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Anesthetic Management of a Patient With Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-Like Symptoms (MELAS): A Case Study

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Abstract

Mitochondrial encephalopathy, lactic acidosis, stroke-like symptoms (MELAS) syndrome is a specific mitochondrial myopathy that results in defects in respiratory enzyme complexes I and IV. This ultimately causes defects in aerobic metabolism, especially in high-energy-requiring organs, leading to an obvious concern with anesthetic management. Some mitochondrial myopathies have speculative linkages to malignant hyperthermia. This case report examines the anesthetic implications for a patient with MELAS. A 39-year-old man with MELAS underwent a right hip fracture pinning. The patient was successfully managed with a general endotracheal anesthetic using a propofol infusion and <1 minimum alveolar concentration of sevoflurane gas. The patient was extubated without complications. Anesthetic implications for the management of patients with MELAS include a tailored preoperative assessment because of the different phenotypical presentations of mitochondrial diseases. The metabolic burden in MELAS patients can be reduced by avoidance of the following: lactate in intravenous fluids, hypothermia, prolonged fasting, and postoperative nausea vomiting. Varied anesthetic techniques have been documented in multiple case reports. Careful titration of muscle relaxants and opioids is paramount to prevent postoperative respiratory failure. According to the Malignant Hyperthermia Association of the United States, avoidance of volatile anesthetics is not necessary in patients with mitochondrial myopathy.

INTRODUCTION

Mitochondrial myopathies (MMs) represent a wide range of defects in the mitochondria.[1] Mitochondrial encephalopathy, lactic acidosis, and stroke-like symptoms (MELAS) syndrome is a type of mitochondrial disease that is systemic in nature.[2] This is because of the multiple functions mitochondria serve in oxidative phosphorylation. MELAS has been speculated to affect respiratory enzyme complexes I and IV, which are essential in converting substrates from glycolysis, fatty acid oxidation, and the tricarboxylic acid cycle to ATP.[1,3]

This disease is thought to pass maternally and to result from a mutation in mitochondrial DNA.[1,2] Because MELAS involves a mitochondrial defect in aerobic metabolism, the disease has implications for anesthesia management. Anesthetic medications, surgery itself, and fasting in preparation for surgery can all increase the metabolic burden, leading to possible exacerbations in tissues dependent on large amounts of oxygen, such as the heart, muscle, and central nervous system.[4,5] MMs have also been speculatively linked to malignant hyperthermia owing to the similar presentation of symptoms. Controversy exists, however, over whether anesthetic management should be based on concerns to avoid malignant hyperthermia triggers.

CASE SUMMARY

A 39-year-old Hispanic male, with a weight of 49 kg and a height of 157 cm, presented with a right hip fracture. The surgical procedure planned for this patient was a right hip fracture pinning. His previous medical history included a cerebrovascular accident in 2008 apparently while operating a motor vehicle. Immediately before this motor vehicle accident, the patient had blurry vision and a subsequent seizure. Upon admission to the hospital after the motor vehicle accident, a muscle biopsy was performed and the myopathy MELAS was discovered. The patient's other medical conditions included hearing loss, diabetes, and an unsteady gait related to the motor vehicle accident. The patient's medications included aspirin, insulin, pantoprazole, carbamazepine, zonisamide, co-enzyme Q10, iron, loratadine, and morphine. He was assessed as having an airway classification of Mallampati II, with a 4-fingerbreadth oral excursion and thyromental distance, normal upper and lower dentition, and normal neck extension and flexion. He had no known allergies to food or drugs.

A review of his symptoms was essentially negative. The results of his physical exam were unremarkable other than a Foley catheter that was in place and musculoskeletal decompensation from a worsening gait with no assistive device use. A 22-guage intravenous catheter was started in the right antecubital vein with an infusion of lactated Ringer's solution. The serum complete blood count showed a slightly elevated white blood cell count of 9.2 and a hemoglobin level of 11.9 g/dL. However, the results of the basic metabolic panel and coagulation studies were all within normal limits. His preoperative vital signs included blood pressure of 121/77 mm Hg, heart rate of 90 beats per minute, normal sinus rhythm, respiratory rate of 16 breaths per minute, and skin temperature of 37.2 degrees Celsius. His American Society of Anesthesiologists classification was designated as a III.

The anesthetic plan for this patient included administration of preoperative medications of midazolam 4 mg and ondansetron 4 mg for anxiolysis and prevention of postoperative nausea and vomiting. General endotracheal anesthesia was instituted by use of a conventional Macintosh laryngoscope blade (Welch Allyn, Skaneateles Falls, NY), the muscle relaxant cisatracurium 20 mg, and the induction agents of propofol 50 mg, lidocaine 1% 60 mg, and sufentanil 15 mcg. After securement of the airway, another large-bore intravenous catheter and an arterial catheter were started before the start of the case. Maintenance anesthesia was continued with a propofol infusion set initially to 50 mcg/kg/min, sevoflurane at a goal end tidal concentration of 1.5, <1 minimum alveolar concentration (MAC), and boluses of 10 mcg of sufentanil as needed. The patient was to be woken up fully on emergence with evidence of eye opening, spontaneous ventilation, and sustained head lift to ensure adequate return of respiratory drive prior to extubation.

Upon arrival in the operating room, the patient was preoxygenated with 100% oxygen for 2 minutes with 10 L oxygen through a mask. Pre-induction vital signs were heart rate of 92 beats per minute, normal sinus rhythm, skin temperature of 36 degrees Celsius, noninvasive blood pressure of 111/82 mm Hg, and SpO2 of 100% as measured by pulse oximetry. Intravenous induction medications included those mentioned previously in the anesthetic plan. Induction was initiated with a conventional Macintosh 3 laryngoscope blade. Upon visualization of the airway, a Cormack-Lehane grade 4 was assessed. A gum elastic bougie tube introducer was passed with successful placement of a size 7.5-mm endotracheal tube. Confirmation of adequate placement was by auscultation of equal bilateral breath sounds, bilateral chest rise, and positive end tidal carbon dioxide at 39 mm Hg. Sevoflurane gas was turned on to 1.5% with an end tidal concentration of 1.0 with 2 L of oxygen. The patient was placed on volume control mode on the mechanical ventilator with a tidal volume of 400 mL, rate of 10 breaths per minute, and positive inspiratory pressure of 14 mm Hg. Immediately after, another 18-gauge peripheral intravenous catheter in the left arm and a 20-gauge right radial catheter were started, 1 g of cefazolin was administered intravenously, and a propofol infusion was started. A forced air warmer and an intravenous fluid warmer were used to maintain patient normothermia.

The intraoperative course remained uneventful. Sufentanil boluses of 10 and 15 mcg were given for pain control as well as 100-mcg boluses of Neo-Synephrine (phenylephrine) to help maintain systolic blood pressure > 90 mm Hg. No additional muscle relaxant was given. Acetaminophen 1 g was also administered intravenously before the end of the case. The total crystalloid for the procedure was 1200 mL of lactated Ringer's solution. Foley catheter output was 300 mL of dark amber urine. Estimated blood loss was minimal at 50 mL. Upon emergence, the patient was extubated awake, was spontaneously ventilating for 30 minutes with no pressure support, with eye opening, and with sustained head lift to 10 L of oxygen via a non-rebreather face mask at an end tidal sevoflurane concentration of 0.3.

DISCUSSION

MMs were first discovered 56 years ago in a patient who had large amounts of mitochondria in skeletal muscle.[3] These diseases cause a wide range of clinical problems, including Leber's hereditary optic neuropathy, chronic progressive ophthalmoplegia, Kearns-Sayre syndrome, myoclonic epilepsy and ragged-red fiber disease, and MELAS.[3] The anesthetic management of patients with MMs such as MELAS is complicated for many reasons involving genetic inheritance and mutation as well as the varying phenotypic presentations of these diseases. The same genetic mutation in mitochondrial DNA may have different phenotypes in different patients, while different genetic mutations can also cause overlapping phenotypes.[3] Thus, the safe use of an anesthetic technique in a patient with one mitochondrial defect may not translate to equal safety across other mitochondrial diseases with identical mutations.[5]

One of the genetic mutations that has been attributed to MELAS has been identified as *MTTL1*MELAS3243G* in the $tRNA^{Leu}$ that affects complex I of the respiratory enzyme complexes involved in oxidative phosphorylation.[3] This mutation in mitochondrial DNA when present in a high percentage is associated with stroke-like activity but when present in a low percentage is associated with diabetes and deafness.[3] The patient in the present case report interestingly had stroke-like activity, deafness, and diabetes. Another source identifies the affected respiratory complex as complex IV; other sources identify multiple mitochondrial DNA gene (tRNA and mRNA) mutations and deletions responsible for MELAS.[1,4,6] The patient

in the present case did not have a genetic report and the inability to obtain muscle biopsy records from his previous hospital admission made it difficult to determine the exact inheritance method and specific clinical presentation. Sources do, however, identify MELAS inheritance as being maternal in nature.[2]

Diagnosis of MELAS must be individualized.[6] Most MMs follow a slow and progressive course; thus, clinical investigations must be integrated by the same practitioner.[4] Integrative diagnosis includes clinical, electrophysiological, imaging, biochemical, and genetic investigations.[5] Genetic studies should be the first-line method for diagnosis after clinical features such as diabetes, deafness, and cardiomyopathy together raise red flags.[6] After genetic studies, blood, urine, and cerebrospinal fluid studies should be conducted. If the results of these are negative, electrophysiological and neuroimaging studies should be performed in organs other than the nervous system.[6] Last, a muscle biopsy and biochemical investigations should be conducted for diagnosis if the results of all other testing are negative. These investigations can include electron microscopy and respiratory chain enzyme analysis of the muscle.[6,7]

There is no known cure for MELAS. One study showed marked improvement in stroke-like symptoms after administration of L-arginine, and more recently, exercise programs have been shown to prevent muscle deconditioning.[7] Other treatments include nutritional support with vitamins and cofactors; emotional therapy; physiologic stress reduction, such as environmental temperature control; and reducing toxin exposure, such as smoking.[8]

The clinical presentation of MELAS varies tremendously, and its incidence is rare: 12.5 cases per 100,000.[2] Most importantly for anesthesia management, the respiratory chain is the final common pathway essential for aerobic metabolism. Patients present with symptoms that are dependent on tissues requiring large amounts of oxygen, such as the heart, central nervous system, and muscle.[1] According to the Online Mendelian Inheritance in Man database, the general manifestations of MELAS range from "seizures, hemiparesis, hemianopsia, cortical blindness, to episodic vomiting."[9] Specific central nervous system manifestations of MELAS can also include psychiatric abnormalities, neuropsychological deficits, stroke-like episodes, migraines, epilepsy, ataxia, and hypopituitarism.[4] MMs can affect a single organ system or multiple organ systems as in MELAS. Other organ system manifestations in MELAS can include cardiomyopathies, Wolff-Parkinson-White syndrome, cardiac conduction pathway blockade, diabetes mellitus, sensorineural hearing loss, gastrointestinal dysfunction, malnutrition, and muscle wasting.[2] Preoperative evaluation of these patients must include tests specific to each organ system involved. Cardiomyopathy is most commonly present in MELAS; thus, a 12-lead electrocardiogram and echocardiogram are paramount.[7] The patient in this case report denied any cardiac history and thus this was not obtained in the preoperative evaluation but may have been helpful in developing an appropriate anesthetic plan.

Other preoperative evaluation should include renal, hepatic, and blood glucose tests.[10] A full neurologic evaluation should be conducted because MELAS patients can have stroke-like episodes mostly affecting the occipital and parietal lobes.[4] Exercise tolerance, swallowing, and respiratory functions are other considerations preoperatively, which may include chest x-ray imaging and pulmonary function tests.[10]

As a result of the inability of pyruvate to be integrated into the tricarboxylic acid cycle, MELAS patients have increased susceptibility to lactic acidemia under increased metabolic stress.[4] Therefore, general anesthesia, medications used for anesthesia, and surgery can cause deterioration of clinical manifestations in MMs because of increased metabolic stress.[4] Other circumstances that can cause a metabolic burden in these patients and should be avoided or decreased include prolonged fasting, hypoglycemia, postoperative nausea and vomiting, hypothermia, prolonged tourniquets, acidosis, and hypovolemia.[5] Choice of fluids in MELAS patients remains controversial because whereas hypoglycemia can cause increased metabolic burden, glucose-containing fluids may not be optimal for avoidance of seizures.[5] In one case report, glucose-containing fluid was given intraoperatively in a MELAS patient without adverse effect.[11] Also, owing to the predisposition of these patients to lactic acidosis, lactated Ringer's solution may not have been the best choice of intravenous fluids in this patient.[11,12]

According to the Malignant Hyperthermia Association of the United States (MHAUS), the first association between MMs and malignant hyperthermia was suggested owing to the similar presenting clinical features, such as acidosis.[13] However, recommendations from MHAUS state that avoidance of volatile anesthetics is not necessary because of no increased susceptibility of patients with MMs to malignant hyperthermia.[13] Avoidance of succinylcholine has been discussed because of one case report in 1985 in which life-threatening hyperkalemia occurred in a patient with mitochondrial dysfunction after its administration.[13] However, just as MHAUS suggests, no definitive genetic link has been shown between malignant hyperthermia and mitochondrial diseases such as MELAS.[14] Only central core disease, multi-minicore disease, and King-Denborough syndrome have a more definitive link to malignant hyperthermia.[14] The use of succinylcholine in MELAS patients with muscle wasting can still predispose patients to hyperkalemia, but not as a result of the disease itself.

Most of the evidence in the literature is based on clinical case reports. Various anesthetic techniques have been used in MELAS patients without adverse effects.[15] In a retrospective review of 64 patients with mitochondrial disease (6 cases of MELAS), a variety of anesthetic techniques were used with no significant events such as unanticipated hospital admission, cardiac arrest, hypothermia, hyperthermia, prolonged post-anesthesia stay, increased lactic acidosis, or metabolic decompensation after exposure.[15] These techniques included volatile anesthetic gases, neuromuscular blockers, and analgesics.[15] In yet another case series review of patients with mitochondrial cytopathies, all 39 patients undergoing surgery were anesthetized with inhalational gases, local anesthesia, sedation, and general balanced anesthesia without any complications, which suggested that the routine use of intravenous or inhaled anesthesia did not influence the outcome.[16]

In a pediatric case series review by Footitt et al, 38 patients with confirmed mitochondrial disease underwent 69 cases of general anesthesia.[17] Anesthetic agents included sevoflurane, propofol, midazolam, fentanyl, rocuronium, atracurium, alfentanil,

and even 2 cases of use of succinylcholine with no adverse events noted intraoperatively.[17] Three adverse events were reported, none in MELAS patients, which included postoperative hypovolemia, renal impairment, respiratory failure, and metabolic acidosis.[17] Even though there has been wide documentation of the safety of multiple intravenous anesthetics, careful consideration must still be taken.

Although there are no documented cases of adverse effects from analgesics in MELAS patients, these patients may be at risk for decreased ventilatory response to hypoxia and hypercarbia and may suffer respiratory compromise from muscle wasting, and thus careful titration of analgesics is necessary.[18] Propofol has been implicated in propofol infusion syndrome owing to its inhibition of free fatty acids entering the mitochondria, impairing the electron transport chain, and inhibiting complex II of the respiratory chain. Propofol has been used in MELAS patients without any adverse side effects, but prolonged infusions can mimic MM symptoms such as lactic acidosis.[19,20] Use of muscle relaxants is also controversial. MELAS has been shown to cause focal segmental glomerulosclerosis; thus, it is imperative to take into consideration not administering any nephrotoxic agents.[21] The anesthetic plan for the patient in the present case consisted of using cisatracurium owing to its elimination via Hoffman elimination and ester hydrolysis. There has been one report of resistance to cisatracurium in a MELAS patient, but this patient received a full intubating dose of cisatracurium with full recovery of train-of-four and spontaneous ventilation.[22] The effects of volatile anesthetics on the mitochondria are debated. They may have a protective effect on the mitochondria owing to ischemic preconditioning or they may inhibit NADH oxidation.[20]

Multiple case reports have also documented the successful administration of regional anesthetics in MELAS patients without adverse effects, including spinal anesthesia for a femur fracture, combined general endotracheal anesthesia with epidural anesthesia for gastrectomy, spinal anesthesia for appendectomy, epidural anesthesia for postoperative pain control after laparotomy, combined general endotracheal anesthesia and postoperative epidural anesthesia for colectomy and ovariectomy, and epidural catheter placement for labor analgesia.[12,19,23-26] It is still important for the anesthesia professional to consider any neurologic abnormalities of the spinal cord or peripheral nerves and to carefully consider coagulation status in this patient population. The patient in this case had an unsteady gait and normal coagulation studies, but because of his muscle wasting, respiratory compromise may have been a possibility if a regional anesthetic were chosen and if the level of block was too high. Even though the obvious safety of regional anesthesia has been confirmed, local anesthetics still affect the mitochondrion. This presents another problem that the literature cannot answer regarding MELAS patients. Local anesthetics such as bupivacaine have been shown to inhibit the mitochondrial respiratory chain complex I and cause oxidative phosphorylation uncoupling that is potentially detrimental to MELAS patients.[27]

Upon induction, modified rapid sequence induction with cricoid pressure should be instituted in patients with gastric involvement such as nausea and vomiting.[11] Use of histamine-2 receptor antagonists and proton pump inhibitors may also be helpful to reduce aspiration risk.[11] The patient in this case did not have any gastrointestinal dysfunction and thus this was not performed. A cardiovascularly stable anesthetic is best for MELAS patients because aerobic metabolism is already dysfunctional in this patient group.[11] Intraoperative considerations include maintaining normothermia in the MELAS patient owing to the impaired mitochondrial chain, which is responsible for heat maintenance. This includes monitoring temperature through a nasopharyngeal probe and warming intravenous fluids and using a forced air warmer.[11] These interventions were used in the anesthetic plan for this MELAS patient. Arterial blood gas analysis intraoperatively may be appropriate to check glucose and lactate levels. Careful titration of muscle relaxants and opiates must be evaluated by using a peripheral nerve stimulator and spontaneous ventilation. Adequate hydration is paramount. Postoperative considerations must include possible metabolic disturbances, postoperative respiratory failure, and adequate analgesia to prevent acidosis. Other considerations can include adequate control of nausea and vomiting and postoperative shivering. These patients should be monitored in the intensive care unit because of the potential for metabolic disturbances.

Ideally, clinical trials need to be performed specifically for MELAS patients with the same genetic defect and same presentation, which would require international collaboration to obtain an adequate sample size.[28] These trials would need to investigate the pharmacology of anesthetic agents as it relates to MELAS and other mitochondrial disorders at a similar stage of disease progression and similar mitochondrial DNA mutations with adequate power, statistically validity, and double-blinded randomization.[28] Anesthesia professionals could look to national consortia such as the North American Mitochondrial Disease Consortium to recruit participants for future clinical trials.[28] As more pathophysiologic advances occur in the understanding of MMs, anesthetic management will improve.[28] Meanwhile, each MELAS patient and each patient with MM should be treated individually and the anesthetic plan should be adjusted accordingly.

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Summary of Key Points

MELAS is a mitochondrial disorder due to a mutation in mitochondrial DNA that causes a disruption in aerobic metabolism. MELAS has varied clinical manifestations including cardiac, neurological, and muscular. Patients may have varied cardiac disturbances such as cardiomyopathy, may suffer from strokes, and can also have muscle wasting.

- The Malignant Hyperthermia Association of the United States does not recommend avoiding volatile agents in mitochondrial myopathy patients even though mitochondrial myopathy has a similar presentation of symptoms to malignant hyperthermia.
- The safe use of an anesthetic technique in one type of mitochondrial myopathy does not translate to safety in MELAS. However, epidural anesthesia, spinal anesthesia, and general endotracheal anesthesia have all been used safely with various muscle relaxants and opioids in patients with MELAS in multiple case reports.
- It is paramount for the anesthesia provider to remember that the stress of surgery and anesthesia itself can increase metabolic demand in these patients who are unable to meet the necessary energy requirements. Therefore, a cardiovascularly stable anesthetic is appropriate.
- Avoidance of hypothermia, postoperative nausea vomiting, and lactate in intravenous fluids are mandatory interventions in MELAS patients.
- Careful titration of muscle relaxants, opioids, and other intravenous anesthetics is necessary because these patients are at risk for postoperative respiratory failure.