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# Perioperative White Matter Degeneration and Death in a Patient with a Defect in Mitochondrial Oxidative Phosphorylation

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MITOCHONDRIAL dysfunction is being diagnosed increasingly in children and adults who have hypotonia, seizures, stroke, failure to thrive, renal and hepatic dysfunction, or cardiomyopathy.[1,2] The symptoms and severity of the disorder vary.[2] In this case report, we describe a child with a defect in oxidative phosphorylation whose immediate postoperative course after a semiemergent cholecystectomy was complicated by severe neurologic deterioration and ultimately early death.

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## Case Report

A 13-month-old girl was admitted for a semiemergent cholecystectomy. Her medical history included hypotonia, gross motor delay, intermittent lethargy, and frequent emesis that developed during the first 2 weeks of life. Extensive gastrointestinal investigations did not reveal a cause, but chronically increased lactate and pyruvate levels in blood and urine and Krebs cycle intermediates in the urine suggested a disorder in energy metabolism.[3] Cardiac ultrasound showed normal anatomy and no cardiomyopathy. As a result of persistent vomiting, she received parenteral nutrition and, later, gastrostomy tube feedings after placement of a gastrostomy tube during general anesthesia when she was aged 4.5 months. There were no intraoperative problems, but after operation, she had periods of increased lethargy in part as a result of a urinary tract infection. At age 8 months, as part of a diagnostic evaluation, muscle and liver biopsies were performed during general anesthesia (samples were analyzed in the Molecular Diagnostics Laboratory by Drs. N. Krawiecki and J. Schoff-



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ner, Emory University, Atlanta, GA). For approximately 1 week after operation, she was more lethargic than usual. Her liver biopsy revealed fatty infiltration and no glycogen accumulation. The muscle biopsy showed normal mitochondrial size, number, and structure, but enzymatic evaluation of fresh mitochondria showed decreased activity in complexes I, III, and IV of the respiratory chain. She began receiving carnitine, vitamin C, and coenzyme Q10.

Because of persistent vomiting, a Nissen fundoplication was performed when the child was aged 12 months. She was initially alert and active after operation, but 5 days later she had severe retching and a urinary tract infection and received parenteral nutrition and antibiotics. Four weeks later when the retching had still not improved, endoscopic retrograde cholangiopancreatography was performed during general anesthesia. This revealed cholelithiasis but no common bile duct obstruction. Symptoms of an upper respiratory tract infection developed after this procedure, and a chest radiograph revealed a new onset of cardiomegaly. Echocardiographic investigation at that time revealed severe diffuse nonobstructive hypertrophy of the left ventricle with normal ventricular function.[4]. Hepatobiliary scintigraphy scan performed several days later suggested cystic duct obstruction. In the week preceding the cholecystectomy, an upper respiratory infection developed that was accompanied by increased lactate to 12.6 mM (normal range, 0.5–2.2 mM) and the presence of increased Krebs cycle metabolites, lactic acid, and 3-hydroxybutyric acid in her urine. Her serum lactate concentration gradually decreased to 6.9 mM 24 h before cholecystectomy.

Evaluation immediately before induction of anesthesia for the cholecystectomy revealed a cheerful, interactive infant with mild hypotonia. She was premedicated with intravenous midazolam (0.1 mg/kg). Anesthesia was induced with thiopental and fentanyl and maintained with isoflurane in nitrous oxide and oxygen. Pancuronium was used for relaxation, and her trachea was intubated. To avoid hypoglycemia and to prevent an increase in the child's lactic acid concentration, fluid balance was maintained with a solution of 15% dextrose mixed with normal saline. Venous blood gas and serum glucose concentrations were monitored during the surgery. After a failed laparoscopic attempt, a gangrenous gall bladder was removed by open cholecystectomy. No hypoxia, bradycardia, hypotension, or other complications were noted during surgery. The glucose concentration was briefly increased to 396 mg/dl, but venous *p*H and carbon dioxide tension were maintained within normal limits. The hyperglycemia was slowly corrected by adjusting the intravenous glucose concentrations. The serum lactate level was 6.5 mM. The patient's neuromuscular blockade was reversed with neostigmine and glycopyrrolate, and the trachea was extubated without difficulty after uncomplicated placement of an epidural catheter for postoperative pain management.

After operation, the infant seemed agitated and hypertonic. She was noted to have increased tone in her right arm and leg. She did not seem to recognize her parents or respond to them. A computed tomography scan of the head was performed on the first postoperative day when her fontanel was noted to be bulging. It showed no evidence of cerebral edema or bleeding. She remained agitated, so the epidural bupivacaine fentanyl infusion was discontinued, and an intravenous morphine infusion (0.025 $mg \cdot kg^{-1} \cdot h^{-1}$) was begun. Although her periods of rest increased, she remained agitated whenever awake. She progressively developed further agitation, spasticity, arching, and posturing that was treated with diazepam and opioids. Magnetic resonance imaging of the brain 9 days after operation showed a marked increase in T2 signal intensity in the white matter, including the globus pallidi and cerebellum, without generalized swelling, indicative of white matter degeneration (fig. 1). She was treated supportively with sedatives for agitation and muscle relaxants for spasticity and died at home 5 weeks later. Her parents would not allow postmortem examination of her brain.

## Discussion

Although the number of patients identified with structural and functional mitochondrial abnormalities increases yearly, still little is known about the effects and risks of anesthesia and surgery in these patients. There is often no consistent correlation between the clinical presentation and biochemical profile and many have latent onset of symptoms that only present at times of stress, such as surgery or, more commonly, intercurrent febrile illness.[1]

Mitochondrial diseases or disorders of energy metabolism include defects in pyruvate metabolism, the Krebs cycle, and the respiratory chain. A diagnosis is made based on structural changes in the mitochondria, reduced enzymatic or cytochrome activity, characteristic radiologic or histologic abnormalities, or alterations in mitochondrial or nuclear DNA.[2] With few exceptions, these disorders are not clinically distinct. Instead, there is great overlap in their clinical features, biochemical derangements, and natural history. A review of individual energy disorders is less helpful than an appreciation of the scope of clinicobiochemical problems for which nearly all patients with energy disorders are potentially at risk (table 1). A preoperative assessment of any patient with mitochondrial disease must evaluate these concerns regardless of the nature of the patient's diagnosis.

Defects in the respiratory chain of the mitochondria, as in our patient, are the most common and result in failure to thrive, central nervous system dysfunction (ataxia, seizure, dementia), and cardiac, renal, and hepatic disorders. Elevated serum and cerebrospinal concentrations of lactate and pyruvate and an increased lactate-to-pyruvate ratio is present in these patients. Lactic acidemia that increases with stress is also noted. Most of these children die in early infancy of respiratory failure or metabolic acidosis.

A review of case reports describing the anesthetic management of patients with mitochondrial defects was most remarkable for the different approaches taken.[5–10] Although the number of reports is small, two complications were noted: postoperative respiratory depression that required reintubation of the trachea in a 51-yr-old man with Kearns-Sayre syndrome and muscle weakness



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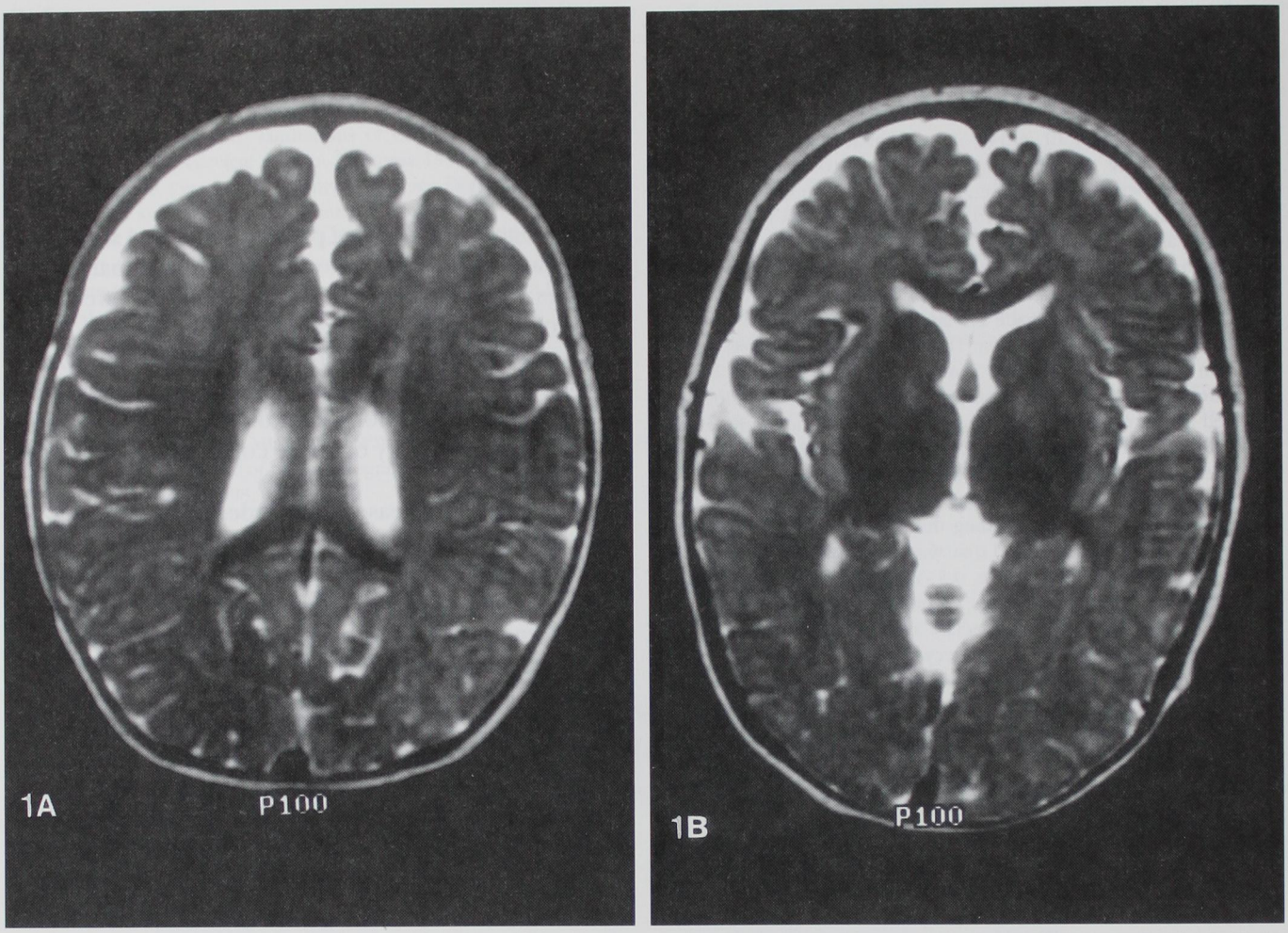


**Fig. 1. Magnetic resonance image scans of the brain, before and after cholecystectomy. *A* and *B* show two representative regions of the brain taken when the patient was aged 10 months. There is overall normal myelination and white matter intensity except for minimally increased signal in the basal ganglia. The ventricles are increased in size for the patient's age.**

***continued***

who underwent an appendectomy during general anesthesia[7]; and malignant hyperthermia in a 2-yr-old girl with mitochondrial dysfunction after halothane and succinylcholine administration for a muscle biopsy.[10]

Our patient had previously undergone four operations during general anesthesia for different procedures with the same agents that were used for the cholecystectomy. Her rapid white matter deterioration after this particular surgery may have been accelerated by stress responses to her perioperative respiratory illness, upper abdominal surgery, anesthesia, and the gangrenous gall bladder. Infection, surgery, and inflammation can lead to activation of the hypothalamic-pituitary-adrenal axis and to stimulation of glucocorticoid secretion. This stress response may lead to an increased adenosine triphosphate requirement. Increased production of tumor necrosis factor and interleukin-6 have been noted during and after upper abdominal surgery even in otherwise healthy patients.[11] Recent evidence suggests that tumor necrosis factor is associated with specific inhibition of the electron transport chain at complex III.[12] In this child, complex III was already an area of decreased activity. Tumor necrosis factor and other cytokines also may interfere with electron transport by inducing the synthesis of nitric oxide, which can inhibit cis-acotinase in the Krebs cycle and the iron-containing electron transport enzymes.[13]

We postulate that the production of inflammatory mediators stimulated by a gangrenous gall bladder combined with that produced by the tissue injury associated



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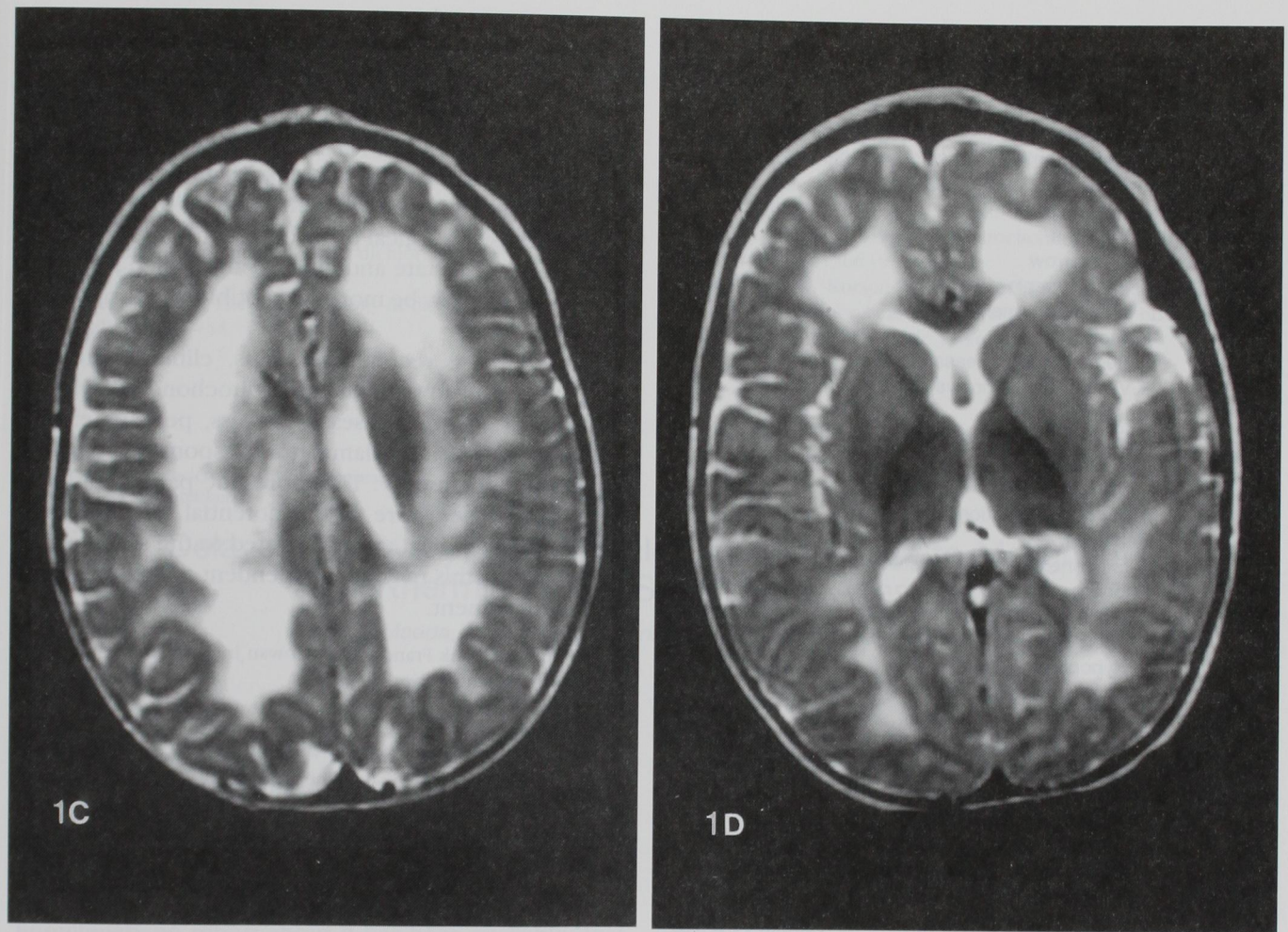


**Fig. 1.** ***continued.*** ***C*** **and** ***D*** **were taken 9 days after the cholecystectomy. There is extensive T2 hyperintensity in the white matter involving the internal capsule and the globus palladi. The ventricles are more prominent.**

with upper abdominal surgery may have led to a decreased ability to produce adenosine triphosphate. This child's preexisting oxidative phosphorylation defect combined with further inhibition of complex III of the electron transport chain by circulating cytokines may have led to a critical degree of mitochondrial failure. Because her mitochondria were already showing signs of dysfunction before surgery, this further stress may have been enough to lead to further mitochondrial damage in her central nervous system and subsequent white matter deterioration.[1,3]

Anesthetic management considerations for children with mitochondrial disorders include attempts to maintain metabolic balance as close to normal as possible, regardless of the urgency or indication for surgery. Infection, exercise, and alcohol ingestion can exacerbate the underlying lactic acidosis in patients with mitochondrial dysfunction, and the acidosis should be corrected before operation with an infusion of sodium bicarbonate.[14] Patients with an increased serum lactate concentration or an increased lactate-to-pyruvate ratio of 15:1 should not receive Ringer's lactate. Chronic, significant elevation in lactate may respond to administration of sodium dichloroacetate.[15] Dichloroacetate may also reduce hyperglycemia, which can occur during stress conditions, by stimulating glucose use peripherally.[16] However, excessive glycolytic oxidation of glucose in the face of disturbed pyruvate metabolism or oxidative phosphorylation also may increase lactate levels, so glucose levels should be monitored closely.[17] A normal and increased sensitivity and response to nondepolarizing muscle relaxants have been noted in patients with mito-



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**Table 1. Clinical Considerations for Preoperative Assessment of Patients with Mitochondrial Disorders**

| |
|---|
| Cardiac |
| Cardiomyopathy |
| Cardiac arrhythmias and heart block |
| Liver |
| Dysfunction |
| Cirrhosis |
| Bone marrow |
| Pancytopenia |
| Macrocytic anemia |
| Kidney |
| Renal tubular disease |
| Vitamin-unresponsive rickets |
| Gastrointestinal |
| Diarrhea, malabsorption |
| Vomiting |
| Failure to thrive |
| Pseudoobstruction |
| Pancreas |
| Exocrine pancreatic dysfunction |
| Endocrine |
| Diabetes mellitus |
| Short stature |
| Hypoparathyroidism |
| Adrenal insufficiency |
| Skin |
| Mottled pigmentation |
| Skin rashes |
| Neurological |
| Hypotonia or spasticity |
| Ataxia |
| Dementia |
| Seizures |
| Muscle weakness |
| Myopathy and myoclonus |
| Stroke-like episodes |
| Developmental delay |
| Sensorineural hearing loss |
| Apnea, abnormal breathing patterns |
| Peripheral neuropathy |
| Temperature dysregulation |
| Eye |
| Cataracts |
| Optic atrophy |
| Retinitis pigmentosa |
| Ophthalmoplegia |
| Metabolic |
| Lactic acidosis |
| Hyperammonemia |
| Inappropriate ketosis |

chondrial dysfunction.[18,19] Screening for adrenal dysfunction may be warranted given the recently described association between mitochondrial disease and primary adrenal insufficiency.[20] Cardiac assessment may uncover an acquired cardiomyopathy or conduction defect.

Elective surgery should be delayed if possible when there is evidence of infection, increasing lactate and glucose concentrations, or a source of stress that can otherwise be managed. Patients with mitochondrial dysfunction undergoing emergent surgical procedures or more extensive surgical procedures with increased concentrations of lactate and glucose and a high lactate-to-pyruvate ratio may be more susceptible to perioperative complications.

Despite these recommendations, clinical deterioration may occur in patients with mitochondrial dysfunction as part of their disease process, perhaps exacerbated by stress and inflammatory responses to trauma, infection, and surgery. Therefore, the patient and relatives should be aware of the potential for neurologic and general medical decline related to the stress of surgery and that this may be independent of the perioperative management.

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# Delayed Recovery from Muscle Weakness Due to Malignant Hyperthermia during Sevoflurane Anesthesia

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MALIGNANT hyperthermia (MH) is a disorder of skeletal muscle metabolism precipitated by volatile anesthetic "trigger" agents, resulting in a various degree of destruction of skeletal muscle tissue.[1] It is not surprising that subsequent muscle weakness might be one of the postoperative manifestations of MH; however, to our knowledge, no report about it has been available. In a patient recovering from MH related to anesthesia with sevoflurane, one of the newer volatile anesthetics, we document post-event muscle weakness.

## Case Report

A 27-yr-old, 85-kg man was scheduled for tonsillectomy because of recurrent tonsillitis. Neither the patient nor his family had any history of neuromuscular disease, and he had not received general anesthesia previously. Preoperative laboratory examinations revealed a slight increase in concentration of serum creatine phosphokinase (CK, 221 U/l; normal range, 20-100 U/l).

Before induction of anesthesia, body temperature was 36.8°C and his heart rate was 78 beats/min. General anesthesia was induced with thiopental (350 mg). Endotracheal intubation was facilitated using vecuronium (10 mg). Anesthesia was maintained with oxygen-nitrous oxide (66%) and sevoflurane (2.5-5.0%). Twenty-five minutes after

**Table 1. Time Course of Manual Muscle Test***

| | 1 mo | | 2 mo | | 3 mo | |
|---|---|---|---|---|---|---|
| Muscles Innervated by: | R | L | R | L | R | L |
| Humerus N. | 4 | 4 | 5 | 5 | 5 | 5 |
| Axillar N. | 4 | 4 | 5 | 5 | 5 | 5 |
| Musculocutaneus N. | 4 | 4 | 5 | 5 | 5 | 5 |
| Radial N. | 4 | 4 | 5 | 5 | 5 | 5 |
| Median N. | 4 | 3 | 4 | 4 | 5 | 5 |
| Ulner N. | 3 | 3 | 4 | 4 | 5 | 5 |
| Femoral N. | 4 | 4 | 5 | 5 | 5 | 5 |
| Obturator N. | 4 | 4 | 5 | 5 | 5 | 5 |
| Gluteus N. | 4 | 4 | 5 | 5 | 5 | 5 |
| Sciatic N. | 4 | 4 | 5 | 5 | 5 | 5 |
| Fibular N. | 4 | 4 | 4 | 4 | 5 | 5 |
| Tibial N. | 3 | 3 | 4 | 4 | 5 | 5 |

* Grading system: Complete range of motion against gravity, 5 = with full resistance at end of range; 4 = with some resistance at end of range. Complete range of motion, 3 = against gravity; 2 = with gravity eliminated. No range of motion, 1 = slight contraction; 0 = no contraction.

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