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Anesthetic care for a child with undiagnosed myopathic/mitochondrial disease for gastrostomy tube placement and muscle biopsy

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Keypoints

1. Patients with diseases of the skeletal muscles (myopathies or mitochondrial disorders) with hypotonia may present for anesthetic care during diagnostic or therapeutic surgical procedures without the establishment of a specific diagnosis.
2. Primary concerns in patients with myopathic conditions include difficulties with endotracheal intubation, impairment of upper airway control, respiratory muscle involvement, myocardial involvement, and primary effects on the central nervous system.
3. Given its potential impact on mitochondrial function, propofol infusions are relatively contraindicated in these patients with mitochondrial disorders. Other myopathic patients may be associated with susceptibility to malignant hyperthermia. Given these concerns, we would suggest total intravenous anesthesia with agents such as ketamine or dexmedetomidine and an opioid.

Abstract

Disorders of the motor nerves, neuromuscular junction or muscle can affect children of all ages. These patients may present for therapeutic or diagnostic procedures (muscle and nerve biopsy) prior to arrival at a definitive diagnosis. The perioperative care of these patients is impacted by end-organ effects of the neuromyopathic condition including skeletal muscle weakness with its impact on upper airway control and respiratory function and myocardial involvement with arrhythmias, conduction disturbances or depressed function. Additionally, specific conditions may impact the choice of anesthetic care including choice of neuromuscular blocking agent, malignant hyperthermia risk, and impact of propofol on mitochondrial function. We present a 12-month girl who presented with hypotonia, failure to thrive and biochemical evidence of a metabolic disorder with an elevated lactate and ammonia suggestive of a primary myopathic condition or a mitochondrial myopathy. Anesthetic care was required for a laparoscopic gastrostomy tube placement and muscle biopsy. The perioperative management of these patients is discussed with specific emphasis on implications of a primary myopathic or mitochondrial process.

Keywords
myopathy, Nemaline myopathy, mitochondrial disease, pediatric anesthesia

Introduction

Disorders of the motor nerves, neuromuscular junction or muscle may significantly impact perioperative care as these patients present for therapeutic or diagnostic procedures (muscle and nerve biopsy). The perioperative care of these patients is impacted by end-organ effects of the neuromyopathic condition including skeletal muscle weakness with its impact on upper airway control and respiratory function and myocardial involvement with arrhythmias, conduction disturbances or depressed function.[1] Anesthetic care may be challenging as a specific diagnosis may not be readily available especially for younger patients who are presenting for diagnostic testing. The specific comorbid condition may impact anesthetic care including choice of neuromuscular blocking agent, malignant hyperthermia risk, and relative contraindications to propofol as it may impair mitochondrial function. We present a 12-month girl who presented with hypotonia, failure to thrive and biochemical evidence of a metabolic disorder with an elevated lactate and ammonia suggestive of a primary myopathic condition or a mitochondrial myopathy. Anesthetic care was required for a laparoscopic gastrostomy tube placement and muscle biopsy. The perioperative management of these patients is discussed with specific emphasis on implications of a primary myopathic or mitochondrial process.

Case report

Presentation of this case report was in accordance with the Institutional Review Board at Nationwide Children's Hospital (Columbus, Ohio). Written consent for anesthetic care and publication was obtained from a parent. A 12-month , 6.5 kilogram girl presented for a laparoscopic gastrostomy tube insertion and muscle biopsy. Her past medical history was significant for hypotonia since birth, failure to thrive and intermittent elevated ammonia and lactate levels without a specific unifying diagnosis, although a primary myopathic or mitochondrial disorder was considered most likely. Associated comorbid conditions included severe malnutrition, developmental delay, exposure to second hand smoke, and central sleep apnea. Preoperative evaluation revealed a thin, malnourished pediatric patient in no acute distress. Although noted to have limited mouth opening on previous examinations, her airway was classified as a Mallampati grade 1 on the day of surgery. An echocardiogram and electrocardiogram were normal with no evidence of arrhythmias, structural defects or compromised function. Laboratory evaluation revealed normal electrolytes and renal function, normal coagulation function, and a normal complete blood count. There was no prior surgical history. After placement of a peripheral intravenous cannula for the administration of maintenance intravenous fluids and glucose, the patient was held *nil per os* for 6 hours and transported to the operating room where routine American Society of Anesthesiologists' monitors were placed. After pre-oxygenation, anesthesia was induced with propofol (20 mg), fentanyl (10 µg), and rocuronium (6 mg). A ketamine infusion was started at 0.5 mg/kg/hr. The first attempt at endotracheal intubation was unsuccessful due to a Cormack-Lehane Grade 3 view using a Miller 1 blade. Following 3 additional unsuccessful attempts using direct laryngoscopy (various laryngoscope blades) and indirect video laryngoscopy, the pediatric otolaryngologist was consulted to secure the airway. The otolaryngologist was able to secure the airway on the third attempt using a suspension laryngoscopy and the pediatric telescope as an intubating stylet. Between endotracheal intubation attempts, there was increased difficulty with bag-valve-mask ventilation, which was thought to be due to partial laryngospasm or bronchospasm. During the intubation attempts, atropine (0.1 mg) and epinephrine (1 µg) were administered to treat bradycardia. After successful endotracheal intubation with a 3.0 mm cuffed endotracheal tube (ETT), albuterol was administered that markedly improved oxygenation and ventilation allowing the surgical team to proceed with the procedure. Following endotracheal intubation,

anesthesia was maintained with a ketamine infusion (0.5 mg/kg/hour) and intermittent doses of fentanyl (5 doses – total of 40 µg), dexmedetomidine (5 doses – total of 10 µg), and one additional dose of rocuronium (3 mg). The surgical procedures were completed without other intraoperative concerns. Surgical time was 2 hours 15 minutes. Total fluids included 75 mL of 5% dextrose in ½ normal saline and 30 mL of normal saline. Due to concerns regarding airway edema, the patient's trachea was left intubated and she was admitted to the Pediatric ICU. There were no significant concerns during the postoperative course. Her trachea was extubated to bilevel positive airway pressure (BiPAP) on postoperative day 2. BiPAP support was slowly weaned over the ensuing 24 hours and the patient was transferred to the inpatient ward. A multidisciplinary team consisting of speech, nutritional, music, and occupational therapy were employed during her hospital stay. In addition to the muscle biopsy, microarray analysis and whole exome sequencing was performed on the patient's blood and revealed variants in *TNNT1*, which is associated with Nemaline myopathy type 5 and *NDUFS,* which is associated with mitochondrial complex I deficiency. The muscle biopsy confirmed changes consistent with Nemaline myopathy.

Discussion

Myopathies (including muscular dystrophies and mitochondrial myopathies) include a wide variety of disorders that impair the structure, function or metabolism of muscle tissue. Approximately 1000 separate entities have been classified as neuromuscular diseases with most being rare, although their cumulative incidence may be as high as 1:1500.[1] As noted in our patient, many of these infants and children present with hypotonia, which may be present at birth, failure to achieve motor milestones, or loss of these milestones after they are obtained. The primary process responsible for the skeletal muscle involvement may include a lack or dysfunction of contractile proteins, cytoplasmic proteins (dystrophinopathies such as the muscular dystrophies), failure to produce adequate substrate for the muscle (mitochondrial myopathy), or defects in ion transport (channelopathies such as myotonic dystrophy).[2-4] In addition to the primary involvement of skeletal muscle, many of these patients will have additional extra-skeletal involvement of the cardiac or central nervous system. Given the diverse diagnosis and cellular mechanisms responsible for the myriad of myopathic conditions, many of these patients present for anesthetic care without a definitive diagnosis. Such was the case in our patient who required a muscle biopsy as part of her diagnostic work-up as well as placement of a gastrostomy tube to allow for adequate home nutrition.

Regardless of the primary disease process, the anesthetic process begins with a thorough preoperative exam with identification of the end-organ involvement related to the primary disease process and associated comorbid conditions. Primary concerns in patients with myopathic conditions include involvement of the airway structures, impairment of upper airway control, respiratory muscle involvement, myocardial involvement, and primary effects on the central nervous system. Airway management including bag-valve-mask ventilation and endotracheal intubation may be problematic in patients with myopathic conditions.[5,6] Additional associated conditions, some of which were noted in our patient, frequently includes facial dysmorphism, micrognathia, midface hypoplasia and other associated dysmorphic features as noted. Difficulties with airway management and endotracheal intubation have been reported to be as high as 3.4% in patients with muscular dystrophy.[6] When there are concerns regarding airway management based on the past history or the preoperative airway examination, spontaneous ventilation should be maintained until the airway is secured or adequate bag-valve-mask ventilation is demonstrated. The appropriate equipment for dealing with the difficult airway including indirect videolaryngoscopes should be readily available prior to anesthetic induction or airway management.[7] Despite the facial dysmorphism noted in our patient, the preoperative airway examination was not indicative of a potentially difficult airway. Fortunately,

despite difficulties with directly laryngoscopy and endotracheal intubation, bag-valve-mask ventilation was feasible after the administration of anesthetic induction agents and rocuronium. As this case occurred during the day in a busy pediatric operating room, pediatric otolaryngology was readily available for consultation for airway management. In our patient, suspension laryngoscopy was used with advancement of the ETT off the optical telescope into the airway. Advantages of the suspension laryngoscope include a flat blade to accommodate a wide and mobile tongue, a left sided adaptor to connect the anesthetic circuit to allow for insufflation of oxygen and anesthetic agents during airway examination, a proximal xenon light to provide illumination of airway structures, and a wide proximal opening that allows passage of other devices such as optical telescopes or bronchoscopes. The rigid arm can be suspended on a Mayo stand, allowing the operator to use both hands.

In addition to concerns regarding airway management, patients with myopathic conditions are also prone to perioperative airway complications related to poor airway control. Our patient presented preoperatively with such issues as she had been diagnosed with obstructive sleep apnea, likely related to involvement of the skeletal muscle of the airway and pharynx. These issues may result in upper airway obstruction with respiratory insufficiency or failure during the postoperative period. Additionally, associated respiratory involvement may result in poor cough effort, chronic aspiration or recurrent pneumonia. In many pediatric patients, given their age or cognitive function, a full preoperative assessment of respiratory function using pulmonary function testing is not feasible. However, a room air oxygen saturation less than 95%, a history of recurrent pneumonia or swallowing problems with aspiration may identify patients that are at risk for postoperative respiratory insufficiency or failure.[8,9] Pre-existing motor weakness and hypotonia may increase sensitivity to the effects of neuromuscular blocking agents (NMBAs), inhalational anesthetic agents, and sedative agents. The use of short-acting anesthetic agents and complete reversal of residual neuromuscular blockade (see below) is suggested. Although we decided to continue mechanical ventilation postoperatively given the airway difficulties encountered during endotracheal intubation, we have also found that postoperative extubation to non-invasive ventilation such as BiPAP is helpful in maintaining upper airway patency and preventing atelectasis thereby allowing for a smooth transition to spontaneous ventilation.[10]

While the initial clinical manifestations of these disorders are generally related to the skeletal muscle with hypotonia and failure to achieve motor milestones, involvement of the cardiac muscle is frequent in many of these conditions. Arrhythmias and depressed myocardial function (cardiomyopathy) are the most frequently encountered cardiac manifestations, often progressing with age. By 15 years of age, approximately half of muscular dystrophy patients develop cardiomyopathy.[11,12] Given the varied clinical manifestations of myocardial involvement and its potential to develop at any age, routine preoperative screening with an ECG and echocardiogram is suggested prior to anesthetic care.

Central nervous system involvement is also a frequent comorbid condition in patients with myopathic and mitochondrial disorders. Such involvement may include seizures, cognitive delay as well as hearing or visual involvement.[13] Cognitive delay, hearing impairment and visual disturbances may impact patient understanding and cooperation during the perioperative process making a preoperative evaluation of such concerns imperative to avoid adverse patient outcomes related to patient agitation or discomfort. Appropriate use of parental presence and premedication may be required to facilitate transport to the operating room and anesthetic induction. Preoperative management to limit the potential for perioperative seizures includes optimizing and confirming therapeutic anticonvulsant levels prior to the surgical procedure. Routine anticonvulsant medications should be administered the morning of the procedure despite concerns of the patient's *nil per os* status with subsequent

intraoperative dosing as needed.[14] Sodium valproate inhibits mitochondrial β-oxidation of fatty acids and should be avoided in patients with mitochondrial metabolic disorders.[15,16]

Additional perioperative concerns related primarily to patients with potential mitochondrial disorders relates to exacerbation of the biochemical defect during periods of stress or prolonged NPO times with the development of hypoglycemia or metabolic acidosis.[17] As these patients may be prone to hypoglycemia due to the inability to mobilize other metabolic substrates, the administration of glucose containing fluids is generally indicated to provide a glucose infusion rate of 5-8 mg/kg/min. As was done in our patient, glucose administration should be titrated to provide basal requirements as excessive administration can result in hyperglycemia. Additionally, lactate containing fluids are generally avoided due to the concerns of inability to metabolize lactate in some patients with mitochondrial disorders.[17,18]

The medications used for the induction and maintenance of anesthesia are guided by the primary disease process and its end-organ involvement and any specific intraoperative surgical requirements. There are significant concerns with the choice and use of neuromuscular blocking agents (NMBAs) when caring for patients with myopathic conditions or a mitochondrial myopathy. Succinylcholine is generally contraindicated, especially in the absence of a definitive diagnosis, due to the risk of hyperkalemia.[19] Although non-depolarizing neuromuscular blocking agents (NMBA's) are generally safe, a prolonged effect can be seen even with intermediate-acting agents.[20] Although we chose to use rocuronium in our patient, concerns regarding its potential prolonged effect did not impact perioperative care as mechanical ventilation was continued during the postoperative course. Alternatively, the novel reversal agent for NMBAs, sugammadex, offers the potential to reverse neuromuscular blockade in patients with neuromyopathic conditions.[21]

A more challenging topic is the choice of anesthetic agent. The reader is referred to reference 17 for a full review of the impact of anesthetic agents on mitochondrial function.[17] Given its potential impact on mitochondrial function, caution has been expressed regarding the use of propofol infusions in patients with mitochondrial disorders. The clinical manifestations of propofol infusion syndrome (cardiac failure, arrhythmias, metabolic acidosis) mirror the clinical findings of several mitochondrial disorders.[22,23] Volatile anesthetic agents may be contraindicated given their effects on mitochondrial function and susceptibility to malignant hyperthermia (MH) in specific myopathic conditions. Even if not specifically MH-sensitive, the prolonged administration of volatile anesthetic agents may result in destabilization of the sarcolemma with rhabdomyolysis and hyperkalemia in patients with myopathic conditions including Duchenne muscular dystrophy.[24] Given these concerns, we chose to administer a single dose of intravenous propofol for anesthetic induction followed by maintenance anesthesia with a ketamine infusion supplemented with bolus doses of dexmedetomidine and fentanyl. Alternatively, recent success has been demonstrated with total intravenous anesthesia using a combination of dexmedetomidine and remifentanil in various clinical circumstances.[25,26]

In summary, we present the anesthetic considerations when caring for a child with a suspected primary myopathic condition or a mitochondrial myopathy. Pediatric anesthesiologists may be confronted with such patients during diagnostic testing or therapeutic interventions. In addition to the primary disease process which generally manifests as hypotonia, additional end-organ involvement should be identified given its potential impact on perioperative care. Additionally, the primary disorder may impact perioperative fluid/glucose management as well as choice of anesthetic agents. In specific circumstances, regional anesthesia may offer an effective alternative to general anesthesia and avoid the need for airway instrumentation and general anesthesia.

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