Anesthetic Management in Mitochondrial Encephalomyopathy: A Case Report

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We report on a morbidly obese 16-year-old boy (weight, 116 kg; height, 176 cm; body mass index, 35.5 kg/m²) with mitochondrial encephalomyopathy and a history of cerebral infarction, epilepsy, and severe mental retardation. The patient was scheduled for elective surgery under general anesthesia for multiple dental caries and entropion of the left eye. Preoperative examination results, including an electrocardiogram, were normal. No obvious cardiac function abnormalities were observed on echocardiography. Midazolam (10 mg) was administered orally as premedication 30 minutes before transfer to the operating room; however, the patient was uncooperative, and his body movements were difficult to control upon entering the operating room. This complicated our attempts to establish a peripheral intravenous line and necessitated volatile inhalational induction, followed by maintenance using total intravenous anesthesia. General anesthesia was used to minimize metabolic system stress. We did not use an infusion solution containing sodium lactate. The operation and subsequent clinical course until discharge were uneventful. Because aerobic metabolism is already compromised in patients with mitochondrial encephalomyopathy, anesthetic management should be designed to avoid placing additional stress on the metabolic system.

Key Words: Congenital disorder; General anesthesia; Mitochondrial encephalomyopathy; Morbid obesity.

Mitochondrial disease, a rare congenital disorder presenting as progressive multiple organ failure, is caused by dysfunctional mitochondrial energy production or conversion.^{1,2} Normally, adenosine triphosphate is biosynthesized via the Krebs cycle and oxidative phosphorylation reactions in mitochondria. However, patients with mitochondrial encephalomyopathy have a biochemical defect that impairs oxidative phosphorylation and integration of pyruvate into the Krebs cycle. This leads to dysfunction of mitochondrial energy production or conversion. Mitochondrial diseases have varied etiologies and are difficult to classify. Some are caused by mitochondrial DNA mutations such as those in the mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) syndrome. Abnormalities

due to mitochondrial disease occur in organs with high energy consumption, such as skeletal muscle, and in the central nervous system (CNS). Clinical symptoms of mitochondrial disease include skeletal muscle weakness and atrophy, as well as damage to the CNS, liver, kidney, and heart.³ Therefore, this disease is also called mitochondrial encephalomyopathy. The estimated incidence for this disease is 1 in 4000 live births.⁴ Patients with mitochondrial encephalomyopathy who undergo surgery have a risk of perioperative death due to preexisting functional impairment of multiple organs and abnormal responses to drugs used during surgery.⁵ General anesthesia should be planned to minimize stress on the metabolic system in patients in whom aerobic metabolism is already compromised.^{6,7}

Here, we report our management of general anesthesia in a severely obese pediatric patient with skeletal muscle weakness and CNS abnormalities caused by mitochondrial encephalomyopathy classified as MELAS. Written informed consent was obtained from the patient's guardian for treatment and publication of the case report.

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CASE REPORT

The male patient (age 16 years and 9 months) measured 176 cm (69 in) in height and weighed 116 kg (body mass index 35.5 kg/m²). He was diagnosed with multiple dental caries and entropion of the left eye and was scheduled for elective surgery for conservative dental treatment and entropion surgery. He had not previously undergone sedation or general anesthesia. There was no relevant family history. However, the patient was morbidly obese and had a history of mitochondrial encephalomyopathy, cerebral infarction, epilepsy, and severe mental retardation. At the time of his scheduled treatment, the patient was regularly receiving antiepileptic drugs including sodium valproate, carbamazepine, clonazepam, clobazam, diazepam, and the mitochondrial function-activating drug levocarnitine. He had no known allergies. His status at the time of the procedure was as follows: (a) he could communicate but his level of comprehension was low, (b) he used a wheelchair for activities of daily living, and (c) he had frequent epileptic seizures and sometimes showed agitated behavior such as shouting and physical aggression. A preoperative examination including standard biochemical tests indicated a low level of alkaline phosphatase (137 U/L; normal range, 220–1050 U/L). Other lab findings were within normal ranges. He did not have lactic acidosis. Chest radiography showed no obvious pulmonary opacity; the cardiothoracic ratio was over 50%, indicating enlargement of the cardiac silhouette, and there was diaphragmatic eventration, which was thought to be congenital. An electrocardiogram showed normal sinus rhythm with a heart rate of 102 beats/min. There were no obvious cardiac function abnormalities on echocardiography. Therefore, the patient had most of the features of the MELAS syndrome.

Midazolam (10 mg) was administered orally as premedication 30 minutes before anesthetic induction, but the patient was uncooperative, and his body movements were difficult to control upon entering the operating room. As a possible difficult airway was anticipated, several oropharyngeal airways and a video laryngoscope (Airwayscope) were prepared as secondary devices for anesthesia induction. Oxygenation with 6 L/min O₂ was performed after confirming proper mask fitting. This was followed by volatile inhalational induction with 2 L/min O₂, 4 L/min N₂O, and 8% sevoflurane. A peripheral intravenous line was established after the patient lost consciousness. Solutions containing sodium lactate were avoided; instead, acetated Ringer solution and bicarbonated Ringer solution were used. At that time, his axillary body temperature was 36.5°C. Atropine (0.5 mg), midazolam (5 mg), and propofol (50 mg) were then administered, followed by

implementation of total intravenous anesthesia with continuous infusions of remifentanyl (0.2 µg/kg/min) and propofol (6–10 mg/kg/h or 100–166 mcg/kg/min). Mask ventilation was difficult and was improved following oropharyngeal airway placement and using a 2-person technique. Rocuronium (50 mg) was then administered for muscle relaxation, and nasotracheal intubation was performed with a Macintosh laryngoscope No. 3 (Cormack grade II with BURP manipulation). There were no remarkable intraoperative abnormalities in vital signs.

Before extubation, full recovery from muscle relaxation was promoted by the administration of 200 mg sugammadex, although the patient appeared to have recovered muscle function 2 hours after the initial administration of the muscle relaxant, as he was noted gripping objects with his hand at that time. The patient awakened smoothly from anesthesia, and the tracheal tube was removed after effective spontaneous ventilation and muscle recovery were confirmed. The total crystalloid infusion volume was 550 mL, and blood loss was minimal. The duration of surgery was 1 hour and 43 minutes, and the anesthesia time was 3 hours and 6 minutes. After surgery, there were no marked irregularities in breathing, circulation, or body temperature. A blood test showed no appreciable abnormalities such as exacerbation of acidosis, and the patient was discharged from our dental hospital 7 days after the operation. The patient's condition was stable after leaving the hospital.

DISCUSSION

Perioperative management is challenging in patients with mitochondrial encephalomyopathy (Table). Acidosis due to hypermetabolism is considered a potential problem, and hypermetabolism can develop owing to increased stress associated with shivering from hypothermia, perioperative pain, or preoperative anxiety. Therefore, we were careful to maintain the patient's temperature and keep his pain levels low. Because lactate metabolism is impaired in patients with MELAS, infusion solutions containing sodium lactate should be avoided, as the metabolic conversion of lactic acid to bicarbonate is required for lactate to act as a buffer. In contrast, infusion solutions containing acetate were considered an option because acetate itself has a buffering action and does not lead to an increase in lactic acid levels. As lactate is metabolized by the liver, the acetate solution, which is converted to bicarbonate not in liver but in muscle, was originally developed for patients with liver dysfunction. Notably, bicarbonated Ringer solution has been reported to be more effective in maintaining pH than acetated Ringer because the

Major Anesthetic Concerns for Patients With Mitochondrial Myopathy

<i>Anesthetic Concerns</i>	<i>Recommendations</i>
General condition	The primary mitochondrial diseases associated with respiratory chain defects have varied clinical manifestations such as diabetes, endocrine dysfunction, hearing loss, hypertrophic cardiomyopathy, liver failure, ptosis of eyelids, obstructing vision, and seizures.
Minimal malignant hyperthermia risk	Recent evidence indicates that there is no association between mitochondrial disease and malignant hyperthermia.
Selection of anesthetic agents	Propofol should be used with caution, especially if prolonged infusions are required. Nondepolarizing neuromuscular agents should be used with caution. When prolonged paralysis occurs, anticholinesterases should be avoided because they can trigger a myotonic crisis.
Intravenous fluid selection	Solutions buffered with acetate, bicarbonate, or plain 0.9% normal saline should be used rather than lactated solutions.
Body temperature	Aggressive warming has been suggested as a requirement during general anesthesia, as heat production is impaired in mitochondrial myopathy.

bicarbonate is physiologic and therefore does not require a metabolic process to alkalinize.⁸ Normal saline (0.9% NaCl) may also be used as an intravenous fluid provided large volumes are not infused. In consideration of acid-base equilibrium, we should therefore use crystalloid solutions buffered with acetate or bicarbonate or plain 0.9% normal saline rather than lactated solutions in patients with MELAS who have impaired lactate metabolism. Glucose administration during surgery was also considered necessary because hypoglycemia promotes hyperlactacidemia. However, hyperglycemia may also worsen lactic acidosis; therefore, acetated Ringer solution containing 1% glucose, which can easily maintain the glucose level within the normal range, was used in this case. Peripheral circulatory failure due to an inadequate infusion volume is another risk for acidosis, and the infusion volume is therefore considered important for patients such as those described here.

A low body temperature inhibits mitochondrial function and increases metabolic stress. Therefore, aggressive warming has been suggested as a requirement during general anesthesia because heat production is impaired in mitochondrial encephalomyopathy.⁹ The patient's body temperature was closely monitored during surgery, and an electric warmer was used for heating. No rapid changes in body temperature were detected during the surgery. The risk of malignant hyperthermia in children with muscular disorders, including those with mitochondrial diseases, has been suggested to be similar to that in healthy individuals, even if inhalational anesthetics are used on a regular basis.¹⁰ Other recent evidence indicates that mitochondrial disease is not highly associated with malignant hyperthermia.^{10–13} Some reports indicate that propofol should be avoided in patients with MELAS syndrome, especially if prolonged infusions are required for

sedation or anesthetic maintenance.^{14,15} On the other hand, some anesthetic management reports describe total intravenous anesthesia using propofol in patients with mitochondrial disease.¹⁶ In this case, volatile inhalational induction was performed to obtain intravenous access because of the patient's uncooperative state. We then switched from inhaled anesthesia to total intravenous anesthesia to avoid emergence agitation or delayed awakening due to accumulation of inhaled anesthetic in adipose tissue.

We attempted to use oral midazolam as a premedication to improve behavior for obtaining intravenous access. The 10-mg dose may have been insufficient for this patient but was limited according to our hospital's guidelines. However, we were also concerned with obtaining deeper sedation because of concerns over airway patency and the unpredictable response because of cognitive deficits. Other options may have included oral or intramuscular ketamine and/or eutectic mixture of local anesthetic cream to facilitate better preoperative sedation and easier intravenous access. We chose not to use ketamine, as it increases salivary secretions and overall metabolism. We did not have eutectic mixture of local anesthetic cream in our hospital. Although the patient followed standard nil per os guidelines, we could have considered a modified rapid sequence induction to decrease the risk of pulmonary aspiration, but this is difficult with nasotracheal intubation.¹⁷ Despite mask ventilation being somewhat difficult because of his obesity and uncooperative state, we treated the patient with a muscle relaxant, as the use of a proper dose of muscle relaxant may improve ventilation efficiency when using a face mask.^{18–21} However, an abnormal response might occur in patients with some rare genetic diseases. We therefore prepared airway-securing devices in advance in case of difficulties with airway patency leading to a cannot intubate–cannot ventilate scenario.

The present patient was morbidly obese (116 kg, body mass index 35.5 kg/m²), but this was not directly related to his medical condition, as the clinical manifestations of mitochondrial disease do not include obesity.¹³ Despite cardiomegaly, the patient had no functional cardiac or endocrine abnormalities. However, the possibility of cardiac complications (eg, cardiac conduction blocks) and endocrine abnormalities (eg, type 2 diabetes) should be considered before planned surgery for patients with mitochondrial disease.

In this report, we describe the administration of general anesthesia in a severely obese pediatric patient with skeletal muscle weakness and CNS abnormalities caused by mitochondrial encephalomyopathy. The patient was uncooperative and also had epilepsy and delayed mental development. Despite these challenges, perioperative management was performed uneventfully, including switching from inhaled sevoflurane at the time of anesthesia induction to total intravenous anesthesia. Moreover, prolonged muscle relaxation did not occur despite the use of a nondepolarizing muscle relaxant. Previous reports have shown that nondepolarizing neuromuscular agents can be used in patients with mitochondrial disease.²² However, it is recommended that they be used with caution, as the response to this drug group cannot be predicted with certainty in this patient population. The duration of paralysis may be prolonged, in which case anticholinesterases should be avoided because their use can trigger a myotonic crisis.²³ Accordingly, we used sugammadex to ensure complete recovery from neuromuscular blockade. Extra caution was required for potential postoperative falls because the patient's risk was thought to be high owing to the administration of various antiepileptic drugs and the observed loss in muscle strength.

Functional deterioration of multiple organs, abnormal responses to drugs, and perioperative death have been reported in anesthetic cases of mitochondrial encephalomyopathy. These responses are thought to be due to exacerbation of aerobic metabolism disorders due to perioperative stress. Thus, in patients with mitochondrial encephalomyopathy, it is important to avoid additional stress on the already compromised metabolic system.

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