Anesthetic Care of a Child With Merosin-Deficient Muscular Dystrophy

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Abstract

Merosin-deficient congenital muscular dystrophy (MDCMD) is a progressive autosomal recessive disorder caused by the lack of expression of the α_2-chain of laminin-211 glycoprotein. The defect results in skeletal muscle dysfunction with severe muscle weakness, hypotonia, proximal joint contractures, facial dysmorphism, and late or failed ambulation. Given the progressive neuromuscular involvement and the potential for neuromuscular scoliosis, patients frequently require anesthetic care during surgical procedures to correct orthopedic deformities. We present a 9-year-old girl with MDCMD who required anesthetic care during insertion of growing rods to correct neuromuscular scoliosis. Previous reports of anesthetic care for patients with MDCMD are presented and options for perioperative care are reviewed.

Keywords: Scoliosis; Merosin; Congenital muscular dystrophy; Laminin-α_2

Introduction

Merosin-deficient congenital muscular dystrophy (MDCMD) is a progressive autosomal recessive disorder that results in the deficient production of the α_2-chain of laminin (merosin), a protein of the extracellular matrix of skeletal muscle that is encoded by genes located on chromosome 6q22-23 [1, 2]. First described in 1994 by Tome et al, it is one of the most common forms of CMD [3]. The cellular defect results in the premature truncation, and thereby defective function of the laminin-211 glycoprotein, which plays a crucial role in establishing the structural and functional scaffolding between the basement

membrane and the extracellular matrix in cardiac muscle, skeletal muscle, Schwann cells, oligodendrocytes and trophoblasts [1, 4-8]. The mechanical stress on muscle fibers without basement membrane support from laminin-211 leads to progressive muscle injury and atrophy, resulting in inflammation, scarring and elevation of creatinine phosphokinase (CPK) levels.

Clinical signs and symptoms include severe muscle weakness, hypotonia, proximal joint contractures, delayed and often unachieved ambulatory efforts and facial dysmorphism [8-12]. Muscle weakness, particularly of the intercostal and accessory muscles, predisposes patients to respiratory infections, which are the most common cause of death [1]. These clinical signs may be present at birth and generally manifest by 1 year of age. Central nervous system (CNS) and white matter abnormalities of the brain lead to intellectual disabilities and seizures [5, 10]. The diagnosis of MDCMD is confirmed by the clinical sign and symptoms, elevation of serum CPK levels, muscle biopsy showing abnormal basement membrane structure and gene analysis to determine LAMA2 mutations [1, 12].

Surgical intervention may be required in patients with MDCMD to correct neuromuscular and orthopedic deformities including kyphoscoliosis. We present a pediatric patient with MDCMD who required anesthetic care for a posterior spinal fusion secondary to neuromuscular scoliosis. Previous reports of anesthetic care for patients with MDCMD are presented and options for perioperative care are reviewed.

Case Report

Review of this case and presentation in this format is in accordance with the guidelines of the Institutional Review Board at Nationwide Children's Hospital (Columbus, OH). The patient was a 9-year-old, 15-kg girl with MDCMD who presented for the insertion of growing rods to treat neuromuscular scoliosis of the thoracic region. She was diagnosed with MDCMD at 10 months of age, following a muscle biopsy and gene sequencing analysis. Significant past medical history included a birth injury to the brachial plexus, previous respiratory infections including left lower lobe pneumonia and rhinovirus infection as well as age-related osteoporosis with low bone density for age. Past surgical history included a diagnostic muscle biopsy at 10 months of age. Current medications included bisphosphonate infusions for osteoporosis, and as needed albuterol and saline aerosol treatments to facilitate clearance of respiratory secretions. Her physical examination demonstrated gen-

eralized hypotonia, scoliosis and contractures at the elbows, hips and knees. Preoperative echocardiogram and electrocardiogram were unremarkable. On the morning of the procedure, the patient was kept *nil per os* for 6 h. The patient was transported to the operating room where standard American Society of Anesthesiologists' (ASA) monitors were placed. After breathing 70% nitrous oxide in oxygen, a 20-gauge peripheral intravenous cannula was placed. Anesthesia was induced with propofol (3 mg/kg) and fentanyl (1 µg/kg). After effective bag-valve-mask ventilation was demonstrated, neuromuscular blockade was provided by rocuronium (0.6 mg/kg). Direct laryngoscopy with a Wis-Hipple 1.5 blade revealed a Cormack-Lehane grade 2 view and a 5.0 cuffed endotracheal tube (ETT) was placed without difficulty. After anesthetic induction, a second peripheral intravenous cannula and a radial arterial cannula were placed using ultrasound guidance. Maintenance anesthesia included methadone (0.1 mg/kg) and total intravenous anesthesia (TIVA) with infusions of remifentanil and propofol. Intraoperative neurophysiological monitoring was performed with somatosensory and motor evoked potentials. The propofol infusion was titrated to maintain the bispectral index at 40 - 60 and the remifentanil was titrated to maintain the mean arterial pressure at baseline. To limit the need to allogeneic blood products, tranexamic acid (bolus of 50 mg/kg followed by an infusion at 5 mg/kg/h) and intraoperative blood salvage were used. Intraoperative hypotension was treated with intermittent doses of phenylephrine as needed. Submuscular MAGEC™ (Magnetic Expansion Control System) rods were placed with rib hooks at T5 through S2 with sacroiliac screws. Total intraoperative fluids included 200 mL of crystalloid, 450 mL of 5% albumin and 200 mL of packed red blood cells. The procedure lasted for approximately 6 h. Following the procedure, the patient was transported to the pediatric intensive care unit (PICU). When awake, her trachea was extubated to bilevel positive airway pressure (BiPAP) via a mask. The BiPAP was continued overnight and then intermittently for the first 48 postoperative hours. Postoperative analgesia was provided by intermittent intravenous acetaminophen and ketorolac administered around the clock for 48 h and nursing-controlled analgesia with hydromorphone. The remainder of the postoperative period was unremarkable and she was discharged to home on postoperative day 5.

Discussion

MDCMD is one of the congenital muscular dystrophies, a group of conditions that share early onset and a similar histologic appearance of the muscle. MDCMD typically presents with decreased *in utero* movement followed by hypotonia at birth. Differential diagnoses include other congenital neuromuscular disorders including peripheral neuropathy, limb-girdle muscular dystrophy, Emery-Dreifuss muscular dystrophy, central demyelination diseases, congenital myopathy and spinal muscular atrophy [1, 2, 5, 10]. The diagnosis is suggested by high serum CPK levels and a muscle biopsy showing the abnormal basement membrane structure. Definitive identification of the disorder is confirmed by gene sequencing analysis

identifying the mutations in LAMA2. As there is no treatment for MDCMD, symptom management is tailored to correct the anatomical and physiologic consequences of the primary disease process and ameliorate the quality of life.

Anesthetic care begins with a thorough preoperative exam with identification of the end-organ involvement related to the primary disease process and associated comorbid conditions. In patients with MDCMD, primary anesthetic concerns include airway involvement as well as the respiratory and cardiovascular systems [13-15]. Airway management including bag-valve-mask ventilation and endotracheal intubation may be problematic in patients with facial dimorphism including micrognathia, midface hypoplasia, and other associated dysmorphic features as noted in our patient [16]. The potential for difficulties with airway management in patients with muscular dystrophy has been previously reported to be 3.4%, a percentage that is significantly higher than that routinely encountered in the pediatric population [17]. When there are concerns regarding airway management, 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 [18, 19]. Despite the dysmorphic features noted in our patient, airway management including bag-valve-mask ventilation and endotracheal intubation was not problematic.

The medications used for the induction and maintenance of anesthesia are guided by the primary disease process, its end-organ involvement and the need for intraoperative neurophysiological monitoring. A single case report has suggested the potential for malignant hyperthermia (MH) in patients with MDCMD [20]. Even if not specifically MH-sensitive, the prolonged administration of volatile anesthetic agents may result in destabilization of the sarcolemma with rhabdomyolysis and hyperkalemia [14]. Furthermore, maintenance anesthesia with TIVA may be preferred to facilitate intraoperative spinal cord monitoring with motor and somatosensory evoked potentials [21, 22]. Given these considerations, we chose to administer 50-70% nitrous oxide followed by placement of a peripheral intravenous cannula and intravenous induction. Additionally, as indicated, a topical anesthetic cream may also be placed preoperatively to provide cutaneous analgesia and facilitate peripheral venous cannulation.

An invariable finding with MDCMD is hypotonia with the potential involvement of upper airway and respiratory musculature. These issues may predispose these patients to upper airway obstruction or respiratory failure during the postoperative period. The risk of perioperative respiratory failure may be increased by pre-existing respiratory dysfunction from hypotonia, poor cough effort, chronic aspiration or recurrent pneumonia. Preoperative assessment of respiratory function using pulmonary function testing (PFT) is limited due to the cognitive involvement and age of these patients as PFT is cooperation and effort dependent [23, 24]. However, a room air oxygen saturation less than 95%, a history of recurrent pneumonia, or swallowing problems with aspiration may identify at risk patients. Preoperative preparation should include aggressive treatment of respiratory infections and as cognitive

Table 1. Reports of Anesthetic Care in Patients With Merosin-Deficient Congenital Muscular Dystrophy

Reference	Study cohort or demographics	Findings
Scrivener et al [13]	Ten children (average age 3.1 years, range 42 days to 11 years) requiring anesthetic care on 16 occasions	Volatile-based anesthetic agent in 13 and TIVA in three. No perioperative complications. No clinical signs of MH.
Shukry et al [20]	A 7-year-old boy undergoing posterior spine fusion under with TIVA	Endotracheal intubation reported as difficult during previous anesthetic so endotracheal intubation performed with a Shikani optical stylet. At the completion of the case, malignant hyperthermia suspected due to muscle rigidity, increase in body temperature, hypercarbia, metabolic acidosis and hyperkalemia. Treated with dantrolene with eventual resolution of symptoms. Muscle biopsy recommended, but results were not provided.
Jimenez et al [35]	A 13-year-old adolescent undergoing posterior spinal fusion with TIVA	Following prone positioning, hemodynamic instability was noted and the surgical procedure aborted. During second attempt at surgical procedure, following prone positioning, hemodynamic instability occurred again with CVP elevation. Surgery completed in lateral position. Intermittent right ventricular outflow obstruction thought to be cause of hypotension.
Pregardien et al [39]	A 2-year-old boy for the placement of an implantable venous access system	Balanced technique with propofol, sevoflurane and alfentanil. Due to concerns of respiratory depression, pressure-support ventilation used intraoperatively.

TIVA: total intravenous anesthesia; MH: malignant hyperthermia; CVP: central venous pressure.

function permits, instruction regarding the use of techniques such as incentive spirometry during the postoperative period. Patients with pre-existing motor weakness and hypotonia may be sensitive to the effects of neuromuscular blocking agent (NMBAs), inhalational agents and sedative agents. The use of short-acting agents (remifentanil) and complete reversal of residual neuromuscular blockade (see below) is suggested. Per our routine for patients with preoperative respiratory comorbidities, we chose to extubate our patient's trachea to non-invasive ventilation (BiPAP) to prevent atelectasis and allow for an easy transition to spontaneous ventilation [25, 26].

Muscular dystrophy and hypotonia have a significant impact on the selection, use and reversal of NMBAs during the perioperative period. Succinylcholine is absolutely contraindicated due to the risk of hyperkalemia [27, 28]. The spread of acetylcholine receptors over the entire sarcolemma leads to potassium efflux on depolarization following the administration of succinylcholine, resulting in potentially fatal arrhythmias related to hyperkalemia [27, 28]. Non-depolarizing NMBAs are safe in patients with various muscular dystrophies; however, a prolonged effect can be expected even with intermediate-acting agents such as atracurium, rocuronium or vecuronium [29]. Prior to their withdrawal, rapacuronium and mivacurium, two short-acting NMBAs, offered the potential option to achieve complete neuromuscular blockade for endotracheal intubation with an acceptable recovery time even for briefer procedures [30, 31]. More recently, the novel reversal agent for NMBAs, sugammadex, offers the potential to reverse even profound neuromuscular blockade in patients with neuromyopathic conditions [32].

As opposed to patients with Duchenne or Becker muscular dystrophy, there is limited information regarding the potential for and the magnitude of cardiac involvement in patients with MDCMD [33, 34]. As the expression of the laminin-α_2 chain is particularly high in the heart, cardiac involvement may occur in a significant percentage of patients. Reported comorbid cardiac involvement has included conduction disturbances (right bundle branch block), dilated cardiomyopathy, systolic dysfunction, mitral valve regurgitation, pulmonary hypertension, arrhythmias and wall motion hypokinesis. Spyrou et al studied the cardiac function of a cohort of 16 children with CMD using echocardiography. Two of six merosin-deficient children had an ejection fraction less than 40%. The average ejection fraction of the merosin-deficient children was 43±11% compared to 53±5% in merosin-positive children [34]. Manifestations of cardiac involvement may occur later in the disease than the skeletal muscle hypotonia. Additionally, as reported by Jimenez et al, due to the extreme scoliosis and positioning required intraoperatively, hemodynamic compromise may occur related to anatomical obstruction of cardiac output [35]. Due to these concerns, preoperative echocardiography and electrocardiography are recommended to screen for comorbid cardiac involvement. If significant cardiac involvement is noted, preoperative consultation with pediatric cardiology may be indicated. Additionally, the presence of depressed myocardial function may impact the choice of agents for anesthetic induction as well as the need for invasive monitoring of central venous pressure.

Merosin is also expressed in the brain and magnetic resonance has demonstrated white matter involvement and other CNS involvement [36]. Microcephaly, mental retardation, cerebral atrophy, cortical dysplasia, white matter changes, pontine and cerebral atrophy or cerebral cyst can be found on brain magnetic resonance imaging (MRI). Clinical findings have included mental retardation, developmental delay and seizures [37, 38]. Preoperative identification of CNS involvement, optimization of preoperative seizure control and continuation of anti-epileptic medications when necessary during the perioperative period are required in these patients.

To date, we identified only four published reports involving a total of 19 anesthetics in 13 patients regarding the anesthetic care of patients with MDCMD (Table 1) [13, 20, 35, 39]. Aside from concerns for MH in one patient, the remainder of the peri-

operative care was uneventful. Fourteen anesthetic encounters included a volatile-based anesthetic and five TIVA. When caring for patients with MDCMD, perioperative concerns include potential difficulties with airway management and endotracheal intubation, cardiac involvement, hypotonia with a risk for postoperative respiratory insufficiency or failure and CNS involvement including seizures and developmental delay.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

In accordance with IRB of Nationwide Children's Hospital, need for documentation of informed consent waved.

Author Contributions

Dolly M. Munlemvo contributed to preparation of secondary and final drafts. Anuradha Kanaparthi contributed to preparation of initial drafts, review of final manuscript. Joseph Tobias contributed to concept, review of all drafts.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

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