Anesthetic Management of a Child With Unspecified Mitochondrial Disease in an Outpatient Dental Setting

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Mitochondrial disease (MD) represents a category of metabolic disorders with a wide range of symptoms across a variety of organ systems. It occurs with an incidence of greater than 1:5000 and can be difficult to specifically diagnose because of the variety of clinical presentations and multiple genomic origins. Although phenotypically variable, MD symptoms often include hypotonia, cardiac defects, dysautonomia, and metabolic dysfunction. Mitochondrial disease presents a unique challenge in terms of anesthetic management, as many anesthetic drugs suppress mitochondrial function. Additional considerations may need to be made in order to evaluate the patient's metabolic compensation prior to surgery. This article presents an in-depth discussion of a case involving a nearly 10-year-old boy with a history of an unspecified form of MD, who presented for endodontic treatment of tooth No. 30 under deep sedation. The article also provides a thorough review of the current literature surrounding the anesthetic management of patients with MD.

Key Words: Mitochondrial disease; Mitochondrial myopathy; Pediatric; Anesthesia.

Mitochondrial disease (MD) is a relatively rare group of disorders, with a wide range of multisystem symptoms. When associated with skeletal muscle symptoms, these disorders are also referred to as *mitochondrial myopathies*. These disorders may be due to primary or inherited mutations in mitochondrial or nuclear DNA that affect the development and function of cellular mitochondria. The resulting mitochondria are dysfunctional and are characterized by an inability to adequately facilitate oxidative phosphorylation and ultimately adenosine triphosphate synthesis.¹ Consequently, organ systems with a high energy requirement are the most severely affected, including the nervous system, skeletal muscle, cardiovascular system, and many others.² Because of dual genomic origin and wide phenotypic variability over a multitude of organ systems, specific diagnosis and treatment can prove difficult.³ In this case report, we discuss the anesthetic management of a pediatric dental patient with a diagnosis of unspecified mitochondrial myopathy.

CASE REPORT

A nearly 10-year-old boy with a history of an unspecified form of MD presented with a chief complaint of his gums draining next to the mandibular right first molar. Clinical testing showed a diagnosis of necrotic tooth No. 30 with an accessory buccal root. The tooth was also banded with a space maintainer. The patient was uncooperative during the examination and exhibited a significant gag reflex during radiographs, providing sufficient indication for sedation. Dental treatment was to include root canal therapy with apexification of immature roots on tooth No. 30.

Upon review of the medical history, a number of concerns emerged. The patient had a 2-year-old diagnosis of MD of unspecified form. He had a history of dysautonomia related to temperature regulation issues and postural orthostatic tachycardia syndrome, which periodically produced syncope. He had previously been diagnosed with generalized hypotonia and failure to thrive, resulting in placement of a gastrostomy tube. The patient routinely experienced arthralgia, myalgia, and hypermobility of joints. His daily medications included L-carnitine, coenzyme Q10, medium-chain triglyceride oil, and celecoxib (100 mg/d) for arthralgia.

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The medical history was discussed in detail with the mother as well as the primary care physician, cardiologist, and medical geneticist. All pertinent reports were studied, including normal 12-lead electrocardiogram, normal echocardiogram, and 3 anesthetic records from previous procedures. These procedures included general anesthesia for gastrostomy tube placement (1 year prior) and 2 complete oral rehabilitations (2 and 4 years prior). The 3 previous anesthetics, which were managed using inhalation agents, were all unremarkable. Significant family history included a diagnosis of mitochondrial respiratory chain deficiency in the patient's younger brother. The mother also claimed she suspected that she may also have a form of the disease, for which she was planning to be tested. After thorough review of all pertinent information, the case was scheduled for a deep sedation with a total intravenous anesthesia (TIVA) technique. TIVA was selected in order to avoid the mitochondrial suppression that may be induced with inhalation agents.

The patient and his mother were instructed to arrive 2 hours early for the 9:00 AM procedure to allow adequate time for measuring baseline vitals, recording a basic metabolic panel, and administering dextrose to mitigate metabolic consequences of fasting. The patient had been instructed to follow standard 8-hour nil per os guidelines. The operating room was also warmed to 75°F (23.89°C) and stocked with multiple blankets to assist with the patient's temperature regulation issues. Upon arrival, the patient's medical history was reviewed thoroughly, and a physical evaluation was completed. Despite presenting with noticeable hypotonia, his posture and respiratory effort were normal. The patient presented at 57 inches (144.78 cm) and 30 kg with the following baseline vitals: blood pressure, 118/75 mm Hg; heart rate, 75 beats per minute (bpm) in sinus rhythm; room air SpO₂, 98%; and axillary temperature, 35.4°C. Metabolic equivalents were deemed to be greater than 4 based on his reported ability to swim recreationally. However, his mother mentioned that he has occasionally used a powered wheelchair when heavily fatigued, which occurred after strenuous or prolonged periods of activity. The airway was assessed as favorable and classified as a Mallampati II. Preoperative cardiopulmonary evaluation was unremarkable. Routine noninvasive monitors, including axillary temperature probe, were placed after seating the patient. A CO₂ sampling nasal cannula was used for qualitative data about pattern of breathing. Quantitative data regarding end-tidal values of CO₂ were monitored for consistency, but specific values were not recorded because of the unreliability of environmental air mixing with exhaled air.

Oxygen was administered at 2 L/min via nasal cannula. A 22-gauge intravenous (IV) catheter was placed with slight restraint and encouragement from his mother. A

Table 1. Basic Metabolic Panel via i-STAT System, Preoperatively*

<i>Test</i>	<i>Patient's Value</i>	<i>Reference Interval†</i>
Sodium (Na ⁺)	139 mmol/L	138–146 mmol/L
Potassium (K ⁺)	4.2 mmol/L	3.5–4.9 mmol/L
Chloride (Cl [−])	101 mmol/L	98–109 mmol/L
Hemoglobin (Hb)	14.3 g/dL	12–17 g/dL
Hematocrit (HCT)	42% PCV	38–51% PCV
Blood urea nitrogen (BUN)	7 mg/dL	8–26 mg/dL
Creatinine (Crea)	0.4 mg/dL	0.6–1.3 mg/dL
Glucose (Glu)	98 mg/dL	70–105 mg/dL
Ionized calcium (iCa ⁺⁺)	1.28 mmol/L	1.12–1.32 mmol/L
Total CO ₂ (TCO ₂)	26 mmol/L	24–29 mmol/L
Anion gap	17 mmol/L‡	10–20 mmol/L

* mmol/L indicates millimoles per liter; g/dL indicates grams per deciliter; PCV indicates packed cell volume; mg/dL indicates milligrams per deciliter.

† Reference range adapted from the iSTAT webpage at abbottpointofcare.com.

‡ Although within this reference range, the anion gap value of 17 mmol/L is often considered mildly acidotic.

basic metabolic panel was obtained via the i-STAT System (Abbott Laboratories, Abbott Park, Ill), a chair-side blood analysis device. The results revealed a blood glucose level of 98 mg/dL and a mild metabolic acidosis, based on slight anion gap elevation (Table 1). It would have been preferable to have pH values; however, the pH value was unavailable on the i-STAT CHEM8+ cartridge used. Preoperative fluid replacement was initiated with 5% dextrose solution (D5W) to mitigate potential hypoglycemia and acidosis during the procedure. A total of 175 mL of D5W was administered (8.75 g dextrose).

The subsequent fluid administered was 0.9% normal saline, and the IV anesthetic was administered using primarily dexmedetomidine and remifentanyl infusions, with preliminary doses of midazolam (titrated to 4 mg) and diphenhydramine (titrated to 25 mg). Glycopyrrolate (0.1 mg) was given initially for antisialagogue effects and to maintain a stable heart rate, given that dexmedetomidine infusion may produce bradycardia. A conservative loading dose of dexmedetomidine (8 µg over 10 minutes) was delivered. Low doses of ketamine (10–20 mg each) were also used at particularly stimulating times during the appointment, such as the injection of 2.7 mL of 2% lidocaine with 1:100,000 epinephrine and intraoperatively during 2 instances of light anesthesia. A total of 50 mg of ketamine was used. Dexamethasone and ondansetron were administered for antiemetic effects. The absence of propofol from the pharmacologic regimen provided a unique challenge for this anesthetic. Since a less common combination of infusions was used to maintain a level of deep sedation, titrating the 2 infusions required a longer period of

Table 2. Preoperative Considerations for MD

<i>Consideration</i>	<i>Rationale</i>
Schedule early appointment	Mitigates necessary fasting period, since MD patients may have reduced ability to utilize a shift toward beta-oxidation of fatty acids.
Monitor blood glucose/consider dextrose	Fasting for nil per os status means less glucose available for anaerobic glycolysis, which is a significant pathway of adenosine triphosphate synthesis in MD. Consider IV dextrose administration in preop room.
Preoperative electrolyte and pH screening	Electrolytes and anion gap can provide insight into metabolic status and potential acidosis. Analysis of pH in the perioperative period would provide the best indication of acid/base status.
Assess respiration	Pronounced hypotonia and fatigue may impair respiratory efforts, possibly contraindicating sedation and outpatient general anesthesia.
Evaluate nervous system functional reserve	MD affects the nervous system more quickly than less metabolically active systems. Titrate drugs to effect. Extreme sensitivity to anesthetics may indicate reduced neurologic reserve and a decreased anesthetic requirement.

refinement. After the patient was sufficiently anesthetized, airway management techniques were required, including placement of a foam shoulder roll, 24 French nasal pharyngeal airway, and constant chin lift, provided by the endodontic assistant. Approximately 1 hour after D5W administration, a blood glucose level of 129 mg/dL was measured.

For most of the case, the patient maintained a heart rate at, or slightly above, his baseline of 80 bpm, with brief deviations as high as 120 bpm during periods of light anesthesia and ketamine administration. However, immediately following administration of the local anesthetic and the first 20 mg bolus of ketamine, a transient period of supraventricular tachycardia at a rate of 219 bpm was noted. This was followed by a brief sinus block and a return to normal sinus rhythm. This cycle of supraventricular tachycardia to sinus block to normal sinus rhythm repeated itself 2 more times. In total, the 3 cycles lasted approximately 2 minutes. The supraventricular tachycardia was successfully treated with esmolol (10 mg). These anomalies did not return upon successive ketamine boluses, and no additional lidocaine with epinephrine was given during the procedure. There were 2 other instances of light anesthesia, which were managed by deepening the anesthetic level with remifentanyl. In both instances, the patient became apneic and required jaw thrust maneuvers and mask ventilation to regain appropriate oxygen saturation. The patient demonstrated a low respiratory reserve and a tendency to desaturate very quickly, but airway management techniques quickly resolved the issue on both instances. Although minimal temperature instability was detected initially, the patient's skin temperature still decreased slightly from 35.4°C to 34.9°C over the course of the case, which may have been related to the dysautonomia. This was despite the patient being covered with multiple blankets to assist in thermoregulation. The surgery time totaled 160 minutes. The patient emerged slowly over the

course of 30 minutes and transitioned smoothly into the postoperative period. The patient was monitored for 75 minutes postoperatively. The IV was discontinued without incident approximately 60 minutes after the procedure end time.

DISCUSSION

Numerous preoperative anesthetic considerations must be made when treating a patient with a mitochondrial myopathy (Table 2). Complete review of medical history with all relevant care providers is imperative. In addition, a thorough preoperative anesthetic evaluation is important to gauge the degree and type of organ system involvement, specifically cardiac, neuromuscular, and respiratory. Extreme sensitivity to the administration of anesthetic agents represents a low nervous system functional reserve and may indicate a more severe disease state.⁴ This type of reaction calls for a lower anesthetic dosage to maintain the desired level of anesthesia. Because of the uncommon combination of IV anesthetic agents utilized in this case, it was difficult to assess the relative anesthetic requirement of our patient. However, there was no obvious anesthetic sensitivity throughout the case. Both episodes of apnea occurred following boluses of remifentanyl, which is a known respiratory depressant. Titration of the remifentanyl infusion to a higher rate provided a depth of anesthesia that did not necessitate further boluses. As a result, the patient did not experience further apneic events.

Based on preoperative cardiology reports and cardiac auscultation, our patient was understood to be cardiovascularly stable. However, he did experience the 2-minute cycle of supraventricular tachycardia converting to and from sinus rhythm. This could have been related to a number of possible causes, including his dysautonomia and related postural orthostatic tachycardia

syndrome or the administration of IV ketamine, glycopyrrolate, and submucosal lidocaine with epinephrine around the time of the cardiac anomaly.

Evaluations revealing poor neuromuscular tone and limited ventilatory function may also be strong indicators for respiratory complications intraoperatively and postoperatively.⁵ Although our patient presented with conspicuous hypotonia, his ventilatory effort was not labored. Preoperative basic metabolic panels are also good indicators of the MD patient's metabolic status, especially in terms of blood glucose and acidosis, which have potential to worsen with surgical stress.⁶ For this case, the i-STAT System was used preoperatively to obtain a metabolic panel (Table 1), paying close attention to the glucose and anion gap values, as MD patients are known to be at risk for metabolic decompensation.² It is notable that although the minimal elevation in the anion gap could indicate a tendency toward metabolic acidosis, it may also be inaccurate due to the use of total CO₂ in the calculation as a proxy for HCO₃⁻.⁷

Additional considerations must be made when selecting anesthetic agents and fluid replacement options for MD patients. These patients are very susceptible to entering states of ketoacidosis and lactic acidosis. The ability to use aerobic respiration to generate adenosine triphosphate is impaired with MD, requiring increased anaerobic metabolism to compensate.⁸ This increase in dependence on anaerobic glycolysis creates a higher demand for glucose, especially in a patient who is required to fast to maintain a preoperative nil per os status. In addition, fasting in an anaerobic glycolysis-dependent state will deplete the glucose supply over time, causing a shift in metabolism to beta oxidation of fatty acids. Patients with MD have a limited ability to derive energy in this manner, as beta oxidation creates acetyl-CoA, which normally enters the Krebs cycle to form adenosine triphosphate and the liver to form ketone bodies. During periods of fasting in these patients, the Krebs cycle may not be fully functional, leaving more acetyl-CoA to form ketone bodies. Ketone bodies are acidic in nature and may contribute to ketoacidosis, which may be appreciated as an increased anion gap. Hence, the appointment was scheduled early in the morning, and D5W was administered in the preoperative period to mitigate the metabolic effects of fasting, despite a normal initial blood glucose level of 98 mg/dL.⁹ By estimating an elevation in blood glucose of roughly 3 mg/dL per gram of dextrose administered, 8.75 g (175 mL D5W) was selected as an appropriate dose. This would theoretically add approximately 25 mg/dL to the measured blood glucose value, providing sufficient substrate while preventing catabolism. The actual increase in blood glucose was 31 mg/dL, from 98 to

129, over the course of an hour. This was determined by intraoperative blood glucose monitoring. Diligent blood glucose monitoring is indicated to recognize and limit hyperglycemia following dextrose administration, which can occur in the absence of proper glucose management. A postoperative blood glucose level was not measured, although this would have been a prudent measure.

In MD patients, anaerobic glycolysis can also lead to the formation of lactate. This commonly leads to lactic acidosis in MD patients, due to the production of pyruvate, which is converted to lactate in myocytes when it is not used in the Krebs cycle. Furthermore, MD patients have an impaired ability to metabolize lactate.¹⁰ Since administration of lactated Ringer's solution has the ability to potentiate further lactic acidosis, lactated Ringer's solution is contraindicated in patients with MD.¹¹ The isotonic crystalloid chosen in this case was normal saline (0.9%), although Plasmalyte would also have been appropriate for administration. Normal saline is an isotonic solution and does not have a large effect on acid/base balance at lower doses. When administered in large volumes, normal saline can result in a hyperchloremic metabolic acidosis associated with a normal anion gap. During the entirety of the case, only 300 mL of normal saline was administered. At this low volume, the effects on pH would be negligible. Similarly, D5W, in large enough volume, may contribute to dilutional acidosis, since the solution becomes hypotonic following tissue utilization of the dextrose. In this case, a small volume of D5W was given, which would have minimal effects on pH and electrolyte balance.

Older studies regarding mitochondrial myopathies suggest an in vitro association with malignant hyperthermia, although not necessarily a causal one.¹² Current literature, however, suggests that existing MD does not increase the risk of malignant hyperthermia but may increase the risk of rhabdomyolysis.^{13,14} It is therefore unlikely that strict malignant hyperthermia preparation would be necessary for an MD patient. However, it is recommended to avoid depolarizing neuromuscular blockers for prevention of rhabdomyolysis, which has been associated with neuromuscular and mitochondrial disorders.¹⁵ Longer-acting nondepolarizing neuromuscular blockers should also be avoided, as they may have prolonged effects in patients with mitochondrial myopathies.¹⁶

Many anesthetic agents suppress mitochondrial function, which is of greater concern in an MD patient. Propofol is among the most significant suppressors of mitochondrial activity due to its inhibition of multiple electron transport chain complexes and uncoupling of oxidative phosphorylation.¹⁷ Propofol has, however, been used successfully and without significant adverse effects as an induction agent in bolus form.¹⁷ There are

Table 3. Anesthetic Treatment Considerations for MD

<i>Consideration</i>	<i>Rationale</i>
Avoid Lactated Ringer's solution	Lactated Ringer's solution contains lactate, which cannot be metabolized properly in MD. This further contributes to metabolic acidosis.
Consider alternatives to propofol	Propofol may strongly suppress mitochondrial function, especially in prolonged infusions. Successful use has also been reported.
Several anesthetic drugs affect mitochondria	This includes propofol, barbiturates, etomidate, benzodiazepines, and volatile anesthetic agents.
Avoid long-acting nondepolarizing neuromuscular blockers	Myopathy is common in MD patients, which may increase sensitivity and prolong effects with paralytics.
Avoid depolarizing neuromuscular blockers	Use of depolarizing neuromuscular blockers poses the risk of rhabdomyolysis in patients with myopathies. This can progress to hyperkalemic cardiac arrest.
Keep dantrolene available with triggering agents	Links to malignant hyperthermia appear to have been invalidated; basic preparation is always indicated if using potential triggering agents, especially in children.

additional reports of successful TIVA administration of propofol for procedural anesthesia for this patient population, although other literature suggests avoiding its use, especially in pediatric MD patients.^{17,18} Inhalation agents have also been shown to affect mitochondrial function by depressing oxidative phosphorylation, but they, alike, have been used without incident in numerous anesthetics.^{17,19} While lidocaine has been used in MD without apparent complications, caution is recommended with the use of other local anesthetics, including bupivacaine and articaine, as they have been shown to inhibit mitochondrial bioenergetics.^{9,20,21} As for the common preoperative hypnotic agent midazolam, it has been shown in vitro to inhibit part of the mitochondrial respiratory chain in a dose-dependent manner.²² The use of midazolam as an anesthetic adjunct has been successfully demonstrated in case reports, but caution is warranted.^{9,23} Opioids do not appear to have a significant effect on mitochondrial function, but they remain a concern for the spontaneously ventilating MD patient. In the treatment of patients with MD, titration of opioids should be done with caution as the respiratory depression can lead to hypoxia and hypercarbia.²³ Furthermore, the resultant hypercarbia can contribute to respiratory acidosis, which may be compounded with underlying lactic acidosis.²⁴ For opioid maintenance in TIVA with spontaneous respiration, a remifentanyl infusion is a logical option, given the ultra-short-acting opioid's ability to be titrated to a rate that is conducive to normocarbia. The effects of ketamine on mitochondrial function have been a topic of disagreement in the current literature. While a recent study concluded that ketamine impairs mitochondrial complex I function in rat brains, a subsequent letter to the editor rebutted the claim, suggesting that the claim was premature because

of controls that deviated from those previously published.^{25,26} Meanwhile, previous guidelines indicated that no adverse events have been associated with ketamine use in MD patients.⁹

Given the potential for metabolic decompensation in patients with mitochondrial conditions receiving anesthetics, it is important for the clinician to be competent in recognizing signs of a metabolic emergency. Signs and symptoms of acute metabolic decompensation include episodes of vomiting with dehydration, hypoglycemia, and lethargy. More emergent signs may even include shock, coma, and rhabdomyolysis. Supportive therapy for metabolic decompensation may include ventilatory support if indicated, fluid resuscitation with saline to promote circulation, and bicarbonate administration to correct metabolic acidosis. In addition, IV dextrose administration may be indicated to supply energy and prevent catabolism, which could otherwise potentiate acidosis and metabolic crisis.²⁷

CONCLUSION

Despite its significant diagnostic difficulties, mitochondrial disorders are estimated to have an incidence greater than 1:5000.²⁸ It is therefore very likely that most anesthesiologists will encounter patients with a history positive for a variation of MD throughout their careers. Although most anesthetic treatments in patients with MD are without complications, these patients are considered to be at higher risk due to surgical and anesthetic stress.²⁴ It falls upon the anesthesiologist to purposefully gather a complete and relevant medical history on the patient in question. Thorough preoperative examination, with a focus on neurologic, respiratory, and cardiac function, is imperative, especially for the anes-

thesiologist working in a dental office or other outpatient facility (Table 2). In addition, the practitioner should review a preoperative basic metabolic panel with an understanding of the metabolic processes related to MD. In the ambulatory setting, proper patient selection with these criteria minimizes the chance for adverse perioperative events, which may otherwise require hospitalization. Preparation of a specific anesthetic plan is also of great importance, as current literature suggests many pharmacologic considerations (Table 3). As for the treatment of our patient, all medical records, consults, and examinations indicated that his MD was metabolically well compensated. Regardless, strict selection of pharmacologic agents was employed in providing the anesthetic. The resulting procedure was reasonably well tolerated by the patient in the non-hospital-based ambulatory setting.

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