Pediatric Anesthesia and Critical Care Journal 2017;5(1):31-39
doi:10.14587/paccj.2017.5

PACCJ

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

NH. Tran, D. Smith

Department of Anesthesiology and Pain Management, Pediatric Anesthesiology Division, University of Rochester Medical Center, New York, USA

Corresponding author: NH Tran, Department of Anesthesiology and Pain Management, Pediatric Anesthesiology Division, University of Rochester Medical Center. Email: nobuyukihai_tran@urmc.rochester.edu

Keypoints

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[1] and occurs in approximately two per 100,000 live births[2]. 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.[3-9] 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%).[10]

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), cofilin-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);[2, 11] and the ryanodine receptor 1 (RyR1)[6] (Table 1.). NEB mutations may account for up to 50% of NM cases. ACTA1 mutations are involved in 15%-25% of cases.[2, 10] Multiple genes are often involved. There is often no specific single gene to subtype correlation.[2]

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.[12, 13] 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, polio-myositis and HIV.[14-16] 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.[17]

Table 1. Molecular Genetic Basis and Phenotypic Correlation in Nemaline Myopathy

Gene symbol	Chromosomal locus	Protein name	Mode of inheritance	Phenotype	Proportion of NM attributed to mutations in this gene
ACTA1	1q42.1	Actin, a skeletal muscle	AD/AR	Range – severe congenital to childhood onset	15–25%
NEB	2q22	Nebulin	AR	Typical congenital (majority); other phenotypes (less common)	up to 50%
TPM3	1q22–q23	Tropomyosin α-3 chain	AD/AR	Severe congenital (AR)	2–3%
				Intermediate congenital	
				Childhood onset (AD)	
TPM2	9p13.2–p13.1	Tropomyosin β-chain	AD	Typical congenital	51%
TNNT1	19q13.4	Troponin T, slow skeletal muscle	AR	Amish NM	Unknown – Old Amish only
CFL2	14q12	Cofilin-2	AR	Typical congenital	Unknown
KBTBD13	15q22.31	Kelch repeat and BTB domain-containing protein 13	AD	Childhood onset, characteristic slowness of movements	Unknown
KLHL40	3p22.1	Kelch-like family member 40	AR	Severe congenital	~5%
RYR1	19q13.2	Ryanodine receptor 1	AR	Severe congenital	Unknown

AD, autosomal dominant; AR, autosomal recessive. Adapted from Romero et al. and Sandaradura et al.

Although some posit that mutations of the ryanodine receptor (RyR1) are features of core and rod myopathies,[18-20] 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)].[6] 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.[6, 18-21] 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.[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).[18]

Table 2. Causative Malignant Hyperthermia Mutations

		RyR1 Mutations			CACNAS1 Mutations		
#	Exon	Nucleotide	Aminoacid	Causative	Nucleotide	Aminoacid	Causative
1	2	c.103T>C	p.35Cys>Arg	Yes	c.3257G>A	p.Arg1086His	Yes
2	6	c.487C>T	p.163Arg>Cys	Yes	c.520C>T	p.Arg174Trp	Yes
3	6	c.488G>T	p.163Arg>Leu	Yes			
4	9	c.742G>A	p.248Gly>Arg	Yes			
5	9	c.742G>C	p.248Gly>Arg	Yes			
6	11	c.1021G>A	p.341Gly>Arg	Yes			
7	12	c.1209C>G	p.403Ile>Met	Yes			
8	14	c.1565A>C	p.522Tyr>Ser	Yes			
9	15	c.1589G>A	p.530Arg>His	Yes			
10	15	c.1654C>T	p.552Arg>Trp	Yes			
11	17	c.1840C>T	p.614Arg>Cys	Yes			
12	17	c.1841G>T	p.614Arg>Leu	Yes			
13	39	c.6487C>T	p.2163Arg>Cys	Yes			
14	39	c.6488G>A	p.2163Arg>His	Yes			
15	39	c.6502G>A	p.2168Val>Met	Yes			
16	40	c.6617C>G	p.2206Thr>Arg	Yes			
17	40	c.6617C>T	p.2206Thr>Met	Yes			
18	43	c.7007G>A	p.2336Arg>His	Yes			
19	44	c.7048G>A	p.2350Ala>Thr	Yes			
20	44	c.7124G>C	p.2375Gly>Ala	Yes			
21	45	c.7282G>A	p.2428Ala>Thr	Yes			
22	45	c.7300G>A	p.2434Gly>Arg	Yes			
23	45	c.7304G>A	p.2435Arg>His	Yes			
24	46	c.7360C>T	p.2454Arg>Cys	Yes			
25	46	c.7361G>A	p.2454Arg>His	Yes			
26	46	c.7372C>T	p.2458Arg>Cys	Yes			
27	46	c.7373G>A	p.2458Arg>His	Yes			
28	47	c.7522C>T	p.2508Arg>Cys	Yes			
29	47	c.7523G>A	p.2508Arg>His	Yes			
30	100	c.14387A>G	p.4796Tyr>Cys	Yes			
31	100	c.14477C>T	p.4826Thr>Ile	Yes			
32	100	c.14497C>T	p.4833His>Tyr	Yes			
33	101	c.14512C>G	p.4838Leu>Val	Yes			
34	101	c.14582G>A	p.4861Arg>His	Yes			
35	102	c.14693T>C	p.4898Ile>Thr	Yes			

Adapted from the European Malignant Hyperthermia Group Website

RyR1 - ryanodine receptor 1, CACNAS1 - calcium voltage-gated channel subunit alpha1 S

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[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;[25] intermediate congenital; typical congenital; childhood-onset; and adult-onset.[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.[27, 28] 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.[27] 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.[29] 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.[30, 31]

Table 3. Reported Anesthetic Management of Nemaline Myopathy

Year	*Author*	*# of Pts*	*Surgery*	*TIVA*	*Inhalational*	*Regional*	*Muscle Relaxant*	*Reversal*	*Difficult Airway*
1983	Heard et al.	1	Oromaxillo-facial		Enflu/NOS		Sux/Pan	Yes	No
1985	Cunliffe et al.	1	Ortho-Spine fusion		Halo/NOS				Yes
1990	Felber et al.	1	Orthopedic	Prop/Fent	NOS		Atra		No
1992	Asai et al.	3	Cardiac	Fentanyl			Pan		No
				Diazepam					
1994	Stackhouse et al.	1	C-section		Iso		Vec	Yes	Yes
			C-section			NR			
1995	Wallgren-Pettersen et al.	1	C-section			Epidural/ Bupi			
1999	Ryan et al.	135				NR			
1999	Nishihara et al.	1	Dental	Prop/Fent			Vec	Yes	No
2000	Shenkman et al.	1	Gastrotomy			Spinal/Bupi			
2007	Eskanda et al.	1	C-section		NR				No
2008	del Valle et al.	1	Maxillofacial	Prop/Remi					No
2012	Raveau et al.	1	Cataract			Local-sedation			
2015	Bezak et al.	1	Oromaxillo-facial		Iso/NOS				No
2015	Tran et al.	2	Spine fusion	Propofol			Roc	Yes	No
				Sufentanil					
			Craniofacial	Prop/Fent			Roc	Yes	No

Pts – patients; TIVA - total intravenous anesthesia; NR - not reported; Atra - atracurium; Bupi - bupivacaine
Enflu – enflurane; Fent - fentanyl; Halo - halothane; Iso - isoflourane; NOS - nitrous oxide
Pan - pancuronium; Prop – propofol; Remi - remifentanyl; Roc - Rocuronium; Sux - succinylcholine; Vec - vecuronium

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.[32] 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.[33, 34] 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.[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.[33]

Five articles reported the use of muscle relaxants in patients with NM including succinylcholine, pancuronium, vecuronium, and atracurium.[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.[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.,[35] Cunliffe et al. advocated refraining from muscle relaxants altogether due to concern of worsening respiratory weakness.[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.[29, 34] Two obstetric patients were managed with general anesthesia without clear explanations.[30, 34]

One study detailed spinal anesthesia for an infant with NM undergoing gastrostomy and quadriceps femoris muscle biopsy.[36] Another study described anesthetic management for cardiac surgery for three NM patients with high dose fentanyl and diazepam.[3]

Four studies reported TIVA for maintenance of anesthesia due to concern for increased risk of malignant hyperthermia.[3-5, 7] Four cases involved the use of potent inhalational agents (halothane, enflurane, and isoflurane) for maintenance of anesthesia.[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.[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.[39] Both of our patients received total intravenous anesthesia, including non-depolarizing 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

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, cardiac 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 inhalational 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.[39] 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[38]. 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.[28, 38, 40-42] 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.[35] 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.[43] 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.[3] 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.[44, 45] 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.

References

1. Shy GM, Engel WK, Somers JE, Wanko T. Nemaline Myopathy. A new congenital myopathy. Brain: a journal of neurology 1963;86:793-810.

2. Romero NB, Sandaradura SA, Clarke NF. Recent advances in nemaline myopathy. Curr Opin Neurol 2013;26:519-26.

3. Asai T, Fujise K, Uchida M. Anaesthesia for cardiac surgery in children with nemaline myopathy. Anaesthesia 1992;47:405-8.

4. del Valle V, Trigo Rubio P, Bermejo Alvarez MA, Taboada C. [Anesthetic considerations in nemaline myopathy]. Revista espanola de anestesiologia y reanimacion 2008;55:122-3.

5. Felber AR, Jelen-Esselborn S. [Anesthesia in a patient with congenital nemaline type myopathy]. Der Anaesthesist 1990;39:378-81.

6. Kondo E, Nishimura T, Kosho T, Inaba Y, Mitsuhashi S, Ishida T, et al. Recessive RYR1 mutations in a patient with severe congenital nemaline myopathy with ophthalomoplegia identified through massively parallel sequencing. Am J Med Genet A 2012;158A:772-8.

7. Nishihara M, Satoh KI, Yokoyama K, Yoshitomi T, Ogi H, Nakagawa M, et al. Propofol anesthesia for a patient with nemaline myopathy. Journal of Japanese Dental Society of Anesthesiology 1999;27:165-9.

8. Romero A, Joshi GP. Neuromuscular disease and anesthesia. Muscle & nerve 2013;48:451-60.

9. Veyckemans F. Can inhalation agents be used in the presence of a child with myopathy? Current opinion in anaesthesiology 2010;23:348-55.

10. Wallgren-Pettersson C, Pelin K, Hilpela P, Donner K, Porfirio B, Graziano C, et al. Clinical and genetic heterogeneity in autosomal recessive nemaline myopathy. Neuromuscul Disord 1999;9:564-72.

11. Sandaradura SA, North KN. Molecular Genetics of Nemaline Myopathy. eLS: John Wiley & Sons, Ltd 2001.

12. Wallgren-Pettersson C, Jasani B, Newman GR, Morris GE, Jones S, Singhrao S, et al. Alpha-actinin in nemaline bodies in congenital nemaline myopathy: immunological confirmation by light and electron microscopy. Neuromuscul Disord 1995;5:93-104.

13. Witt CC, Burkart C, Labeit D, McNabb M, Wu Y, Granzier H, et al. Nebulin regulates thin filament length, contractility, and Z-disk structure in vivo. The EMBO journal 2006;25:3843-55.

14. Engel AG. Late-onset rod myopathy (a new syndrome?): light and electron microscopic observations in two cases. Mayo Clinic proceedings 1966;41:713-41.

15. Rowland LP. HIV-related neuromuscular diseases: nemaline myopathy, amyotrophic lateral sclerosis and bibrachial amyotrophic diplegia. Acta myologica : myopathies and cardiomyopathies : official journal of the Mediterranean Society of Myology / edited by the Gaetano Conte Academy for the study of striated muscle diseases 2011;30:29-31.

16. Wallgren-Pettersson C, Sewry CA, Nowak KJ, Laing NG. Nemaline myopathies. Semin Pediatr Neurol 2011;18:230-8.

17. Michele DE, Albayya FP, Metzger JM. A nemaline myopathy mutation in alpha-tropomyosin causes defective regulation of striated muscle force production. The Journal of clinical investigation 1999;104:1575-81.

18. Monnier N, Romero NB, Lerale J, Nivoche Y, Qi D, MacLennan DH, et al. An autosomal dominant congenital myopathy with cores and rods is associated with a neomutation in the RYR1 gene encoding the skeletal muscle ryanodine receptor. Human molecular genetics 2000;9:2599-608.

19. Pallagi E, Molnar M, Molnar P, Dioszeghy P. Central core and nemaline rods in the same patient. Acta Neuropathol 1998;96:211-4.

20. Scacheri PC, Hoffman EP, Fratkin JD, Semino-Mora C, Senchak A, Davis MR, et al. A novel ryanodine receptor gene mutation causing both cores and rods in congenital myopathy. Neurology 2000;55:1689-96.

21. Hernandez-Lain A, Husson I, Monnier N, Farnoux C, Brochier G, Lacene E, et al. De novo RYR1 heterozygous mutation (I4898T) causing lethal core-rod myopathy in twins. Eur J Med Genet 2011;54:29-33.

22. Gommans IM, Davis M, Saar K, Lammens M, Mastaglia F, Lamont P, et al. A locus on chromosome 15q for a dominantly inherited nemaline myopathy with core-like lesions. Brain 2003;126(Pt 7):1545-51.

23. Romero NB, Lehtokari VL, Quijano-Roy S, Monnier N, Claeys KG, Carlier RY, et al. Core-rod myopathy caused by mutations in the nebulin gene. Neurology 2009;73:1159-61.

24. Klingler W, Rueffert H, Lehmann-Horn F, Girard T, Hopkins PM. Core myopathies and risk of malignant hyperthermia. Anesthesia and Analgesia 2009;109 :1167-73.

25. Johnston JJ, Kelley RI, Crawford TO, Morton DH, Agarwala R, Koch T, et al. A novel nemaline myopathy in the Amish caused by a mutation in troponin T1. American journal of human genetics 2000;67:814-21.

26. Sharma MC, Jain D, Sarkar C, Goebel HH. Congenital myopathies--a comprehensive update of recent advancements. Acta neurologica Scandinavica 2009;119:281-92.

27. Finsterer J, Stollberger C. Review of Cardiac Disease in Nemaline Myopathy. Pediatric neurology 2015;53:473-7.

28. Marseglia L, D'Angelo G, Manti S, Salpietro V, Arrigo T, Cavallari V, et al. Sudden cardiac arrest in a

child with nemaline myopathy. Italian journal of pediatrics 2015;41:20.

29. Wallgren-Pettersson C, Hiilesmaa VK, Paatero H. Pregnancy and delivery in congenital nemaline myopathy. Acta obstetricia et gynecologica Scandinavica 1995;74:659-61.

30. Eskandar OS, Eckford SD. Pregnancy in a patient with nemaline myopathy. Obstetrics and gynecology 2007;109(2 Pt2):501-4.

31. Thomas V, Jose R. Nemaline myopathy and pregnancy: a challenge indeed. Neurology India 2012;60:524-5.

32. Raveau T, Lassalle V, Dubourg O, Legout A, Tirot P. [Nemaline rod myopathy revealed by acute respiratory failure after an outpatient cataract surgery]. Annales francaises d'anesthesie et de reanimation 2012;31:638-40.

33. Cunliffe M, Burrows FA. Anaesthetic implications of nemaline rod myopathy. Canadian Anaesthetists' Society journal 1985;32:543-7.

34. Stackhouse R, Chelmow D, Dattel BJ. Anesthetic complications in a pregnant patient with nemaline myopathy. Anesthesia and Analgesia 1994;79:1195-7.

35. Heard SO, Kaplan RF. Neuromuscular blockade in a patient with nemaline myopathy. Anesthesiology 1983;59:588-90.

36. Shenkman Z, Sheffer O, Erez I, Litmanovitc I, Jedeikin R. Spinal anesthesia for gastrostomy in an infant with nemaline myopathy. Anesthesia and Analgesia 2000;91:858-9.

37. Bezak BJ, Arce KA, Jacob A, Van Ess J. Orthognathic Surgery in Patients With Congenital Myopathies and Congenital Muscular Dystrophies: Case Series and Review of the Literature. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons 2015.

38. Ryan MM, Schnell C, Strickland CD, Shield LK, Morgan G, Iannaccone ST, et al. Nemaline myopathy: a clinical study of 143 cases. Annals of neurology 2001;50:312-20.

39. Tran NH, Chhibber A. Anesthetic Management of a Pediatric Patient with NEB1-Genotype Nemaline Rod Myopathy for Cleft Plate Repair. PACCJ. 2016;4(2):78-82.

40. Apfelbaum JL, Hagberg CA, Caplan RA, Blitt CD, Connis RT, Nickinovich DG, et al. Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology 2013;118:251-70.

41. D'Amico A, Graziano C, Pacileo G, Petrini S, Nowak KJ, Boldrini R, et al. Fatal hypertrophic cardiomyopathy and nemaline myopathy associated with ACTA1 K336E mutation. Neuromuscular disorders : NMD 2006;16:548-52.

42. Finsterer J, Frank M. Potential causes of sudden cardiac death in nemaline myopathy. Italian journal of pediatrics 2015;41:67.

43. Nakajima M, Shima Y, Kumasaka S, Kuwabara K, Migita M, Fukunaga Y. An infant with congenital nemaline myopathy and hypertrophic cardiomyopathy. Journal of Nippon Medical School = Nippon Ika Daigaku zasshi 2008;75:350-3.

44. http://www.emhg.org. European Malignant Hyperthermia Group. 2016.

45. Badurska B, Fidzianska A, Jedrzejowska H. Nemaline myopathy. Neuropatologia polska 1970;8:389-97.

46. Brownell AK, Gilbert JJ, Shaw DT, Garcia B, Wenkebach GF, Lam AK. Adult onset nemaline myopathy. Neurology 1978;28:1306-9.