, urate, and creatinine. Amino acid levels are also helpful.⁹ However, a muscle biopsy is the most specific test, even though an agreed-upon standard for enzyme testing has not been determined.² Ragged red fibers are commonly seen on biopsy if muscle tissue is affected.⁶

Mitochondrial cytopathy has no cure and no evidence-based treatment guidelines. Empiric treatment should include promoting energy production, reducing energy loss, alleviating symptoms, and slowing disease progression.¹⁰ Good nutrition, proper rest, exercise, and effective stress management are very important treatment modalities. In addition, nutrition supplements can also be helpful (see Table 2). Treatment must be individualized to each patient because measures that may help one patient could exacerbate symptoms in another patient. Metabolic specialists and geneticists can be valuable members of the health care team for these patients.

During a mitochondrial crisis, patients are experiencing an energy-deficient state. Any physiologic stressor can result in additional manifestations such as a stroke, a seizure, or organ failure (Sumit Parikh, MD, e-mail communication, December 2006). Treatment is IV administration of dextrose and carnitine. Dextrose replenishes nutrients needed to generate energy, and carnitine is needed for mitochondrial beta oxidation of fatty acids. Lactated Ringer's solution should be avoided because it contains lactic acid, which is already present in excess and can be neurotoxic. Vital signs, blood glucose levels, and routine chemistry panels should be monitored. According to a letter from Dr Parikh (August 2006), valproic acid, statins, erythromycin, and propofol should be avoided. Valproic acid is metabolized by the liver's mitochondria; statins stop the body's production of coenzyme Q₁₀; erythromycin inhibits mitochondrial translation; and propofol inhibits the mitochondrial membrane potential.¹¹

Multidisciplinary routine health maintenance is critical for maintaining the patient's level of function. Annual ECGs are necessary because the heart is highly susceptible to the disorder. Specialists that may be on the patient's health care team include a neuro-ophthalmologist, a dietitian, a physical and occupational therapist, and a speech and language therapist. Some patients may need a pulmonologist or a gastroenterologist as well.¹² If the patient must undergo a surgical procedure that requires anesthesia, vital signs, blood glucose levels, and acid-base balance must be monitored.¹²

CONCLUSION

No current diagnostic test or treatment protocol has been established for mitochondrial cytopathy. The disorder can manifest with a vast array of symptoms. These limitations, coupled with a lack of in-depth knowledge of the disease, make achieving adequate management of the disorder difficult. However, a basic knowledge of this group of disorders can make them more easily understood, accurately diagnosed, and optimally treated. All clinicians need to be able to

TABLE 2. Supplements effective in mitochondrial cytopathy

• Antioxidants	• Nicotinamide (vitamin B ₃)
• Biotin	• Potassium
• Calcium 2+	• Riboflavin (vitamin B ₂)
• Levocarnitine	• Succinate
• Citrate	• Thiamine (vitamin B ₁)
• Coenzyme Q ₁₀	• Uridine
• Creatine	• Vitamin K ₃
• Magnesium ²⁺	

Data from Chinnery P, Bindoff L. 116th ENMC International Workshop: The treatment of mitochondrial disorders, 14th-16th March 2003, Naarden, The Netherlands. *Neuromuscul Disord.* 2003;13(9):757-764; Gold DR, Cohen BH. Treatment of mitochondrial cytopathies. *Semin Neurol.* 2001;21(3):309-325; About Mitochondrial Disease. United Mitochondrial Disease Foundation Web site. http://www.umdf.org/site/c.dnJEKLNqFoG/b.3042169/k.7A8C/About_Mitochondrial_Disease.htm. Accessed January 6, 2009; and Tarnopolsky MA. Nutritional, pharmacological and exercise treatment strategies for mitochondrial disorders. *Mitochondrial News.* 2004;9:1,8-12.

recognize the signs and symptoms of acute and chronic mitochondrial cytopathy to prevent morbid events. **JAAPA**

Note: The author dedicates this article to the loving memory of Derrick Schmidt (August 1, 1996-May 11, 2008) and to his family. They are all angels in our eyes.

Tracy Deutsch practices at Quello Clinic—Family Practice, Burnsville, Minnesota, and at various Target MinuteClinics in Minnesota. She has indicated no relationships to disclose relating to the content of this article.

DRUGS MENTIONED

Dextrose	Erythromycin
Carnitine (Carnitor)	Propofol (Diprivan)
Valproic acid (Depakene, Depakote)	

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