

Anesthetic management of a pediatric patient with NEB1-Genotype Nemaline Rod Myopathy for cleft palate repair

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Keypoints

Anesthetic care for patients with nemaline myopathy is challenging due to the rarity of the disease and the lack of consensus on optimal anesthetic management. We presented a pediatric patient with nemaline myopathy undergoing cleft palate surgery. The anesthetic management was planned and executed uneventfully with total intravenous anesthesia without succinylcholine as requested by the patient's parents and neurologist.

Abstract

Manufacturing defects of endotracheal tube (ETT) are not so common but not so rare in anesthesia practice. The important thing is to identify these defects by careful examination of ETT prior to use. However, many defects remain unnoticed during routine inspection. This may lead to partial or complete airway obstruction of airway. Here we are reporting a case in which complete airway obstruction occurred due to manufacturing defect of prepacked single use (PVC) endotracheal tube connector which was promptly recognized and further complications were prevented. This case report highlights the importance of careful vigilant examination of ETTs before use to prevent any untoward events that can be life threatening to the patient.

Keywords: nemaline myopathy, anesthetic management, malignant hyperthermia

Introduction

Nemaline myopathy or nemaline rod myopathy (NM) is a rare disease with a wide spectrum of symptoms and severities. Characteristically, NM is a congenital non-progressive myopathy with prominent proximal muscle

weakness. Children with NM appear physically underdeveloped, with small muscles and thin limbs.¹ They may display micrognathia, prognathia, limited mouth opening and a high arched palate. Bulbar muscles are often involved, leading to dysphagia and increased risk of aspiration. Respiratory muscle involvement is common, ranging from mild impairment to severe respiratory failure. Cardiac muscle involvement may manifest as cardiomyopathy and dysrhythmias. Other signs of the disease include pectus excavatum, kyphosis, scoliosis, pes cavus, talipes equinovarus and joint contractures. With the symptomatology noted above, patients with nemaline myopathy may present as a challenge for the anesthesiologist in the perioperative period. There may be difficulties in intravenous access, airway instrumentation, positioning, and post operative disposition. Additionally, underlying cardiac and pulmonary pathologies require vigilant attention and individualized management. As NM is a rare condition, occurring in approximately two cases per every 100,000 live births,² there is currently no consensus on an optimal anesthetic approach in the care of children with this condition.

Though commonly assumed, there is no clear documented association between NM and malignant hyperthermia (MH). This presumptive association may have developed because NM is clinically indistinguishable from central core disease (CCD) and core-rod myopathy (CRM), two conditions that are known to increase the risk for MH. To make matters worse, CRM is often confusingly referred to as NM with cores. CRM, however, is a distinct entity with possible ryanodine receptor 1 (RyR1) and an increased risk of MH.³ In this case report, we describe the intraoperative management of a toddler with known nemaline myopathy. The different aspects of his perioperative care illuminate the current incomplete understanding of the disease, the dearth of consensus on anesthetic management, and an uncertainty in possible risk for MH.

Case report

The patient is a 3-year old boy who presented for repair of a cleft palate. He has a known history of typical congenital nemaline myopathy (NEB1 mutation) with associated developmental delay, feeding difficulties, restrictive lung disease, central and moderate obstructive sleep apnea, scoliosis, hypotonia, and arthrogryposis multiplex congenita. His obstructive sleep apnea was somewhat improved after tonsillectomy, though he continued to require nightly CPAP therapy. He has no underlying cardiac problems. The patient presented to our institution from a neighboring city as part of a referral network for complex pediatric craniofacial reconstructive surgery. Although pertinent parts of his medical record were scanned into our electronic medical record system, prior anesthetic records were not available. There was no mention of any prior anesthetic difficulties or adverse outcomes on chart review. On physical exam in the preoperative holding area, the patient was noted to be non-ambulatory, though he was able to crawl and scoot independently. He could stand with parental assistance. He was easily agitated, had limited speech and hypotonia. He had dysmorphic facial features including micrognathia. He drooled copiously and choked fre-

quently on his saliva between crying episodes. He demonstrated shallow breathing and had coarse breath sounds. His cardiac exam was normal. He had club feet and contracture of the wrists. With prior surgeries, the patient was managed with nontriggering anesthetic regimens due to the presumptive increased risk for malignant hyperthermia. His parents were unaware if there were any difficulties with airway management. They described previous difficult intravenous access. The family also provided a list of perioperative recommendations from the patient's neurologist and prior intensivist; they recommended a non-triggering anesthesia technique, delayed extubation, and post operative management in the intensive care unit. We did not succeed in contacting the patient's physicians to discuss their recommendations. The risks and benefits of various anesthetic techniques were discussed with the patient's parents. Despite the reassurance and explanation that there is no evidence to suggest an increase risk for malignant hyperthermia with succinylcholine and volatile agents in patients NM type NEB1, the parents requested that the anesthesia team adhere to their doctors' recommendations. They did agree however, to allow volatile anesthetic induction if nitrous oxide was inadequate for the placement of peripheral intravenous access. They indicated that in past surgeries, parental presence helped alleviate anxiety associated with induction. The parents declined any premedication for the child. After administering 70% nitrous oxide, intravenous access was tenuously established. We used propofol and fentanyl for induction, followed by direct laryngoscopy and intubation with a size 4.5 cuffed Oral Rae endotracheal tube. After the airway was secured, another intravenous catheter was placed. Rocuronium 0.6 mg/kg was administered intravenously per the surgeon's request for maximum facial muscle relaxation. Maintenance of anesthesia consisted of a total intravenous anesthetic with propofol and fentanyl infusions. Esophageal temperature monitoring occurred throughout the case and was kept warm with an underbody convection blanket.

The surgery was uneventful with approximately 100 ml of blood loss. At surgery completion, the train-of-four was 4/4 without fade. Reduced dosages of neostigmine and glycopyrrolate were administered at this time. With the child breathing spontaneously, maintaining adequate tidal volumes and respiratory rates, he was transported directly to the pediatric intensive care unit (PICU). Several hours later in the PICU, he was weaned from the ventilator and extubated successfully. His PICU stay was uneventful and he was discharged from the hospital at his baseline level of health on post-operative day three.

Discussion and conclusion

The dilemma in anesthetic management of patients with nemaline myopathy lies in the disease's heterogeneous phenotypes, the complexity of the patients, and a current lack of consensus on anesthetic management. The genetic basis of nemaline myopathy has been described. NM's heterogeneity is linked to nine distinct genes (Table 1).^{2,4,5} These genes encode for integral proteins in excitation-contraction coupling such as actin, tropomyosin and troponin. The majority (63%) of children with NM have sporadic mutations.⁶ Often multiple genes are involved in a single phenotype.⁷

The histologic characteristics of NM are thick sarcoplasmic inclusions in skeletal muscle fiber cells composed of disintegrated and disorganized z-disk proteins arranged in a rod-like fashion.^{8,9} Pathologic rod formation and irregular muscle cell contraction underlies the hypotonia that is characteristic of the disease. Clinically, NM manifests with a continuum of symptoms of ranging from mild findings to lethality.

The disease can be organized into six categories, though there is significant overlap.¹⁰ The severe congenital form of the disease is the most lethal, presenting with profound hypotonia and respiratory failure in the first year of life.¹¹ The Amish variant is found among the communities in western Pennsylvania, with similar though less critical symptoms compared to the severe congenital form, often leading to death by two years of

age.¹² Patients with the intermediate form of the disease may demonstrate independent respiratory function at birth, with deterioration overtime leading to wheelchair dependence and ventilator support by age eleven.

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) Intermediate congenital Childhood onset (AD)	2–3%
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.^{2,5}

In the typical congenital form, patients are asymptomatic until age one, followed by truncal weakness, feeding difficulties, and hypotonia. The childhood onset form manifests before 18 years of age, often presents with gait abnormalities, delayed motor milestones or poor exercise tolerance. Some also have proximal muscle weakness and facial diplegia. The adult onset forms are progressively less severe, presenting in the fourth to sixth decades of life, with mild facial and proximal muscle weakness. Anesthetic care of patients with NM can be fraught with challenges. Extremity contractures and atrophy may make peripheral intravenous access difficult. Facial dysmorphisms can lead to problems with mask ventilation and intubation.^{13, 14} Hypotonia, diaphragmatic abnormalities and scoliosis contribute to poor pulmonary reserve and may lead to rapid oxygen desaturation after induction. Preinduction preparations should be made to ensure availability of anesthesia staff support along with difficult airway resources. Patients with NM may have cardiomyopathy and dysrhythmias, necessitating careful cardiac evaluation and vigilant perioperative monitoring.^{10, 15, 16} Invasive interarterial monitoring may be considered depending on the surgery and the patient's underlying cardiac comorbidities. With musculoskeletal deformities, time must be dedicated for optimal positioning. Currently, there is currently no documented association between nemaline myopathy and malignant hyperthermia. Nevertheless, patients, their families, and even their physicians may raise MH as a concern. To date, succinylcholine and volatile anesthetics have been used successfully in NM children without hyperthermic sequelae.^{13, 17} In Japan, there was one case of severe congenital nemaline myopathy with novel ryanodine receptor mutations [(c.4718C>T (p.1573 Pro>Leu) in exon 33 and c.7585 G>A (p.2529 Asp>Asn) in exon 47)].⁴ These two mutations, however, were not among the 35 causative mutations known to be associated with MH as listed by the European Malignant Hyperthermia group. The study subjects had no documented family history of MH, and unfortunately, susceptibi-

lity testing for MH was not performed on the patient. Our current understanding suggests that the risks of patients with NM having MH under anesthesia is probably no different from that of the general population. In bed-bound patients, the standard concern of hyperkalemic crises with the use of succinylcholine should be considered, but this would be a separate issue unrelated to MH. Without clear recommendations or guidelines from an authoritative study, the unproven association between NM and MH persists, as in our patient's case. Though we had little concern for MH, the family's concern prompted us to choose a total intravenous technique without succinylcholine, opting to honor their request. With elective surgeries, it would be optimal for myopathy patients to have histologic and genetic testing prior to anesthesia. In the absence of a diagnosis with genetic sequencing and histology, it would be prudent to avoid potent inhalational anesthetics and succinylcholine because NM is clinically indistinguishable from CRM and CCD, two conditions that are known to be MH susceptible. CRM and NM share three pathologic genes including NEB on chromosome 2, TMP1 on chromosome 15 and RyR1 on chromosome 19.^{3, 4, 18-21} The novel Y4796C mutation that lies in the C-terminal channel-forming domain of the RyR1 protein of chromosome 19 has been shown to be MH susceptible in a patient with CRM.³

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