Title: The Challenges of Undiagnosed Hypotonia

Goals: Following completion of the PBLD, participants will be able to discuss the anesthetic considerations for patients presenting with undiagnosed hypotonia in terms of:
1. Preoperative assessment and preparation
2. Nontriggering anesthetics and malignant hyperthermia precautions.
3. Implications of muscle biopsy and genetic testing
4. Anesthetic choices to minimize complications of underlying mitochondrial disease or neuromuscular disease
5. Multidisciplinary team management

Case Description: A 13 year old girl with a history of hypotonia, ophthalmoplegia, and ptosis is scheduled for a posterior spinal fusion for scoliosis. The patient has had resolution of hypotonia and ptosis, except for facial muscle weakness and mild ophthalmoplegia. A muscle biopsy procedure is planned immediately prior to the spinal fusion in the operating room.

Questions: What are the causes of hypotonia? What is mitochondrial disease? Which organ systems are affected in mitochondrial disease? What are the anesthetic implications of mitochondrial disease and neuromuscular disease? How do these implications compare?

Case History and Physical Exam: At six years of age, she developed hypotonia with mild facial and proximal muscle weakness, ophthalmoplegia, and ptosis. She was evaluated by a neurologist; however no definitive diagnosis was made. Over time, her hypotonia improved with residual ophthalmoplegia and facial muscle weakness. She has scoliosis of the thoracolumbar spine with no cardiopulmonary sequelae. She takes no medications and has not had prior anesthesia or surgery. She was evaluated by a neuro-ophthalmologist who is concerned about possible ryanodine defect or mitochondrial disease, and requests a muscle biopsy. Family history is incomplete, but no complications from anesthesia are known. Physical examination revealed a thin girl wearing glasses without distress. Vital signs were within normal limits. She appeared expressionless and had difficulty with smiling. She had complete motor strength of her limbs and no other neurologic deficits. The airway was appropriate with adequate neck mobility, mouth opening, and a Mallampati I score. Both cardiac and lung examinations were normal.

Questions: What is the typical medical management of mitochondrial disease? Is this management different for neuromuscular disease? Is this idiopathic scoliosis? Does it matter? Should other health care specialists be involved in her care? Is there any further preoperative testing that would be useful? Would the presence of cardiopulmonary compromise change your preoperative assessment?

Preoperative Studies: A chest x-ray showed thoracolumbar scoliosis with a 50 degree curvature. Lung fields were clear and the cardiac silhouette normal. An EKG showed normal sinus rhythm with no abnormalities. A transthoracic echocardiogram revealed no structural or valvular abnormalities with a normal ejection fraction.
Questions: What are your specific concerns regarding this case? Are you anticipating any anesthetic risks or complications? What will you discuss with the family? Would your concerns change if the only procedure planned was a muscle biopsy?

Case Progression: A contracture test of the muscle biopsy specimen is planned to determine MH susceptibility. Her neurologist and muscular disorder specialist suggest genetic testing for possible mitochondrial or neuromuscular disease.

Questions: Is a contracture test necessary? Are there any specific receptors that would be targets for genetic testing? If you could obtain a muscle biopsy for MH susceptibility would you delay the scoliosis repair until the test results were known? Should nontriggering anesthetics be used in all cases of hypotonia? Are patients with neuromuscular disease at increased risk for MH? Is hyperkalemia a concern? Does the use of nontriggering anesthetics change if the diagnosis is mitochondrial disease?

Case Progression: A multidisciplinary approach was maintained and involved her neurologist, orthopedic surgeon, and general surgeon. The neurologist conveys a high index of suspicion for mitochondrial disease. In discussion with her family, we decided to proceed with the spinal fusion following the muscle biopsy during a single anesthetic. We expected the results of the contracture test within less than two hours of the specimen and planned to alter our anesthetic as necessary. Monitoring of both SSEPs and MEPs was planned to be used during the scoliosis repair.

Questions: What is your anesthetic plan? Would you agree to proceed with the spinal fusion following the muscle biopsy? How will you induce anesthesia? Does the possibility of mitochondrial disease affect your drug choices? What are the anesthetic goals concerning mitochondrial disease? How will you provide analgesia?

Intraoperative Care: She tolerated preoperative IV placement and is induced in the OR with a mixture of nitrous oxide and oxygen via mask and IV midazolam and ketamine. MH precautions were employed. Lidocaine spray was applied to the vocal cords on direct laryngoscopy to facilitate endotracheal intubation. An asleep radial arterial line was placed and a second large bore IV. Infusions of IV ketamine, dexmedetomidine, and fentanyl with inhaled nitrous oxide and oxygen were used for maintenance. She was administered D10 with normal saline for IV fluid maintenance. Following the muscle biopsy, intrathecal morphine was injected by spinal technique. A CSF sample for lactate was also obtained. She was placed in prone position for the spinal fusion. Serial arterial blood gases with lactate and glucose levels were followed. An hour into the spinal fusion, the muscle biopsy contracture test result was reported as negative.

Questions: Does a negative contracture test alter your anesthetic maintenance plan for the spinal fusion? Does neuromonitoring of SSEP and MEP affect your anesthetic choices? How will intraoperative blood gases and lactate levels affect the anesthetic? What is the significance of CSF lactate?

Case Progression: Following negative contracture test results, nitrous oxide was discontinued and 0.5 MAC of inhaled desflurane started in combination with the IV infusions. Laboratory results including lactate and glucose remained within normal limits throughout. Blood loss was approximately 500cc and she received one unit of autologous blood. There was no hemodynamic instability during the case.

Questions: Does this patient require postoperative ICU care? Would you attempt to extubate this patient? Would you be concerned if she had preexisting pulmonary compromise? How will you provide
Postoperative analgesia? What are your concerns during the postoperative period regarding mitochondrial disease? Would you involve any other health care specialists for postoperative care?

**Postoperative Care:** She was extubated in the OR after meeting criteria following the spinal fusion and recovered overnight in the PICU. A morphine PCA was started 12 hours after the intrathecal morphine administration for postoperative pain control. She remained stable and was transferred to the floor on postoperative day one with an uneventful recovery. Serum lactate and creatinine kinase levels remained normal postoperatively prior to discharge.

**Discussion:**

Two broad categories in the differential diagnosis of hypotonia include neuromuscular and mitochondrial disease. Both diseases include a wide spectrum of clinical presentation and symptoms. During perioperative care of a patient with undiagnosed hypotonia, the anesthesiologist must consider treatment strategies for both neuromuscular and mitochondrial disease.

Mitochondrial disease is a heterogeneous disorder of both genotype and phenotype and has varying multi-organ system involvement. Inherited or acquired genetic mutations of either mitochondrial or nuclear DNA lead to mitochondrial dysfunction with impaired oxidative phosphorylation. This impairment leads to decreased ATP production and the production of damaging reactive oxygen species. Symptoms correlate to the severity of the DNA mutation, amount of affected mitochondria, and tissue susceptibility. Tissues with high oxygen requirement and metabolic demand are typically affected first. Disease onset is variable and progressive, with the most severe forms presenting earliest in life. The most common disease presentation involves proximal muscle weakness with lactic acidosis. Other symptoms are variable and include respiratory problems, bulbar dysfunction, encephalopathy, hepatorenal dysfunction, cardiomyopathy, and cardiac conduction blocks. Patients with mitochondrial disease are medically managed using a variable multidisciplinary approach depending on organ system involvement and dysfunction.

The diagnosis of both neuromuscular and mitochondrial disease is confirmed by a skeletal muscle biopsy. Genetic analysis may follow a positive muscle biopsy to provide specific classification of the disease subtype. Preoperative work up of hypotonia should include a thorough history and physical in order to discern various organ system involvements. An EKG and CXR may detect subclinical cardiopulmonary dysfunction. Lab testing is often nonspecific, and should be directed toward organ system dysfunction. In mitochondrial disease, serum or CSF lactate may be elevated. The absence of lactic acidosis does not exclude disease, as it may only elevate during acute exacerbations. A multidisciplinary plan should be utilized in order to provide adequate symptomatic management and the prevention of perioperative disease exacerbation during acute stress.

Anesthetics provided for muscle biopsy typically involve precautions for neuromuscular disease and mitochondrial disease. Nontriggering anesthetics are used in prevention of MH with the possibility of central core disease. Patients with neuromuscular disease without central core involvement are not at increased risk of MH. However, in the presence of neuromuscular disease, nontriggering anesthetics are employed in order to prevent life threatening rhabdomyolysis and hyperkalemia. The use of propofol is avoided in mitochondrial disease in order to prevent metabolic decompensation. Propofol is a direct mitochondrial depressant, and when used in the presence of mitochondrial disease it may cause a clinical spectrum of lactic acidosis and rhabdomyolysis, similar to propofol infusion syndrome. The use of nondepolarizing neuromuscular blocking agents is undesirable in both neuromuscular and mitochondrial disease, with inconsistent patient sensitivity and increased risk of postoperative respiratory dysfunction. Avoidance of prolonged fasting, and maintaining adequate hydration and glucose replacement during the perioperative period is necessary for patients with mitochondrial disease in order to prevent an acute lactic acidosis and exacerbation.
Patients with hypotonia are at increased risk of postoperative complications including respiratory depression and delayed awakening. Pain management is a concern and should be managed appropriately to avoid metabolic decompensation and stress. Narcotics may be used safely with cautious dosing to prevent increased risk of respiratory impairment. Regional and neuraxial techniques have been used safely with reduced amount of local anesthetic in mitochondrial disease. A thorough postoperative plan should involve necessary medical subspecialists in order to treat further symptoms and avoid disease complications during recovery.

References:


