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Running head: MELAS AND ANESTHESIA

ANESTHESIC IMPLICATIONS FOR PATIENTS WITH MELAS

By

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Abstract

Title: Anesthesia Implications for Patients with MELAS

Background: A 5-year-old male patient presented for a dental restoration due to dental caries. The patient had a history of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). This syndrome is a subtype of mitochondrial myopathy that is inherited from maternal mitochondrial DNA. Mitochondria are necessary for multiple functions including cellular energy production through the Krebs cycle. The reduction in aerobic metabolism causes various systemic involvement that differs from patient to patient.

Purpose: To evaluate the current data and recommendations regarding anesthesia management in patients diagnosed with MELAS.

Process: A systematic literature review was carried out using the University of North Dakota's Harley E. French Library. Databases used include CINAHL, PubMed, and Scopus. The search was conducted using controlled vocabulary and limits on publication dates to allow for recent and efficacious data. Information was synthesized to develop evidence-based anesthetic recommendations for patients presenting with MELAS.

Results: Due to the unethical nature of randomized controlled studies for this population, case reports are the highest level of evidence for review. The most recent data revealed that multiple anesthetic techniques have been used in patients with MELAS without consequence. However, many anesthetics including volatile agents, propofol, and local anesthetics should be used with caution due to their possible deleterious effects on the mitochondria.

Implications: Anesthesia providers should be aware of MELAS and possible anesthetic implications. Collaboration with other healthcare providers based on organ involvement is vital. A detailed preoperative assessment and indicated testing should be performed. The focus of intraoperative management should be centered on preserving metabolic and hemodynamic stability. Goals include maintaining normothermia, adequate hydration with appropriate fluid, maintaining cardiac function, and optimal medication selection.

Keywords: MELAS, anesthesia, mitochondrial myopathy

Background

Mitochondrial myopathies are a group of neuromuscular diseases resulting from a defect of mitochondrial deoxyribonucleic acid (DNA). Mitochondrial DNA is separate from nuclear DNA and is capable of both mutation and transmission of genetic material (Hilton, 1995). Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is a type of mitochondrial disease. It is a genetically heterogeneous disorder with a variable clinical phenotype and systemic involvement. It is characterized primarily by its effects on the central nervous system, heart, and muscle (Flanagan & Cheek, 2016). The exact incidence of the disorder is unknown; however, when grouped in the category of “mitochondrial diseases”, it is noted to have an incidence of 1 in 4,000 people (Rivera- Cruz, 2013). This statistic may be slightly underestimated. MELAS typically presents before the age of 20 (Gurrieri et al., 2011). It affects all ethnic groups and genders equally.

The syndrome was first described in 1984 by Pavlakis who differentiated MELAS from two other clinical disorders that are also associated with mitochondrial myopathy and cerebral disease: Kearns-Sayre syndrome and Myoclonus Epilepsy Ragged Red Fiber Syndrome (Pavlakis, Phillips, DiMauro, De Vivo, & Rowland, 1984). The two patients Dr. Pavlakis reported on and nine other patients shared the common clinical features of ragged red fibers on muscle biopsy, normal early development, short stature, seizures, hemiparesis, hemianopia, and lactic acidemia (Pavlakis et al., 1984).

Although the condition is rare, the anesthetic implications of this syndrome are critical for providers to be aware of when delivering care to patients with the diagnosis of MELAS. Research continues to surface on the topic regarding management of specific procedures and patient classifications. Current research discusses considerations of patients with MELAS in

regards to neuromuscular blockers, cardiac function, malignant hyperthermia, and electrolyte balance. The following is a description of a pediatric case along with a discussion of anesthesia considerations of MELAS.

Case Report

A 5-year-old, 36cm, 13.8 kg male patient presented for dental restoration secondary to dental caries. The patient was categorized as an ASA 2. He had no known allergies. The patient's past medical history included MELAS and a hearing deficit. He was born via cesarean section at 38 weeks and 2 days. He was small for gestational age at 2.4 kg. His surgical history included a neonate circumcision. No history of anesthesia was noted. His mother reported no immediate familial complications with general anesthesia. However, both his maternal aunt and grandmother died of MELAS before age 50. His current medication regimen included cetirizine 5mg/5ml syrup. A comprehensive preoperative assessment was performed and revealed the following vitals: blood pressure 94/60, heart rate 66, respiratory rate 20, oxygen saturation 100% on room air, no temperature was recorded. Laboratory data was not collected prior to the case. He was determined to be a Mallampati I with full range of motion of the neck and a thyromental distance of greater than three fingerbreadths. A preoperative EKG was performed and evaluated by a cardiologist which revealed a sinus bradycardia rhythm with a heart rate of 62 and left ventricular hypertrophy. A transthoracic echocardiogram was also performed and revealed normal cardiac structure and function without cardiomyopathy. Therefore, no preclusion to general anesthesia was established by cardiology. During the cardiology interview, the mother of the patient reported breath-holding spells causing him to pass out on three occasions. The patient was scheduled with a geneticist prior to the procedure; however, he was unable to attend for unknown reasons.

Upon arrival to the operating room, the child was induced via a facemask with 70% nitrous oxide, 30% oxygen, and sevoflurane. After induction a combination of air/ oxygen with sevoflurane was titrated to allow for a sufficient anesthetic depth. A 24-gage IV was inserted with one attempt into the left hand. 12.5 mcg of fentanyl was given IV. Neosynepherine 0.5% spray was administered to each nare. The child was bag/mask ventilated for approximately 2 minutes. A 4.0 cuffed nasal RAE endotracheal tube was nasally inserted into the oropharynx without difficulty, a McGills forceps was used to guide the tube through the glottis. A grade I Cormack-Lehane view was established. A leak of less than 20cmH2O was noted. The presence of end tidal carbon dioxide and bilateral breath sounds to auscultation confirmed proper ETT placement. The patient was placed on volume control auto flow with a rate of 14 and volume of 120ml.

Sevoflurane was used to maintain anesthetic depth. The patient was adjusted to pressure support to allow assistance with spontaneous respirations. An additional 22.5mcg of fentanyl was given after procedure start, totaling 35mcg. Anti-emetics including 2mg ondansetron and 3mg of dexamethasone were given. A total of 130ml of lactated Ringers was administered via intravenous infusion. All vital signs remained stable throughout the case. The patient was able to maintain sufficient tidal volumes and had no response to suctioning. An oral airway was inserted and the patient was extubated deep. Six liters of oxygen was applied via simple mask. The patient was brought to the PACU in stable condition. One hour later, a post-operative anesthesia assessment revealed no apparent anesthetic complications.

Discussion

Pathophysiology

MELAS is caused by mutations in mitochondrial DNA that are inherited from the mother. Mitochondria are double membrane organelles that are found in nucleated cells (EI-

Hattab, Adesina, Jones, & Scaglia, 2015). Each cell contains multiple mitochondria with different genomes. When the cell divides, random distribution to daughter cells occurs, allowing dissemination of both mutant and normal mitochondria (Maurtua, Torres, Ibarra, DeBoer, Dolak 2008). Symptoms may not appear until the mutation affects a substantial amount or threshold level of the DNA. Given that normal and mutated mitochondrial DNA can exist in the same cell, a diverse presentation of symptoms may be present even within the same family. This effect is known as heteroplasmy (Maurtua et al., 2008).

The inner membrane of the mitochondria contains the electron transport chain complex (El-Hattab et al., 2015). This is necessary for oxidative phosphorylation converting substrates from glycolysis, fatty acid oxidation, and the tricarboxylic acid cycle through five respiratory enzyme complexes (Rivera- Cruz, 2013). This process produces adenosine triphosphate (ATP), necessary for cellular energy. MELAS typically affects the respiratory complexes I and IV, which are essential for normal aerobic metabolism. The result is an imbalance between the energy requirements and the energy available. Multiple organs including the central nervous system, kidneys, liver, and the heart are dependent on this metabolism, causing concerns in patients with MELAS (Flanagan & Cheek, 2016). In addition to cellular energy, mitochondria also play a role in apoptosis, calcium homeostasis, antiviral signaling, cell division, steroid synthesis, and heat production (Park, et al., 2010; Rivera-Cruz 2013).

The specific point mutation involved is most commonly (80%) an A-to-G transition in the gene MT-TL1 at nucleotide 3243 in the transfer RNA gene (Hsu et al., 2016). Multiple other point mutations and deletions have also been associated with MELAS (Fayssoil, 2009). Although usually genetic in nature, mitochondria myopathy may be acquired due to the toxic effects of

drugs, such as doxorubicin (Hsu et al., 2016). Systemic involvement is influenced according to the mutation present.

The impaired energy production leads to oxidative stress causing mitochondrial proliferation, lactate accumulation, decreased nitric oxide production, and decreased arginine synthesis (El-Hattab et al., 2015). Nitric oxide allows for vascular smooth muscle relaxation. This combination leads to endothelial dysfunction and impaired perfusion. This is thought to be a contributory factor to various symptoms of MELAS (El-Hattab et al., 2015).

Signs & Symptoms

Clinical features of MELAS are represented by the syndrome's title: myopathy, encephalopathy, lactic acidosis, and stroke-like episodes. Presentation is typically between ages two and ten (DiMauro & Hirano, 2013). Phenotypic variability is noted in patients with MELAS due to three contributing factors: heteroplasmy, tissue distribution, and threshold effect (DiMauro & Hirano, 2013). Therefore, the severity and specific signs and symptoms are unpredictable among cases. The first symptoms often include muscle weakness or pain, headaches, anorexia, difficulty breathing, exercise intolerance, short stature, and seizures (DiMauro & Hirano, 2013). Patients typically present with more than one initial symptom (El-Hattab, 2015).

Central nervous system manifestations

Stroke-like episodes are a principal feature of MELAS as a result of neurovascular impairment (Randhawa, Wilson, Mann, Sirrs, & Benavente, 2016). This most commonly affects the occipital and parietal lobes (Flanagan & Cheek, 2016). Often referred to as "metabolic strokes", these episodes are characterized by cell death due to high metabolic demand which cannot be compensated for with abnormal mitochondria. Hence, vascular territory is not always

noted with imaging (Bolton, 2003). Cerebral flow, however, may be affected by the proliferation of mitochondria, causing small occlusions. This phenomenon also contributes to the stroke-like episodes (Bolton, 2003). Residual effects often include transient hemiparesis, vision loss, hearing loss, impaired motor skills, and intellectual disability. Seizures and dementia are also common (El-Hattab et al., 2015). Psychiatric illnesses including anxiety, major depressive disorder, psychotic disorder, personality changes, cognitive impairment, and frontal lobe syndrome have all been associated with MELAS (DiMauro & Hirano, 2013). Peripheral neuropathy due to axonal loss and demyelination is also a common finding (Sasano et al., 2016).

Muscular manifestations

Myopathy is a consistent feature in MELAS. Muscle weakness has been reported in 89% of patients with MELAS (El-Hattab et al., 2015). Exercise intolerance, fatigue, atrophy, and muscle pain during low to moderate physical intensity work are the main symptoms. It typically affects the proximal muscle groups (Thambisetty & Newman, 2004).

Cardiac manifestations

The heart is dependent on energy from aerobic metabolism. According to Hsu, et al. (2016) mitochondrial oxidative metabolism contributes to 90% of the heart's energy needs. A significant 38% of patients with MELAS have been reported to have cardiac manifestations (Fayssoil, 2009). The involvement is variable and ranges from conduction abnormalities to severe cardiomyopathy. Wolff-Parkinson-White (WPW) syndrome, short PR interval, third degree atrioventricular block, aortic regurgitation, and other conduction pathway blockades have been noted (Gurrieri et al., 2011).

Hypertrophic cardiomyopathy is the most common cardiac manifestation associated with MELAS. Echocardiography usually reveals hypertrophy and hypokinesis of the left ventricle

(Fayssoil, 2009). The mechanisms of this are not completely understood, but the increased abnormal mitochondria present are thought to be a compensatory response to the metabolic adaptations and impaired ATP production (Fayssoil, 2009). It may also be related to microangiopathy, apoptosis, and reactive oxygen species (Fayssoil, 2009). In a study by Malfatti et al. (2012), the authors postulated an association between diabetes and hypertension to the progression of hypertrophy. The author also suggested that proliferation of mitochondria leads to endothelial and systolic dysfunction. Hypertrophic cardiomyopathy can progress to dilated cardiomyopathy and heart failure (Flanagan & Cheek, 2016).

Endocrine manifestations

Possible endocrine manifestations include diabetes mellitus, growth hormone deficiency, hypothyroidism, hypoparathyroidism, and hypogonadotropic hypogonadism. Diabetes is the most common endocrine abnormality in MELAS (Tan et al., 2009). It is thought that this is due to a beta-cell defect in insulin secretion and synthesis resulting from decreased ATP (El-Hattab, et al., 2015). Also, the mitochondrial dysfunction leads to apoptosis in beta-cells from oxidative stress (Tan et al., 2009). Approximately 85% of patients with MELAS will develop diabetes or impaired glucose tolerance by age 70 (Tan et al., 2009).

Gastrointestinal manifestations

Common presenting GI symptoms include vomiting, abdominal pain, and fatigue. Vomiting can result in weight loss and electrolyte disturbances from dehydration (Bolton, 2003). In addition, patients are at risk for aspiration of gastric contents secondary to myopathy. Other possible gastrointestinal manifestations include constipation, gastric discomfort, hepatic pathology, pancreatitis, gastroparesis, pseudo-obstruction, and malabsorption (El-Hattab et al., 2015).

Other manifestations

Renal, pulmonary, dermatological, and hematological complications are rare (El-Hattab et al., 2015). However, if activity intolerance is substantial, the patient may be susceptible to significant pulmonary issues. Atelectasis, pneumonia, and the need for ventilation support may present in severe cases (Hilton, 1995). Pulmonary hypertension has also been reported (El-Hattab et al., 2015) Renal dysfunction may include Faconi syndrome, proteinuria, and focal segment glomerulosclerosis (El-Hattab et al., 2015).

Diagnosis

Diagnosis of MELAS is based on clinical presentation along with biochemical, histochemical, and genetic analysis. El-Hattab et al., (2015) described the following diagnostic criteria established in 1992 on three characteristics:

1. Stroke-like episodes before age of 40
2. Encephalopathy characterized by seizures or dementia
3. Myopathy evident by lactic acidosis and/or ragged-red fibers

The diagnosis is confirmed with normal early psychomotor development, recurrent headaches, and vomiting episodes. (El-Hattab et al., 2015). Laboratory tests include increased lactate and pyruvate concentrations of patients in both serum and CSF. A fasting lactate level of 3mmol/L or fasting CSF lactate above 1.5mmol/L are supportive of a mitochondrial defect (Wang & Le, 2015). The increase in lactic acid is due to impaired oxidative phosphorylation (Bolton, 2003). This leads to proliferation of mitochondria, increased metabolites, and decreased cellular energy (Bolton, 2003). It is important to note that normal lactate levels do not eliminate a potential mitochondrial defect (Wang & Le, 2015).

Molecular genetic testing with targeted analysis is used to determine pathogenic variants. Variants are usually present in all tissues and may be detected by a blood sample (DiMauro & Hirano, 2013). However, with the high replication rate and selectivity against mitochondrial DNA, detection in the blood may be difficult (Wang & Le, 2015). Skeletal muscle is the most reliable tissue source (DiMauro & Hirano, 2013).

A muscle biopsy will commonly show ragged red fibers with Gomori trichrome staining or ragged blue fibers with succinate dehydrogenase (SDH) histochemistry. This identifies an accumulation of mutant mitochondrial in the sub-sarcolemmal areas, causing irregular contour of the muscle (El-Hattab et al.; Wang & Le, 2015). Cytochrome C oxidase (COX) activity and the presence SDH or lack thereof is also noted with histochemical staining. This test evaluates respiratory enzymes IV and II, respectively. The stain allows for differentiation from other mitochondrial related disorders (Fayssol, 2009). COX negative staining with a mosaic pattern and SDH positive muscle fibers are the most sensitive and specific test for mitochondrial myopathies. Mitochondrial proliferation and SDH reactive blood vessels can be detected in electron microscopic examination of frozen smooth muscle cells, demonstrating abnormal mitochondria (Wang & Le, 2015). Respiratory chain enzyme analysis is also available, testing fresh or snap- frozen muscle tissue samples for defects. This should be completed for diagnosis in patients, especially children, with normal muscle histochemistry (Wang & Le, 2015).

Magnetic resonance imaging may reveal stroke-like lesions, usually to the posterior cerebrum. Computerized tomography images may show basal ganglia calcifications, cerebellar atrophy, cortical atrophy, and lucencies consistent with infarcts (Rivera-Cruz, 2013). Brain metabolites, including lactate are evaluated via magnetic resonance spectroscopy (Wang & Le,

2015). Positron emission tomography is also valuable for assessment of blood flow and pathogenesis of stroke-like lesions in response to oxidative stress (Wang & Le, 2015).

Treatment

There is no known cure for MELAS (Flanagan & Cheek, 2016). Treatment considerations should be based on symptoms and approached in a multidisciplinary manner. Specialty providers including a cardiologist, neurologist, endocrinologist, audiologist, ophthalmologist, physical/occupational therapists, psychologist, and social worker may be necessary for management. Pharmacological, nonpharmacological, gene therapy, and surgical means should be implemented to decrease symptoms and improve quality of life. The progression of the syndrome should be monitored annually (El Hattab et al., 2015).

Exercise training, specifically aerobic, allows for mutant mtDNA to facilitate normal function (Rivera-Cruz, 2013). Resistance training is also beneficial in lowering the mutation heteroplasmy, transferring normal mitochondria to muscle (El-Hattab et al., 2015). A ketogenic diet allows for metabolism via β -oxidation of fatty acids, decreasing reactive oxygen species (Rivera-Cruz, 2013).

Supplements including Coenzyme Q10, vitamins, L- carnitine, creatine, L- arginine, folic acid, and copper have been used in patients with MELAS (El-Hattab et al., 2015). L-arginine is suggested to decrease stroke-like episodes by increasing NO availability, thus increasing cerebral blood flow. Through the same mechanism of increasing NO production, it may also decrease muscle weakness and improve exercise tolerance and lactic acidosis (El-Hattab et al., 2015). One case report revealed benefits related to citrulline administration. Citrulline increases arginine in the subcellular compartment where NO is synthesized. In fact, Citrulline administration was

shown to increase NO production even more than arginine supplementation (El-Hattab et al., 2015).

CoQ10 is beneficial as it facilitates electron transfer, stabilizing ECT complexes. Subsequently, improving muscle weakness, fatigue, and lactate levels. CoQ10 is unable to cross the blood-brain barrier, limiting CNS effects (El-Hattab et al., 2015). Conversely, idebenone (a CoQ10 analog) does cross the blood-brain barrier and may help to decrease negative neurologic events. Creatine is naturally occurring and participates in ATP regeneration in muscle and brain tissue. It has been shown to increase strength in aerobic and anaerobic exercise (El-Hattab et al., 2015).

Other treatment options are largely specific to the presentation of MELAS. In sensorineural hearing loss, cochlear implants have been successful. Diabetes may be type I or II, therefore management could include dietary alterations, oral hypoglycemic agents, or insulin. Cardiac complications resulting in conduction blocks may require implantation of a pacemaker. Anticonvulsant therapy is necessary to treat seizures (Thambisetty & Newman, 2004).

There are several medications that impede mitochondrial function and should be avoided in patients with MELAS. Valproic acid, phenobarbital, carbamazepine, phenytoin, oxcarbazepine, ethosuximide, zonisamide, topiramate, gabapentin, and vigabatrin should not be used for anti-seizure precautions (El-Hattab et al., 2015). Diabetes should not be controlled with metformin due to the increased risk of lactic acidosis. Dichloroacetate was previously thought to be advantageous due to the removal of metabolites, including lactic acid. However, one double blind placebo study was discontinued due to peripheral nerve toxicity, thus the risk outweighed the positive effects (El-Hattab et al., 2015). Aminoglycosides, linezolid, and alcohol have the

potential to cause mitochondrial toxicity. Smoking, carbon monoxide, nicotine, and heavy metals can all further impair mitochondrial function and should be avoided (El-Hattab et al., 2015).

Genetic counseling should be offered to those who have a known family history of mitochondrial diseases. MELAS is maternally inherited and will be passed on to all offspring both male and female. However, only females are capable of passing the mutation on to more generations. There are multiple options regarding gene technology that should be discussed with families to prevent reoccurrence of MELAS to further generations (El-Hattab et al., 2015).

Mitochondrial Crisis

Mitochondrial crisis results in acute or subacute organ failure due to fever, illness, stress, or medications that further impede mitochondrial respiratory chain function (Myers, Basha, & Koenig, 2013). This can result in extreme elevations in serum lactate levels and acidemia. Consequences include cardiogenic shock, dilated cardiomyopathy arrhythmias, and sudden cardiac death (Myers et al., 2013).

Treatment should be based on the underlying cause and improving mitochondrial function. A complete set of laboratory tests should be completed (Myers et al., 2013).

Medications that may worsen mitochondrial function should be avoided. If an infection is suspected, empiric antibiotics should be started. Mechanical ventilation may be used if respiratory failure presents, however, careful titration of oxygen levels to a PaO₂ of 50-60 mmHg is necessary to avoid free-radical production (Myers et al., 2013). Fluids containing dextrose should be started at a maintenance rate in patients who are unable to eat or drink. An intravenous infusion of 10% arginine through a central line is recommended to treat hyperammonia and improve blood flow. Patients with deteriorating renal function may require hemodialysis to correct electrolyte balance (Myers et al., 2013).

Cardiac complications require close observation with EKG monitoring and serial echocardiography during hospital stays and at follow-up visits (Myers et al., 2013). Current research guiding cardiac pharmacology for these patients is yet to be published. The use of beta-blockers and angiotensin-converting enzyme inhibitors is thought to be advantageous for patients with cardiomyopathies through well-established mechanisms (Myers et al., 2013). However, Fayssoil (2009) cautions the use of beta-blockers in MELAS due to the inhibition of ATPase. Other cardiac medications that can anecdotally worsen mitochondrial function include statins and acetylsalicylic acid secondary to their role in reducing coQ10 and inhibition of the respiratory chain electron transport. A heart transplant may be required in severe cases (Fayssoil, 2009).

Anesthesia Considerations

Preoperative considerations

All patients should have a comprehensive preoperative evaluation prior to undergoing anesthesia. Due to the multi-system organ involvement of MELAS, it is vital to conduct an in-depth interview and obtain testing accordingly. All patients with known or suspected MELAS should have a 12 lead electrocardiogram and echocardiogram to evaluate cardiac function (Flanagan & Cheek, 2016). Laboratory values including glucose, renal function, and hepatic function should also be evaluated (Flanagan & Cheek, 2016). A full neurologic exam is necessary due to the stroke-like episodes and other possible deficits. Pre-procedural documentation of any abnormalities is vital. Pulmonary function, chest x-ray, and exercise tolerance may also be assessed. Prolonged fasting and hypoglycemia should be avoided to prevent further metabolic stress (Flanagan & Cheek, 2016).

Intraoperative considerations

An anesthetic plan should be developed specific to the patient and their presentation of MELAS. According to Sasano et al. (2007) anesthetic goals include the following: maintaining normal glucose levels, preventing lactic acidosis, maintaining sufficient oxygenation, maintaining cardiovascular function, normothermia, and adequate gas exchange. In addition to standard monitoring, an arterial line may be used for continuous blood pressure readings and frequent lab draws. Blood gases, serum electrolytes, and lactate levels should be monitored as necessary (Ellinas & Frost, 2011).

Induction should be based on the patient's specific manifestations. If muscle weakness is present, a rapid sequence with cricoid pressure may be used due to risk of aspiration. However, succinylcholine should be used with caution due to the possibility of myotonic crisis and hyperkalemia (Ellinas & Frost, 2011). If there are increased risks for the adverse effects of succinylcholine, replacement with a nondepolarizing neuromuscular blocker (NDMR) such as rocuronium or cisatracurium may be used to facilitate a rapid sequence induction. The avoidance of succinylcholine due to malignant hyperthermia is not necessary in this patient population (MHAUS, 2016). The response to other nondepolarizing neuromuscular blockers in patients with mitochondrial myopathies has been controversial. Increased sensitivity to vecuronium, mivacurium, rocuronium, and atracurium has been reported.

Conversely, one case study reported resistance to cisatracurium (Aouad, Gerges, Baraka, 2005). The case involved a seventeen-year-old female who was on chronic antiepileptic therapy including lamotrigine, carbamazepine, clobazam, and phenobarbital. The authors attributed the resistance to factors associated with the patient's medication regimen and prolonged immobility (Aouad et al., 2005). Up-regulation of acetylcholine receptors and increased alpha-1-acid

glycoprotein concentrations can occur after chronic antiepileptic treatment. The increased acetylcholine receptors lead to resistance of NDMRs (Aouad et al., 2005). Alpha-1-acid glycoprotein can increase the binding of the NDMR, reducing the amount of free drug available for binding to acetylcholine receptors, where they exhibit their mechanism of action (Aouad et al., 2005). Finally, the patient was bed-ridden and had significant muscle atrophy. Although the motor neurons remain intact, up-regulation of mature and fetal acetylcholine receptors occurs and consequently may have contributed to the resistance of cisatracurium (Aouad et al., 2005).

In acute administration of antiepileptic therapy, increased sensitivity of NDMBs may result (Gurrieri et al., 2011). Hepatic and renal function can also affect NDMB metabolism. A thorough assessment of myopathy and pharmacokinetics must be considered when neuromuscular blockade is necessary. Due to the inability to predict the response to NDMRs, small incremental doses and careful monitoring with train of four should be implemented (Sasano et al., 2007).

Volatile anesthetics are considered safe in patients with MELAS. However, these agents depress oxidative phosphorylation in a dose dependent manner with complex I being the most affected. Due to the possible metabolic effects on the CNS and cardiac depressant effects, patients could have a higher sensitivity to these agents (Ellinas & Frost, 2011). Further research is needed, but sevoflurane has gained popularity as the anesthetic of choice.

Propofol inhibits mitochondrial function directly at complex I and IV and indirectly on complex II. Additionally, it is involved in uncoupling oxidative phosphorylation and inhibition of transport of long-chain fatty acids (Rivera-Cruz, 2013). These effects can result in propofol related infusion syndrome (PRIS). The characteristics of this syndrome include metabolic acidosis, bradycardia, rhabdomyolysis, and renal failure (Niezgoda & Morgan, 2013). Therefore,

the safety of using this agent in patients who already have mitochondria dysfunction is questionable as they may be at higher risk of PRIS (Niezgoda & Morgan, 2013). However, both induction doses of propofol and maintenance doses have been used in MELAS patients without any adverse effects.

A case report by Park et al. (2010) demonstrated the successful use of total intravenous anesthesia in a 23-year old woman with MELAS undergoing a laparoscopic appendectomy. The patient presented with hyponatremia, hyperglycemia, metabolic acidosis, and no cardiac abnormalities (Park, et al., 2010). Hydration was maintained with .9% normal saline. Endotracheal intubation was facilitated with lidocaine, propofol, remifentanyl, and atracurium. A radial arterial line was inserted after induction for monitoring (Park et al., 2010). Anesthesia was maintained with propofol and remifentanyl. The operation lasted one hour. The patient was discharged three days postoperatively without complications (Park et al., 2010).

Flanagan and Cheek (2016) were also successful with a balanced anesthetic technique that included propofol. The patient was a 39-year-old with MELAS who presented for a right hip pinning. Induction and intubation were facilitated with propofol, lidocaine, sufentanyl, and cisatracurium. Propofol at 50mcg/kg/min and sevoflurane at 1.5% were used to maintain anesthesia. Lactated Ringer's solution was used for hydration. No anesthetic complications were appreciated.

Fortunately, narcotics have not been proven to disrupt mitochondrial function (Niezgoda & Morgan, 2013). Nevertheless, the consequence of respiratory depression with the use of narcotics could be aggravated in MELAS patients whom already exhibit respiratory impairment from muscle wasting. Careful titration of narcotics is necessary to prevent hypoxia and hypercarbia in this population (Flanagan & Cheek, 2016).

Intravenous fluid choice should be based on the patient's acid base status, however, lactated ringers should be avoided due to impaired lactate metabolism. Bicarbonated Ringers has been proven to be more effective in maintaining pH over acetated ringers as acetate is metabolized in the citric acid cycle (Sasano et al., 2007). Bicarbonated Ringer's solution does not require a metabolic process to wield alkalizing effects. If no metabolic disturbance is noted, normal saline is the fluid of choice (Rivera-Cruz, 2013). Glucose maintenance is necessary in this population, yet the addition of glucose to fluids is controversial due to the possibility of seizures (Flanagan & Cheek, 2016)

Maintaining normothermia is essential as thermogenesis is a responsibility of the mitochondria. Hypothermia both depresses mitochondrial function further and increases metabolic stress (Sasano, et al., 2007). Patients with MELAS are at risk of developing hypothermia during anesthesia especially when surgical exposure is significant. Temperature should be controlled with the set room temperature, fluid warmers, and forced air warming blankets (Sasano et al., 2007). Excessive heat gain should also be prevented as an increase in metabolic demands can trigger a mitochondrial crisis or metabolic stroke (Myers et al., 2013; Bolton, 2003)

Malignant hyperthermia

In the past, it was proposed that there is link between mitochondria myopathies (MM) and malignant hyperthermia (MH). The Malignant Hyperthermia Association of the United States (MHAUS) conducted a literature review that revealed no firm data from case reports suggesting the association between MH and MM. Their recommendations regarding anesthesia include the following:

- There is no need to avoid volatile agents with regards to MH.

- Use caution when administering succinylcholine due to possible hyperkalemia in the presence of myopathy.
- Anesthesia should be based on the patient's symptoms, treatment, and type of surgery (MHAUS, 2017)

Local anesthesia considerations

A literature review of regional anesthesia and MELAS revealed no specific recommendations. However, with evidence on local anesthetics effects on mitochondrial function and the symptoms of MELAS, caution is advised when considering neuraxial or regional anesthesia. Bupivacaine has been shown to inhibit the respiratory chain complex I, causing oxidative phosphorylation uncoupling (Gurrieri et al., 2011). Ropivacaine also inhibits complex I and dissipates the electrochemical protein gradient (Rivera-Cruz, 2013). In addition, cocaine, proparacaine, and tetracaine have been implicated in mitochondrial dysfunction through interference of its membrane potential (Rivera-Cruz, 2013).

The presence of peripheral neuropathy, sensory loss (hearing or vision), and learning difficulties should be considered by the provider prior to regional anesthesia. The dose should be carefully calculated due to the possibility of short stature to prevent a high spread (Bolton, 2003). Lastly, myopathy may further increase the risk of respiratory depression in the presence of a high block (Bolton, 2003).

Multiple case reports have demonstrated successful use of local anesthetics in neuraxial blockade. Epidural anesthesia has been used for labor analgesia, in combination with general anesthesia, and for post-operative pain management (Flanagan & Cheek, 2016). A case report by Maurtua et al. (2008) described a 31-year-old parturient with MELAS at 38 weeks of gestation requesting a labor epidural. The epidural was placed at the lumbar 3-4 interspace in the sitting

position using an 18-gauge Tuohy needle. After a negative test dose, a bolus of .125% bupivacaine with 5ug/ml fentanyl and 1.65ug/ml of epinephrine was given. Analgesia was maintained with .0625% bupivacaine with 1.25ug/ml fentanyl and 1.25ug/ml epinephrine at 12ml/hr. The patient did have elevated lactate levels post-partum; however, no other abnormalities were noted. The patient and infant were discharged home on post-partum day two (Maurtua et al. 2008).

Spinal anesthesia has been used for multiple surgical cases in patients with MELAS. A case report by Blair & Heard (2011) described a 33-year-old patient diagnosed with MELAS along with severe myopathy, neuropathy, recurrent seizures, cognitive decline, and asthma, presenting for fixation of a femur fracture. It was determined that a spinal anesthetic would be optimal for the patient due to the possibility of prolonged intubation related to severe myopathy. A dose of 2.75ml of .5% bupivacaine was administered in the L4/5 space to a T8 sensory level. No complications were noted and his postoperative course was unremarkable (Blair & Heard, 2011).

Conclusion

After completing a literature review of MELAS, the pediatric case described was reviewed. The patient did not have any laboratory data available for review to demonstrate any metabolic disturbance. This would have been appropriate to collect prior to the procedure. Regardless of laboratory data, .9% normal saline would have been a prudent fluid choice over lactated ringers for the patient. Normothermia was maintained throughout the case with warm blankets. Because the procedure was minimally invasive, an arterial line would not have been required intraoperatively. Clearance from the cardiologist was imperative in this case as cardiac involvement can be the first manifestation noticed. Cardiac abnormalities add discernible

intraoperative risk. In retrospect, further evaluation from neurology and a geneticist would have been appreciated. Consequently, it is unknown if the patient and family have followed recommendations to seek care from these providers after the date of his procedure. It would be valuable due to his “breath holding spells” to continue monitoring of cardiac status annually and to pursue care from the aforementioned providers.

Although rare, MELAS is a condition that requires knowledge and vigilance from the anesthesia provider. The diverse systemic involvement makes a multi-disciplinary approach is vital. The perioperative period poses significant risks that can be minimized with appropriate patient care. An anesthetic plan must be tailored to organ involvement, patient, and the procedure.

Multiple anesthetic techniques have been used with success in MELAS patients. Regional anesthesia may be beneficial in the appropriate setting, resulting in a reduction of metabolic demands. However, local anesthetics must be used with caution due to their effects on mitochondrial function. General anesthesia may also be used with careful selection of medications

A thorough history and physical assessment of the patient should be completed and a collaborative plan formed with all providers. Preserving metabolic and hemodynamic stability are the principal objectives in MELAS patients. This can be accomplished through proper fluid choice, glycemic control, optimal medication selection, maintaining normothermia, maintaining cardiac function, and adequate gas exchange.

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Anesthetic Considerations of Patients with MELAS


Maxine Lemaster, SRNA



MELAS

- Mitochondrial myopathies are a group of neuromuscular diseases resulting from a defect of mitochondrial deoxyribonucleic acid
- Mitochondrial Myopathy, Encephalopathy, Lactic acidosis, and Stroke-like episodes (MELAS) is a type of mitochondrial myopathy.
- MELAS was first discovered in 1984 by Pavlakis, who differentiated the syndrome from other mitochondrial disorders through clinical features and muscle biopsy
- The approximate incidence is 1 in 4,000, affecting all ethnic groups and both males and females equally


(Hilton, 1995; Rivera-Cruz, 2013)



Pathophysiology

- Mitochondria are double membrane organelles that are found in nucleated cells
- The inner membrane contains the electron transport chain, serving as the site for oxidative phosphorylation via the Krebs cycle to produce adenosine triphosphate (ATP)
- ATP is necessary for cellular energy and aerobic metabolism
- Mitochondria also serve in apoptosis, cell division, steroid synthesis, heat production, and calcium homeostasis
- MELAS primarily affects respiratory enzymes I and IV, resulting in an imbalance of energy requirements and availability
- Organ deterioration occurs with high energy demand


(Park, et al., 2010; Rivera-Cruz 2013).



Pathophysiology


- Mutations in mitochondrial DNA are inherited maternally
- When the cell divides, random distribution to daughter cells allows both mutant and normal mitochondria to occur
- Symptoms of MELAS may not occur unless the mutation affects a threshold level
- **There is a diverse presentation of symptoms among those diagnosed with the disorder**
- Most common mutation is A-to-G transition in the gene MT-TL1 at nucleotide 3243

(Hsu et al., 2016 ; Maurtua, et al., 2008)




Case Information

- Surgical Procedure
 - Dental restoration secondary to dental carries
- Pertinent patient information
 - 5 year old male
 - **13.8 kg, 36cm**
 - ASA 2
 - No known allergies



Pre-operative Evaluation

- Past Medical History
 - Born cesarean section at 38 weeks and 2 days
 - Small for gestational age at 2.4kg
 - MELAS
 - **Hearing difficulty**
- Surgical History
 - Neonate circumcision
- Pre-op VS
 - BP 94/60, HR 66, RR 20, O2 saturation 100%
- EKG/Echo
 - **EKG showed sinus bradycardia with left ventricular hypertrophy**
 - Echocardiogram revealed normal cardiac structure and function without cardiomyopathy
- Airway evaluation
 - Mallampati I, FROM, thyromental distance of 3 fingerbreadths



Anesthetic Course

- Induction
 - Inhalational via facemask with 30% Oxygen/70% nitrous and titration of sevoflurane
 - 24 gauge IV inserted
 - 12.5 mcg fentanyl
- Technique
 - Neosynepherine spray to nares
 - 4.0 cuffed nasal RAE ETT inserted nasally
 - Mac 2 blade used to establish grade 1 view
 - McGills forceps used to guide

- ETT through glottis
- +BB5,+EtCo2, leak of <20mmhg
- Ventilator settings
- Spontaneous respirations with PSV pro assistance

- Maintenance
- Sevoflurane to maintain anesthetic depth
- 2mg ondansetron
- 3mg dexamethasone
- 22.5 mcg fentanyl (35mcg total)

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Intraoperative Issues

- Surgical course uneventful
- Total anesthesia time
 - 1 hour 20 minutes
- Fluid administration
 - 130 ml lactated ringers
- Blood loss negligible

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PACU

- An oral airway was inserted and a deep extubation was performed when spontaneous respirations were maintained with sufficient tidal volumes and no response to suctioning noted
- 6 liters of oxygen applied via simple mask
- Transferred to the PACU without incidence
- Postoperative assessment revealed no apparent anesthetic complications
- Discharged home day of procedure

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Presentation of MELAS

- Phenotypic variability secondary to:
 - heteroplasmy
 - tissue distribution
 - threshold effect
- Typically between ages 2-10
- Initial symptoms
 - Muscle weakness/ pain
 - Headaches
 - Anorexia
- Difficulty breathing
- Short stature
- Seizures
- Other common manifestations
 - Cardiomyopathy
 - Conduction abnormalities
 - Dementia
 - Peripheral neuropathy
 - Diabetes
 - Impaired vision or hearing

(DiMauro & Hirano, 2013)

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Diagnosis

- Diagnosis of MELAS is based on clinical presentation along with biochemical, histochemical, and genetic analysis
- Blood Biochemistry
 - Increased lactate and pyruvate
 - May have increase creatinine kinase
- Imaging
 - Computed Tomography
 - Magnetic resonance imaging
 - Magnetic resonance spectroscopy
 - Positron emission tomography
- Muscle Biopsy
- Genetic Testing

(El-Hattab et al.; Wang & Le, 2015)

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Treatment Options


- No cure for MELAS
- Dependent on symptoms
- Multidisciplinary approach
- Supplements
 - CoQ10
 - L-Arginine
 - Creatine
 - Vitamins
- Avoid medications known to cause mitochondrial toxicity
- Genetic counseling

(El Hattab, et al., 2015)

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Preoperative Considerations


- Comprehensive assessment
 - Organ involvement is variable
- Laboratory Analysis
 - Endocrine, renal, hepatic function, metabolic panel, CBC, thyroid function
 - Lactic acid /ABGs
- Pulmonary function
 - Chest X-ray
 - Exercise tolerance
- Full neurologic exam
 - Seizures
 - Neuropathy
 - Stroke-like episodes
- Cardiac
 - 12 lead electrocardiogram for evaluation of conduction abnormalities
 - Echocardiogram to evaluate structure and function



Intraoperative Considerations

- Goals
 - Glycemic control
 - Prevent lactic acidosis
 - Sufficient oxygenation
 - Maintain cardiovascular function
 - Normothermia
 - Euvolemia
- Monitoring
 - Standard monitoring
 - Arterial line
 - Electrolytes, blood gas, lactate levels


(Sasano et al., 2007)



Neuromuscular blockers

- Myopathy may require rapid sequence induction with cricoid pressure
 - Nondepolarizer such as rocuronium or cisatracurium
- Response to NDMRs is controversial
 - Increased sensitivity of vecuronium, mivacurium, rocuronium, and atracurium reported
 - Decreased sensitivity related to antiepileptic therapy
 - Hepatic metabolism
 - Increased protein binding
 - Upregulation of acetylcholine receptors


(Aouad et al., 2005; Ellinas & Frost, 2011; Gurrieri, et al., 2011)



Anesthesia

- Volatile agents
 - Depress oxidative phosphorylation in dose dependent manner
 - May have higher sensitivity
 - Considered safe in MELAS
- Propofol
 - Inhibits mitochondrial function through respiratory enzymes in Krebs cycle
 - Induction doses safe
 - Questionable higher risk for PRIS in long term infusions
- Narcotics
 - Considered safe
 - May be at higher risk for respiratory depression in patients with severe myopathy
- Fluid selection
 - Normal saline


(Ellinas & Frost, 2011; Niezgoda & Morgan, 2013; Rivera-Cruz, 2013; Sasano, 2007)



Malignant Hyperthermia

- Malignant Hyperthermia Association of the United States conducted literature review, **revealing little to no association between MH and Mitochondrial myopathies**
- No controlled trials
- Recommendations from MHAUS
 - No need to avoid volatile agents
 - Use caution with succinylcholine due to possibility of hyperkalemia in myopathic patients
 - Anesthetic plan should be based on patient's symptoms, treatment, and type of surgery


(MHAUS, 2017)



Local Anesthesia

- Regional beneficial in reducing stress response
- Specific local anesthetics found to have negative effects on mitochondria
- Consider possible symptoms that may affect neuraxial anesthesia: peripheral neuropathy, sensory loss, learning difficulties, short stature, and myopathy
- Case reports have demonstrated successful use of neuraxial anesthesia

(Bolton, 2003)



Conclusion

- MELAS has a variable presentation that requires a thorough investigation by the CRNA to devise an anesthetic plan
- Careful administration of neuromuscular blockers, volatile agents, propofol, and regional anesthesia is necessary
- Avoid increases in energy requirements
- Postoperative observation of glucose, temperature, pain, and respiratory efforts
 - May require observation in the ICU

(Flanagan & Cheek, 2016)

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Thank You

Are There Any Questions?