Lesson 305: PreAnesthetic Assessment of the Child Requiring Multiple Organ Transplantation

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Professional Gaps

Mitochondrial disorders (MitoD) are a group of rare heterogeneous diseases involving genetic defects in mitochondrial proteins and function. Most anesthesiologists are unaware of the multisystem involvement that can complicate anesthetic management.

Learning Objectives

At the end of this activity, the participant should be able to:

1. Briefly summarize mitochondrial physiology.
2. Review the pathophysiology of MitoD.
3. Document the clinical presentation of MitoD.
4. Distinguish between different myopathies and their symptoms.
5. Evaluate and order basic tests in patients suspected of MitoD.
6. Identify any association of MitoD with malignant hyperthermia (MH).
7. Design an anesthetic plan for a patient with MitoD.
8. Describe the interaction of propofol in patients with MitoD.
9. Recognize implications about the use of various anesthetic agents in MitoD.
10. List perioperative considerations/complications for patients with MitoD.

Case History

A 7-year-old girl (body weight, 26 kg) presented for multivisceral (liver, pancreas, and small bowel) transplantation for intestinal and liver failure. She had a long-standing history of intestinal pseudo-obstruction with multiple episodes of abdominal sepsis, and eventually was diagnosed with complex I mitochondrial disorder. She had received previous inhalational anesthetics, one followed by a hyperpyrexic course and dark urine and one unremarkable anesthetic with a total intravenous anesthetic technique (TIVA). Because of chronic abdominal pain, she was maintained on
hydromorphone and was opioid-tolerant. Her preoperative evaluation revealed mild cardiomyopathy, mild coagulopathy, and normal intellect.

Background

MitoD are a heterogeneous group of disorders with variable presentations defined by a defect in one of the mitochondrial functions such as Krebs cycle, fatty acid oxidation, or oxidative phosphorylation (OXPHOS). OXPHOS is the main source for the formation of adenosine triphosphate (ATP), the main energy molecule for human cells, and a subclass of MitoD, the mitochondrial myopathies, is caused by OXPHOS defects.

A pioneer in muscle disease research, Shy described mitochondrial proliferation in myopathic patients as early as 1962. Since then, many other researchers have contributed work in this field, with significant publications appearing in 1995. Over the past 20 to 30 years, an increasing number of diseases have been identified as MitoD.

These disorders are rare, with an estimated incidence of about 1:4,000, but the variable symptomatology makes this number most likely an underestimate. To date, more than 500 mutations (updated frequently) to the mitochondrial genome have been reported in the MITOMAP database (www.mitomap.org).

Mitochondrial Physiology

Mitochondria are intracellular organelles consisting of an outer membrane and a folded inner membrane. Embedded in the inner mitochondrial membrane are 5 multimeric proteins involved in OXPHOS known as mitochondrial complexes I to V. Mutations in any of these proteins can produce a range of clinical diseases. These organelles also contain the rate-limiting enzymes for pyrimidine biosynthesis (dihydroorotate dehydrogenase) and heme synthesis (d-aminolevulinic acid synthase) required to make hemoglobin. In the liver, mitochondria are specialized to detoxify ammonia in the urea cycle. Mitochondria also are required for cholesterol metabolism, synthesis of estrogen and testosterone, neurotransmitter metabolism, and the production and detoxification of free radicals.

The first step of the respiratory chain/OXPHOS process is the conversion of NADH to NAD; it also is the most common site of mitochondrial aberrations. The 3 major anomalies that involve this step are the often fatal infantile multisystem disorder, myopathy, and mitochondrial encephalopathy. The latter 2 forms have a variable course and prognosis, and other than metabolic supplements and dietary modifications to slow down the disease, multivisceral organ transplantation may be the only available definitive treatment.

Mitochondrial inheritance behaves differently from autosomal and sex-linked inheritance. Nuclear DNA has 2 copies per cell (except for sperm and egg cells), one copy being inherited from the father and the other from the mother. On the other hand, mitochondrial DNA (mtDNA) is strictly inherited from the mother and each mitochondrial organelle typically ends up containing multiple mtDNA copies. During cell division, these copies segregate randomly between the mitochondria of the resulting 2 daughter cells, and then those mitochondria replicate more copies of their mtDNA. Although a process called mitophagy allows for selective removal of defective mitochondria, when imbalance of mutated mtDNAs to wild-type mtDNAs within the mitochondrial network reaches a critical point, the threshold, mitochondrial diseases may become clinically apparent.
Classification

Although muscle biopsies can be nonspecific, tissue staining with modified Gömöri trichrome allows for a general division of these disorders into those with the presence of ragged-red fibers and those without. Subsarcolemmal accumulation of abnormal mitochondria with this stain gives rise to an intense red appearance over a blue myofibril background. Two additional histologic stains (cytochrome oxidase and succinate dehydrogenase) have allowed for a better delineation of these disorders (Table 1).4

Table 1. Mitochondrial Disorders

<table>
<thead>
<tr>
<th>Mitod</th>
<th>Age of Diagnosis</th>
<th>Manifestations</th>
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<tbody>
<tr>
<td>Kearns-Sayre syndrome</td>
<td>&gt;5 y &lt;15 y</td>
<td>Progressive external ophthalmoplegia, retinitis pigmentosa, cardiac conduction defect, dilated cardiomyopathy</td>
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<tr>
<td>MELAS</td>
<td>Late childhood/young adulthood</td>
<td>Central nervous system symptoms: strokes, seizures, headaches; lactic acidosis, cardiac conduction defect; cardiomyopathy</td>
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<tr>
<td>MERRF</td>
<td>Childhood/young adulthood</td>
<td>Seizures, progressive mental retardation</td>
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<tr>
<td>PEO</td>
<td>Adulthood</td>
<td>Similar to Kearns-Sayre syndrome</td>
</tr>
<tr>
<td>Pearson syndrome</td>
<td>Infancy to childhood, usually fatal</td>
<td>Refractory sideroblastic anemia, insulin-dependent diabetes mellitus, exocrine pancreatic dysfunction</td>
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<tr>
<td>Leigh encephalopathy</td>
<td>Infancy to childhood</td>
<td>Diffuse encephalopathy, dysphagia, hypotonia, central respiratory insufficiency</td>
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<tr>
<td>NARP</td>
<td>Young adulthood</td>
<td>Weakness, ataxia, retinopathy, learning disability</td>
</tr>
<tr>
<td>LHON</td>
<td>Young adulthood (25 y-35 y)</td>
<td>Painless loss of central vision</td>
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Other diseases associated with mitochondrial dysfunction include diabetes mellitus and deafness (the combination at an early age can result from mitochondrial disease); Wolff-Parkinson-White syndrome; and mitochondrial neurogastrointestinal encephalopathy (MNGIE, a gastrointestinal pseudo-obstruction with neuropathy).

Another classification of these disorders uses the clinical manifestations attributed to OXPHOS complex deficiencies. Although most have an acronym label, most people affected by these diseases do not have a syndrome but instead have a single isolated mutation. Deficiencies of each of the respiratory chain complexes can result in separate conditions such as complex I (NADH-CoQ reductase) deficiency. Deficiencies of these complexes both individually and in combination have been associated with ragged-red and non–ragged-red fiber disorders.

Clinical Presentation

The presence of mitochondria in all tissues except red blood cells makes possible involvement of all body systems.1,4 The multitude of mutations seen makes the presentation unpredictable even among
relatives. For example, Leigh syndrome can present differently within the same family and can be inherited both in a maternal-like or Mendelian pattern. Progressive muscle weakness and exercise intolerance usually are the main symptoms. Although weakness of the muscles controlling the eyes and eyelids can be a prominent feature in some patients, in others, weakness of the muscles of the face and neck with subsequent difficulty in speech and swallowing may be the principal clinical manifestation. The degree of exercise intolerance varies with each individual; in some, problems with walking are the issue, in others jogging or more vigorous activities exacerbate symptoms. Muscle pain and muscle injury can result in rhabdomyolysis and myoglobinuria, with the end result of renal insufficiency and failure.

Because deficiency in the production of ATP is the end result of these disorders, organs with high energy demands such as the brain, heart, and kidneys also may be affected. Headaches, hearing deficit, visual impairment, seizures, and learning disability with mental retardation can be the brain manifestations of ATP insufficiency (eg, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes [MELAS; Figure]). Peripheral nervous system involvement with either sensory or autonomic dysfunction provides additional clues toward a more specific diagnosis, such as MNGIE, during neurologic examination. Cardiac conduction abnormalities requiring placement of a pacemaker and cardiac muscle damage with cardiomyopathies of both dilated and hypertrophic varieties are common concerns. Nonspecific nephropathy and renal tubular acidosis are additional red flags for these disorders.

Other affected systems include respiratory, with shortness of breath and insufficiency requiring ventilator support; the gastrointestinal tract, with symptoms ranging from unexplained vomiting and dysphagia to intestinal pseudo-obstruction and liver failure; and endocrine organs with diabetes, exocrine pancreatic insufficiency, hypoparathyroidism, hypothyroidism, and hypogonadism. All manifestations may lead to failure to thrive and an overall developmental regression.

**Diagnostic Considerations**

Evaluation for MitoD is especially important if energy-intense organs such as the brain, heart, and eyes are involved and progressive worsening is noted. Clinicians should pay particular attention to symptoms such as myoclonus and ataxia, unexplained heart block in a child, cardiomyopathy with lactic acidosis, and neonatal failure to thrive, as well as to lactic acidosis and hypotonia. Unfortunately, most symptoms are still nonspecific and may differ upon age of presentation, complicating diagnosis. Diagnostic criteria referred to as the Thor-Byrne-ier criteria for diagnosis of mitochondrial cytopathy (Table 2) can be helpful but are not 100% inclusive.

**Table 2. Thor-Byrne-ier Criteria**

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
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<tr>
<td>Clinical mitochondrial disorder or unexplained infant death</td>
<td>Clinical symptoms without formal diagnosis</td>
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<tr>
<td>&gt;2% ragged red fibers</td>
<td>Electron microscopy changes</td>
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<tr>
<td>Depressed enzymatic activity</td>
<td>mtDNA unidentified mutation</td>
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<tr>
<td>mtDNA mutation</td>
<td>Abnormal laboratory data (lactate, pyruvate)</td>
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<tr>
<td></td>
<td>Impaired positron emission tomography</td>
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<td></td>
<td>Impaired proton magnetic resonance spectroscopy</td>
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Although abnormal test results may support the diagnosis of MitoD, a single normal test cannot rule it out (Table 3). Vasta et al recently found that using the redox status of coenzyme Q10 (CoQ10) in a
nematode can be a diagnostic tool not only to identify respiratory chain complex disorders but also to monitor treatment. Magnetic resonance imaging (MRI) of the brain, audiology testing, ophthalmologic exam, and electroencephalogram may identify involvement of the central nervous system, whereas electrocardiogram and echocardiogram may detect cardiac disease.

Skin biopsy can provide information on both lactate and pyruvate and electron transport chain enzymes and therefore allow for detection of a mitochondrial anomaly. Skeletal muscle biopsy can define morphologic anomalies and offer a biochemical analysis. Both can provide invaluable information but, again, without 100% sensitivity. Fresh muscle biopsy, which allows for specific biochemical testing, may provide better results but can be expensive (up to $10,000 for a complete analysis), and is performed only in a few centers in North America.

Karyotyping and genetics consultation may allow allocation of resources and support of patients with developmental and learning disabilities.

**Management of Mitochondrial Disorders**

No cure for MitoD is currently available. Management is directed at ameliorating symptoms of each disorder, organ manifestation, and complications.

Although many neurologists recommend nutritional supplements, including vitamins and antioxidants, there is little data of their effectiveness other than CoQ10 supplementation. Ubiquinone (CoQ10) gel, approved by the FDA in 1999 as an orphan drug, is present in the mitochondria of eukaryotic cells and is an active element of the electron transport chain and a free-radical scavenger. Because of its antioxidant properties, it is listed among supplements and medications useful for various disease processes. Because of its participation in oxidative phosphorylation and its minimal side effects, it is listed as a possible therapeutic agent in MitoD.

Carnitine infusion is a common additive used in MitoD. Although primary carnitine deficiency is not a common characteristic of these disorders, free carnitine levels are lower than normal in OXPHOS disorders. The possibility of restoring carnitine levels and improving β-oxidation has placed l-carnitine on the list of supplements used for many patients with or without carnitine deficiency, although the benefit may be evident in the former with improvement in muscle strength, cardiomyopathy, or gastrointestinal motility.

Other additives include l-arginine, l-creatine, total parenteral nutrition (TPN), or simply high-dextrose infusions, all of which should be continued intraoperatively to avoid a metabolic crisis.

**Malignant Hyperthermia and Mitochondrial Disease**

The presentation of malignant hyperthermia (MH) first was documented by Denborough in 1960 after a 21-year-old student in Melbourne, Australia, with a family history of multiple deaths during or after

<table>
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<th>Table 3. Laboratory Evaluation</th>
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<tr>
<td>Complete blood count</td>
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<tr>
<td>Electrolytes and glucose</td>
</tr>
<tr>
<td>Creatinine</td>
</tr>
<tr>
<td>Liver tests and ammonia</td>
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<tr>
<td>Coagulation parameters</td>
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<tr>
<td>Creatinine phosphokinase</td>
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<tr>
<td>Plasma lactate and pyruvate levels</td>
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<tr>
<td>Plasma amino acids</td>
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<td>Urine organic acids</td>
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anesthesia nearly died after a halothane anesthetic. At a later conference in Toronto in 1966, additional cases were identified and the disorder was labeled as MH.\textsuperscript{15} Although there are concerns regarding anesthesia and MH, the only known myopathy disorders with true association with MH and the need for nontriggering anesthesia are central core disease, King-Denborough syndrome, and Evans myopathy.

For the undiagnosed myopathic patient, a nontriggering technique should be employed, but the estimated risk for MH or rhabdomyolysis based on record review in a population of children with suspected neuromuscular dystrophy is less than 1\%.\textsuperscript{16}

Two earlier reports of MH in association with MitoD have been recorded.\textsuperscript{17,18} Another review discusses normal general anesthetic administration in a 60-year-old man with a subsequent positive in vitro contracture test.\textsuperscript{19} Most recent anesthesia reviews have suggested that nontriggering anesthetics are not required for the management of these disorders. A wide range of anesthetic techniques has been used including volatile anesthetic agents and TIVA\textsuperscript{20,21} or regional with local anesthetics.\textsuperscript{22,23} MitoD, especially MELAS, are now considered to have separate pathologies from MH.

**Anesthetic Considerations**

**Surgery for Patients With MitoD**

Apart from all surgeries typically required in children, patients with MitoD often present for procedures to diagnose their disease or for procedures to manage the course of the disease or its complications. For example, patients with low muscle tone may present for muscle biopsy or brain imaging studies; patients with seizures may require computed tomography or MRI; patients who fail to thrive may need gastric or jejunal tubes or central access placement; patients with a history of gastroesophageal reflux, aspiration, or pneumonia may require bronchoscopies, gastroscopies, or fundoplication surgery. In extreme cases, anesthesia is indicated for laparotomy or intestinal transplantation.

As patients with MitoD present with a wide range of symptoms and disease severity, the anesthetic plan must be individualized. Patients with minimal symptoms for minor procedures may be safely managed as outpatients with standard anesthetics, while patients with severe symptoms may need postoperative admission to the ICU, perhaps even preoperative admission for evaluation and management.

**Preoperative Evaluation and Workup**

Patients with MitoD should be interviewed by the anesthesiologist early so that history, physical examination, and available diagnostic testing can be reviewed and additional tests and interventions pursued. Communication with the primary physician and specialty physicians (neurology, cardiology, pulmonary, endocrinology, and metabolism) is mandatory to assure stable current status and course of the disease and form a perioperative plan. An ICU bed should be available for postoperative care. Neurologic evaluation includes assessment of mental status and disabilities. Seizure control should be optimized, medications adjusted accordingly, and drug levels documented. Depending on the surgery, a change of enteral to intravenous anticonvulsants should be planned and initiated.

Cardiac evaluation may include a 12-lead electro-cardiogram, chest x-ray, or echocardiogram to evaluate dysrhythmias, cardiomyopathy, and overall cardiac function.
Pulmonary tests are needed to evaluate any respiratory insufficiency associated with muscle weakness. Chest x-ray, pulmonary function tests, and analysis of arterial blood gas may be indicated depending on the severity of the disease.

Metabolic and laboratory testing is directed at evaluation of metabolic control and other organ dysfunction; liver function tests, renal function parameters, electrolytes, creatinine phosphokinase, lactate, and glucose levels are the minimum requirements; complete blood count and coagulation profile may be indicated depending on the surgical procedure.23

Preoperative Management

 Patients with MitoD may require preoperative admission even for minor surgery, for additional preoperative testing (Table 3), for initiation of IV anticonvulsant therapy for seizure control, or for IV dextrose-containing solution to reduce the risk for metabolic crisis related to fasting with fluid deficit and hypoglycemia.6,23,24 Patients on TPN are maintained on their infusion; otherwise, an infusion of 5% to 10% dextrose with 0.45% NaCl at maintenance rate is recommended preoperatively.22,25

Patients should be scheduled early in the day to allow for standard fasting guidelines with a minimum of 6 to 8 hours of solid meal avoidance and 2 hours for clear liquids. In the case of brittle patients or infants, initiation of IV fluids with glucose is warranted to avoid a crisis. However, patients remain at higher risk for aspiration because of bulbar muscle weakness and gut dysmotility.

Intraoperative Management

Monitoring. In addition to standard American Society of Anesthesiologists monitoring, arterial cannulation may be indicated for continuous hemodynamic monitoring as well as for frequent blood gas analyses for acid–base, electrolytes, blood glucose, and lactate levels. Perioperative venous access, either peripheral or central, is essential for the maintenance of dextrose infusion, and for major surgeries and laparotomies placement of a central line may be prudent to avoid interruption of dextrose infusion. Insulin infusion may be required to balance the dextrose infusion and maintain homeostasis. Normothermia should be the goal to prevent added stress and increase in metabolic demands.

Induction. Full stomach precautions with rapid sequence induction and cricoid pressure may be indicated. Safe induction agents in patients with MitoD appear to be etomidate, ketamine, and methohexital. An induction dose of propofol likely is safe. Although there is a paucity of data regarding succinylcholine and MitoD, its association with MH in one case report and possible rhabdomyolysis and hyperkalemic response make it prudent to consider avoiding this agent.17 Although all muscle relaxants can have an effect on the hypotonic child, rocuronium has been reported in more than one case to be safe but should be administered in a reduced dose in the presence of muscle weakness or hepatorenal insufficiency.

Fluid management. TPN should be continued intraoperatively or transitioned to 10% dextrose with electrolytes at maintenance rate. Patients on IV carnitine should receive the scheduled doses intraoperatively. Additional fluid requirements are replaced with lactate-free electrolyte infusions. Normal saline (0.9% NaCl) in large quantities may result in additional hyperchloremic metabolic acidosis and a lactate-free balanced solution may be beneficial. Blood loss should be replaced with synthetic colloids, albumin, or blood products as indicated based on hemodynamic measurements or
poor end-organ perfusion, as indicated by ST-T changes or low urinary output.

**Choice of anesthetic agents:** Although adequate stress protection of patients with mitochondrial disease is desirable, the choice of safe anesthetic agents for maintenance of anesthesia remains controversial. Volatile anesthetics have been used in MitoD without complications, although they have been shown to impair OXPHOS by inhibition of complex I.22 This effect in turn can impair central nervous system metabolism and cause cardiac dysfunction, leading to a potential increase in sensitivity to these agents.

TIVA has been advocated by many as a generally safer, nontriggering anesthetic technique. However, propofol in a continuous infusion as part of a TIVA technique may be contraindicated. Evidence suggests that propofol’s lipid component may affect oxidation of fatty acids; in addition, the agent has a direct effect on the mitochondrial respiratory chain. Both of these effects may predispose patients to changes seen also in propofol infusion syndrome,27,28 a syndrome characterized by lactic acidosis, bradycardia, rhabdomyolysis, and cardiac and renal failure. It is associated mainly with longer duration infusions (>48 hours), but in susceptible patients even short-term infusions can cause symptoms. Ketamine has not been implicated as a deleterious agent in MitoD, and its analgesic properties can be a welcome adjunct to overall anesthetic management.22 Benzodiazepines and opioids generally are considered safe, and a 2011 case report by Schwartz et al reported on the successful use of dexmedetomidine and remifentanil in a child with mitochondrial myopathy.

Regional anesthetics may be an attractive alternative or addition, but local anesthetics have been shown to impair OXPHOS as well and may lead to inefficient synthesis of ATP.6 Clinically, however, regional anesthesia has been used successfully, and supporters indicate that it may allow a decrease in the dosage of opioids and thus lower the risk for respiratory depression with worsening acidosis. In addition, if a regional technique is used alone, both volatile anesthetics and propofol with their respective concerns can be avoided.

**Postoperative Management**

Minimizing metabolic stress and avoidance of increases in metabolic demands are important goals in postoperative management.24 Smooth emergence and extubation, normocarbia, cardiorespiratory stability, and effective analgesia are important. Depending on the baseline degree of muscle weakness, respiratory compromise, operative course, and the potential for postoperative respiratory depression, patients with MitoD may require postoperative ventilation. Even following early extubation, initial postoperative management in an ICU may be justified to monitor and manage cardiopulmonary and metabolic status, pain, and seizures. Multidisciplinary follow-up is advisable.

Postoperative pain management is particularly important and a multimodal approach should be pursued incorporating local, peripheral, and neuraxial regional anesthesia as well as opioids intermittently or by patient-controlled analgesia; nonsteroidal anti-inflammatory drugs and other opioid-sparing analgesics such as acetaminophen, either enterally or intravenously; and α-agonists and ketamine.

Shivering should be treated aggressively with active standard techniques of warming blankets and meperidine to reduce the associated increase in oxygen consumption. Glucose and electrolyte levels should be normalized. Preoperative patient management is re instituted, and patients should not be discharged until they have returned to baseline neurologic, cardiorespiratory, metabolic, and
gastrointestinal status. Hospital admission for patients undergoing procedures normally performed in the outpatient setting may be indicated.

**Management of the Case Presented**

The child received a diagnosis of MitoD, complex I deficiency, after a muscle biopsy was performed because of worsening motor skills and presence of urine organic acids. She experienced several episodes of sepsis requiring colectomy and ileostomy, leading to chronic abdominal pain. After developing high fever with the use of inhalational anesthetics, she was declared MH-susceptible and underwent further uneventful anesthetics using a trigger-free technique. Despite her multiple hospitalizations, she had normal cognitive, cardiac, and renal function. Her recurrent septic episodes resulting from her bowel dysmotility and the combination of intestinal failure and liver dysfunction made her a good candidate for multiorgan transplant, specifically liver, pancreas, and small bowel.

The patient underwent an uneventful anesthetic course with TIVA, which included infusions of fentanyl (4 mcg/kg per hour) and ketamine (100 mcg/kg per minute) with intermittent doses of midazolam. Invasive blood pressure and central venous pressure were monitored. Infusion of L-carnitine and lactate-free crystalloid were provided to avoid metabolic derangements. A 20% dextrose solution and an insulin drip were infused to maintain blood glucose levels between 100 and 150 mg/dL. The total fluid infusion included 2,700 mL of crystalloid and colloid, 6 units of blood (packed red blood cells and fresh frozen plasma), with an estimated blood loss of approximately 500 mL. Her urinary output was maintained with a total of 1,700 mL (>5 mL/kg per hour). The last arterial blood gas in the operating room showed a normal pH (7.39), hematocrit of 30, glucose of 142, and base excess of –2.4.

After approximately 11 hours in the operating room, the patient was taken to the ICU. She remained hemodynamically stable, was extubated on postoperative day 1 and remained hospitalized for 3 weeks, whereupon she was discharged home off TPN and opioids. More than 6 months later, she remains in good condition with mild rejection of her transplant organs but adequately controlled with immunosuppressants.

**Conclusion**

Although uncommon, MitoD can pose many challenges for the practicing anesthesiologist. No one “safest” anesthetic exists for these cases; the choice of anesthetic should be individualized to the needs of the particular patient. Consultation with experts in the field and the subspecialists in a multidisciplinary approach can provide excellent assistance with comorbid issues and allow for good prognosis even in patients with multiorgan disease. Multivisceral organ transplantation is associated with long anesthesia times, large blood loss, massive fluid shifts, and profound disturbances in metabolism, electrolytes, and acid–base status. Diligence and careful perioperative planning can allow safe anesthesia with good results.

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REFERENCES

Post-test

1. The most common site of mitochondrial aberrations is ______________.
   a. inner mitochondrial membrane
   b. complex I deficiency (conversion of NADH to NAD)
   c. complex V deficiency (final pathway)
   d. outer mitochondrial membrane

2. The most common presentation of mitochondrial disorders (MitoD) is ______________.
   a. renal failure
   b. congestive heart failure and conduction abnormalities
   c. progressive muscle weakness and exercise intolerance
   d. seizures and learning disability

3. In patients with MitoD, which of the following should be obtained in all patients?
   a. Cerebrospinal fluid studies
   b. Karyotyping
   c. Basic chemistries, glucose, and serum lactate
   d. Renal ultrasound

4. Which of the following myopathies is known for its association with malignant hyperthermia?
   a. Kearns-Sayre syndrome
   b. Central core disease
   c. Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes
   d. Pearson syndrome

5. In patients with MitoD, meeting metabolic demands is accomplished by _________________.
   a. hypothermia
   b. fluid replacement with lactated Ringer’s solution only
   c. continuous muscle relaxation intraoperatively
   d. seizure control
6. Preoperative evaluation for the patient with MitoD includes all of the following except:
   a. 12-lead electrocardiogram
   b. Electroencephalogram
   c. Arterial blood gas
   d. Pulmonary function tests

7. Recommended intraoperative monitoring for MitoD patients may include all of the following except:
   a. Swan-Ganz catheter
   b. invasive blood pressure
   c. temperature
   d. central venous pressure

8. Which of the following medications does not interact with the respiratory chain and oxidative phosphorylation?
   a. Propofol
   b. Sevoflurane
   c. Ketamine
   d. Bupivacaine

9. Propofol infusion syndrome is characterized by all of the following except:
   a. lactic acidosis
   b. tachycardia
   c. rhabdomyolysis
   d. renal failure

10. Possible complications for MitoD patients during anesthesia are least likely to include which of the following?
    a. Lactic acidosis
    b. Hypoglycemia
    c. Metabolic derangements
    d. Metabolic alkalosis