Anesthetic consideration for patients with nemaline rod myopathy: a literature review

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Key points
The anesthetic management of patients with nemaline myopathy should be deliberate and individualized. One should pay close attention to airway and cardiopulmonary status in the population. These patients should have optimization of their pulmonary function and treatment of any pulmonary infection prior to elective surgery. Currently there are no contraindicated anesthetic techniques, and muscle relaxants can be used. The choice of paralytic agents depends upon the type of surgery and the feasibility of implementing it. As vascular access and airway access may be difficult, the assistance of another anesthesiologist may be helpful. Paying attention to padding and positioning in long and complex surgeries to minimize neuropathy is important. Lastly, patients with NM may benefit from the intensive care unit postoperatively.

Abstract
Nemaline rod myopathy is a rare and heterogeneous condition with an incidence of approximately two per 100,000 per live birth. The disease encompasses a broad spectrum of morbidity ranging from mild symptoms to lethality in the newborn period. Patients with NM can present as a challenge to the anesthesiologist, manifesting with facial dysmorphism, respiratory failure, and cardiomyopathy and dysrhythmias. Controversy remains as to whether patients with NM are predisposed to malignant hyperthermia. There is no consensus on an optimal anesthetic approach to patients with NM. This review summarizes the available literature on the NM, in hope of bringing more clarity to its understanding and management. In the process, we have found that a variety of anesthetic techniques and drugs have been employed successfully in 159 cases since 1983: local-sedation, neuraxial, and general anesthesia; potent inhalational anesthetics, succinylcholine, non-depolarizing muscle relaxant, and reversals. These patients are at risk for difficult airway and vascular access, and respiratory failure after anesthetic exposure. However, there were no instances of malignant hyperthermia reported and there is no scientific evidence to support a correlation between nemaline rod myopathy and malignant hyperthermia.

Keywords: Nemaline myopathy, malignant hyperthermia, succinylcholine, inhalation anesthetic, anesthetic management.

Introduction
Nemaline rod myopathy, also known as nemaline myopathy (NM), is a rare and phenotypically diverse condition. This disease was first described by Shy and Engel in 1963 and occurs in approximately two per 100,000 live births. The disease encompasses a broad spectrum of morbidity ranging from mild symptoms to lethality in the newborn period. Patients with NM can present as a challenge to the anesthesiologist, manife-
sting with difficult airway, respiratory failure, and cardiac dysrhythmias. Controversy remains as to whether patients with NM are predisposed to malignant hyperthermia. There is no consensus on an optimal anesthetic approach to patients with NM. This review summarizes the available literature on the NM, in hope of bringing more clarity to its understanding and management.

Pathogenesis

The genetic underpinning of nemaline myopathy is well described. The majority (63%) of children with this condition have sporadic mutations. The hereditary varieties (37%) can be divided into autosomal dominant (13%) and autosomal recessive forms (24%).

The heterogeneity of the disease can be explained by nine distinct genes with six associated phenotypic subtypes. The specific genes involved encode skeletal muscle thin filaments, muscle-specific ubiquitin ligase, and possibly sarcoplasmic calcium-release channels responsible for excitation-contraction coupling. These include Nebulin (NEB1), ACTA1, beta-tropomyosin (TPM2), slow alpha-tropomyosin (TPM3), slow skeletal muscle troponin-T (TNNT1), coflin-2 (CFL2), and the ubiquitin ligase genes Kelch repeat and BTB domain-containing protein 13 (KBTBD13); Kelch-like family member 40 (KLHL40 - also known as KBTBD5); and the ryanodine receptor 1 (RyR1) (Table 1.). NEB mutations may account for up to 50% of NM cases. ACTA1 mutations are involved in 15%-25% of cases.

Multiple genes are often involved. There is often no specific single gene to subtype correlation.

Histologically, the major characteristics of NM are thick sarcoplasmic inclusions in skeletal muscle fiber cells composed of degraded and disorganized z-disk proteins (alpha-actinin and actin) arranged in a rod-like fashion. These numerous rods, located in uneven collections throughout the cytoplasm, are the hallmarks of NM on muscle biopsy. Rods are not unique to NM; they can occur in normal ocular muscles, in aging muscle, at myotendinous junctions, and in other acquired and inherited disorders such as dermatomyositis, poliomyelitis and HIV.

Pathologic rod formation in NM is due to irregular muscle cell contraction from the altered regulation of calcium-dependent force production in muscle fibers. This process is responsible for the clinical finding of hypotonia in patients with NM.

Although some posit that mutations of the ryanodine receptor (RyR1) are features of core and rod myopathies, existing data to support this claim are sparse. There is only one case report detailing two compound heterozygous missense mutations in RyR1 in a patient with severe congenital NM [(c.4718C>T (p.1573 Pro>Leu) in exon 33 and c.7585 G>A (p.2529 Asp>Asn) in exon 47)]. Modified Gomori trichrome staining and electron microscopic muscle biopsy showed cytoplasmic nemaline bodies without any central cores or minicores. The study subject has no family history of malignant hyperthermia (MH) and no susceptibility testing was done. Furthermore, these two novel RyR1 mutations are not among the 35 RyR1 causative mutations listed by the European Malignant Hyperthermia Group. Currently, there is no scientific evidence to support the hypothesis that children with NM are MH-susceptible.

There is an overlapping myopathy, core-rod myopathy (CRM), that shares features of both core and rod myopathies. CRM is a heterogeneous disease with the alterations of the genes NEB, TPM2, ACTA1, CFL2, and KBTBD13. CRM is genetically and histologically related to, but not identical to, NM. Recent advan-
ces in gene sequencing revealed a RyR1 mutation on chromosome 19, an NEB mutation on chromosome 2 and a TMP1 mutation on chromosome 15.\textsuperscript{18, 20, 22, 23} The novel Y4796C mutation in the C-terminal channel-forming domain of the RyR1 protein on chromosome 19 has met the threshold values for muscle tension for MH susceptibility according to the European Malignant Hyperthermia Group’s protocol in a patient with CRM (Table 2., number 30).\textsuperscript{18}

Clinical manifestations

Nemaline myopathy encompasses a continuum of disease manifestations ranging from mild to severe. Characteristically, patients with NM present with non-progressive myopathy, feeding difficulties and proximal muscle weakness. Children appear physically underdeveloped, with small muscles and thin limbs\textsuperscript{24}. Bulbar muscles are often involved, leading to dysphagia and risk of aspiration. Respiratory muscle involvement is common, and ranges from mild impairment with independent respiratory function to severe failure and complete ventilator dependence. Dysmorphic facial features may include micrognathia or prognathia; limited mouth opening, and a high arched palate. Other signs include chest deformities, such as pectus excavatum; kyphosis; scoliosis; and pes cavus. The extremities may show joint contractures and talipes.

There are six distinct presentations of NM, which can be differentiated from each other based on the age of symptoms presentation and severity of the symptoms. There is significant overlap between the types. In decreasing severity, these types include: severe congenital, Amish,\textsuperscript{25} intermediate congenital; typical congenital; childhood-onset; and adult-onset.\textsuperscript{2, 26} The severe congenital form is the most lethal. These patients present with profound hypotonia, no spontaneous movement, and respiratory failure leading to death in the first year of life. The Amish variant, with a high incidence of 1 in 500, is nearly exclusive to the Old Order Amish community of Pennsylvania. Though less critical than the severe congenital form, patients with the Amish variant have similar symptoms, often leading to death by age two.

Patients with intermediate congenital NM are distinguished from others by having independent respiratory function at birth. Over time, however, their condition deteriorates with generalized hypotonia and contractures; and progressive delay in developmental milestones leads to wheelchair dependence and ventilator support by age eleven. The typical congenital form is the most common, presenting with truncal muscle weakness, feeding difficulties, moderate hypotonia, and partially diminished respiratory function. While the previously described variants are all symptomatic at birth, those with typical congenital NM may not show signs of the disease until one year of age. Childhood-onset NM presents in patients between eight and fifteen years of age. This variant involves normal early motor development. Subsequent disease manifestation begins as a distal symmetric myopathy of the ankles and feet, leading to foot drop.
The adult onset form of NM manifests between twenty and fifty years of age. There is usually no family history of the disease. Patients often present with rapid progression of generalized muscle weakness and pain, and occasionally including neck musculature.

Patients with NM should be assessed for cardiac pathologies. Cardiac muscle involvement is frequent and is often associated with ACTA1 mutations. Cardiac muscle biopsy demonstrates cytoplasmic rod inclusions. Manifestations of cardiac involvement are widely variable, and often present as hypertrophic cardiomyopathy.

Less commonly, patients with NM present with dilated cardiomyopathy, heart failure without cardiomyopathy, and sudden cardiac death. NM patients with cardiac involvement are prone to ventricular arrhythmias, and can be managed by implantation of AICD. When respiratory muscles are involved, NM patients can develop pulmonary hypertension leading to cor pulmonale.

Anesthetic management

There is little available information regarding the anesthetic management of patients with nemaline myopathy. A search performed in PubMed using the keywords “nemaline myopathy” or “nemaline rod myopathy” and “anesthesia” or “anesthetic management” in various combinations showed a total of thirteen journal articles dating back to 1983 reporting 159 patients having anesthetic exposure. Eleven out of thirteen articles are case reports, one is an editorial/case report and one is a clinical study of a large group of NM patients (Table 3.). Common problems requiring early surgical intervention in patients with NM include scoliosis, extremity malformations, and facial dysmorphisms. Those who have the milder forms of the disease and live to childbearing age may require Cesarean section due to muscular weakness, feto-pelvic disproportion, and contractures and the consequent inability to deliver vaginally. Parturients with NM are at risk for preterm deliveries secondary to maternal respiratory compromise from muscle and diaphragmatic weakness; and from fetal size late in the third trimester.

A variety of anesthetic techniques and medications have been used successfully in patients with NM. These include including inhalational anesthetics, total intravenous anesthetic, local-regional, neuraxial technique, and sedation. Both depolarizing and non-depolarizing muscle relaxants have been used. One article reported acute respiratory failure following a routine outpatient cataract surgery under local anesthesia and sedation. The patient is a 63 years old male, ASA physical status 2, without known history of NM. After discharge, he presented to the emergency department post-operative day seven with respiratory distress and oxygen saturation of 85%. His chest roentgenogram showed pneumonia. He subsequently developed respiratory failure, was intubated, and subsequently underwent a tracheostomy. His evaluation revealed nemaline myopathy. The patient was discharged home after one year in the intensive care unit. Notably, two of thirteen articles reported difficult intubation. Stackhouse et al. reported a difficult airway in a parturient undergoing an elective Cesarean section. Airway examination of the patient revealed Mallampati Class I with full neck range of motion and normal thyromental distance. Assisted mask ventilation was straightforward but four, direct laryngoscopic attempts were performed with visualization of only the aryte-
noids and tracheal intubation was successfully done blindly.\textsuperscript{34} Cunliffe et al. reported a patient with dysmorphic facial features undergoing general anesthesia for scoliosis surgery. Direct laryngoscopy revealed only the posterior arytenoids. Her trachea was intubated with the aid of a stylet.

Five articles reported the use of muscle relaxants in patients with NM including succinylcholine, pancuronium, vecuronium, and atracurium.\textsuperscript{3, 5, 7, 34, 35} Two of the earliest case reports of anesthetic management of NM patients offered conflicting recommendations on the use of muscle relaxants. Heard et al. reported the successful use of succinylcholine and pancuronium in a patient with NM. The patient demonstrated an altered response to a 1mg/kg dose of succinylcholine, where the latency period (the time it takes for the train-of-four twitches to diminish) was six minutes rather than the typical 25-45 seconds.\textsuperscript{35} Notably, the patient’s succinylcholine recovery time was normal. Potassium levels remained normal after the administration of succinylcholine. Response to the administration of pancuronium and the reversal agent, neostigmine, was within normal limits. Contrary to the medications utilized by Heard et al.,\textsuperscript{35} Cunliffe et al. advocated refraining from muscle relaxants altogether due to concern of worsening respiratory weakness.\textsuperscript{33}

Of the thirteen articles found, four pertained to the anesthetic management of obstetric patients. One patient received an epidural anesthetic and another received a spinal anesthetic successfully without neurologic sequelae.\textsuperscript{29, 34} Two obstetric patients were managed with general anesthesia without clear explanations.\textsuperscript{30, 34} One study detailed spinal anesthesia for an infant with NM undergoing gastrostomy and quadriceps femoris muscle biopsy.\textsuperscript{36} Another study described anesthetic management for cardiac surgery for three NM patients with high dose fentanyl and diazepam.\textsuperscript{3}

Four studies reported TIVA for maintenance of anesthesia due to concern for increased risk of malignant hyperthermia.\textsuperscript{3, 5, 7} Four cases involved the use of potent inha-

lational agents (halothane, enflurane, and isoflurane) for maintenance of anesthesia.\textsuperscript{33, 35, 37} Ryan et al. performed a clinical study of 143 cases from North America and Australia. They reported each of these patients had at least one anesthetic exposure. The specific details of the type of anesthesia were not included in the journal. The most common complication after anesthetic exposure was unexpected respiratory failure necessitating prolonged ventilation.\textsuperscript{38} There was no MH reported.

We have cared for two additional patients, one underwent oromaxillofacial reconstructive surgery and the other had complex spine fusion. We have published our anesthetic management of a patient undergoing oromaxillofacial reconstructive surgery.\textsuperscript{39} Both of our patients received total intravenous anesthesia, including nondepolarizing muscle relaxants, as requested by their neurologists. These anesthetic techniques worked well for our patients and their anesthetic course was uneventful. Anesthetic considerations for patients with nemaline myopathy are guided by the patient’s underlying pathophysiology. Airway difficulty should be anticipated secondary to facial dysmorphisms. Respiratory compromise and failure may occur due to underlying pulmonary dysfunction, respiratory muscle weakness and kyphoscoliosis. Pathologic involvement of the myocardium can lead to cardiomyopathy, pulmonary hypertension and cor pulmonale. Intravenous access may present as a challenge. The choice of anesthetic technique, from induction to emergence, needs to be carefully considered, including whether muscle relaxation is required, and which of the muscle relaxants to employ. Patient positioning may be difficult. A preoperative consultation with an anesthesiologist is paramount. During the visit, a thorough review of the patient’s problems with special attention to the cardiopulmonary system and airway is critical. Patients with significant pulmonary involvement should consult with their pulmonologists for optimization of pulmonary function prior to surgery. Consultation with a cardiologist is warranted if cardiac
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involvement is suspected in order to optimize baseline cardiac function and to evaluate for the presence ventricular arrhythmias. Further diagnostic testing with echocardiogram, electrocardiogram, arterial blood gas, and pulmonary function test may be indicated. Prior pulmonary test results, card test results, and anesthesia records should be made available. A significant portion of these patients also have sleep apnea; these patients and their families should be reminded to bring their CPAP/BiPAP machines on the day of surgery. Some patients may have significantly elevated serum creatine level so a preoperative baseline determination might be beneficial. Blood count and serum chemistry are appropriate prior to major surgery.

As evidenced by the case reports, airway instrumentation in patients with NM may be challenging due to facial dysmorphism. Bulbar muscles are often involved leading to dysphagia and poorly controlled acid reflux. Patients often have copious oral secretions and are prone to aspiration. One must have a methodic approach to securing the airway with alternative plans. Securing intravenous access for induction is preferred over inhalation induction. An antisialogue should be given preoperatively. Depending on the age of the patient, the airway exam, and prior history, one may choose an awake technique to secure the airway. If conditions allow, and airway instrumentation can be attempted after induction, direct laryngoscopy can be performed provided there is full availability of airway adjuncts such as a video laryngoscope and a flexible fiberoptic bronchoscope. As per the Difficult Airway Algorithm, supraglottic airway devices should be immediately available. Often times, muscle relaxation is not needed for direct laryngoscopy because of the patient’s baseline weakness. At the discretion of the anesthesiologist, muscle relaxation may be used to facilitate direct laryngoscopy if assisted ventilation is not problematic. Pulmonary dysfunction and infections are the leading causes of death in patients with NM. Pulmonary dysfunction results from respiratory muscle weakness. Additionally, chest deformity from pectus excavatum and lordo-kypho-scoliosis alter respiratory mechanics and increases the total dead space leading to dysfunction in pulmonary gas exchange secondary to ventilation-perfusion mismatch. The patient’s pulmonary status should be optimized with chest physiotherapy and pulmonary toilet prior to, during, and after surgery. Any pulmonary infection must be treated prior to elective surgery. Efforts should be made during surgery to avoid worsening any pre-existing pulmonary dysfunction. A ventilation strategy utilizing positive end expiratory pressure and low peak airway pressure to achieve adequate ventilation is recommended. Humidified air is beneficial. Depending on the patient’s baseline pulmonary status and pulmonary function tests, preparations for post-operative respiratory difficulties and mechanical ventilation may be necessary.

Cardiac involvement, although infrequent, should be actively sought because of significant related morbidity and mortality. Some patients with NM may present with an automatic implantable cardioverter-defibrillator (AICD) due to ventricular dysrhythmias; perioperative management of the AICD is important. In patients with diaphragmatic involvement, pulmonary hypertension and cor pulmonale may be present. In these patients, a cardio-protective anesthetic induction along with intra-arterial blood pressure monitoring may be of benefit. In patients with NM, there is inadequate evidence to claim an increased risk for malignant hyperthermia. At the recommendation of their physicians, these patients may present for surgery requesting a total intravenous anesthesia technique without succinylcholine. Understandably, MH would be a consideration since depolarizing muscle relaxants and volatile anesthetics are contraindicated in other myopathies. From the case reports, we know that potent inhalational anesthetics and succinylcholine have been used successfully in these patients without sequela. Heard et al. demonstrated that succinylcholine can be safely administered to patients with.
NM. As mentioned previously, there is one MN case reported where two causative missense mutations in the RyR1 receptor in a NM patient, and the biopsies of patient’s muscle show rods but no cores, and his mutations were not associated with causing MH. Therefore, with our current understanding of this myopathy, there is no scientific evidence to suggest that NM patients are MH susceptible.

Succinylcholine should be used with caution for hyperkalemia. Most NM patients have normal to slightly elevated creatine kinase and aldolase levels. However, Asai et al. reported elevation in serum creatine kinase, specifically the MM isozyme, aldolase, and LDH levels in two of the three NM patients undergoing cardiac surgery. Badurska et al. reported significantly increased serum creatine kinase levels in a patient with NM. Brownell et al. reported an adult-onset NM patient with marked elevation in creatine kinase levels of up to 16 times normal and serum LDH levels up to three times normal. Of course also, the precaution for hyperkalemia with succinylcholine for any patients with prolonged immobility is recommended.

Non-depolarizing muscle relaxants have been safely administered and reversed without sequelae. Results from the cases reports demonstrate that, both long and intermediate acting non-depolarizing agents have been administered and reversed successfully.

Local-regional and neuraxial anesthetics have been employed successfully in patients with NM. As these patients often have bone deformities, contractures, and scoliosis, neuraxial and regional procedures may be challenging. Techniques that cause diaphragmatic weakness and impairment of other respiratory muscles must be undertaken with caution in order to avoid further compromise of already suboptimal respiratory mechanics.

Bone deformities and contractures of the extremities may pose challenges to peripheral vascular access. Ultrasound guidance may be helpful. In major surgeries, central venous catheters may be indicated. Similarly, positioning of NM patients for long, complex surgeries can be difficult. At times, an optimal or desired position for surgery is not possible and compression neuropathy may be unavoidable. In these circumstances, a clear discussion of risks with the care providers is important.

Postoperative disposition for patients with NM depends on the severity of the disease and the type of surgery. This group of patients may benefit from the admission to the ICU after surgery to monitor for respiratory and anesthetic complications.

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