Anesth Pain Med. 2023 February; 13(1):e132088. https://doi.org/10.5812/aapm-132088.

Published online 2023 January 25. **Review Article**

A Review on the Anesthetic Management of Patients with Neuromuscular Diseases

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Received 2022 October 03; **Revised** 2022 December 06; **Accepted** 2022 December 08.

Abstract

Context: Neuromuscular diseases (NMDs) are regarded as a clinically and genetically heterogeneous group of diseases characterized by weakening muscle strength and dystrophic changes in the muscle. Due to the nature of these diseases, it can be challenging for anesthesiologists to provide appropriate pain medications, symptom management, and other necessary techniques that are implemented to anesthetize the patient properly.
Evidence Acquisition: This study was based on the available literature and the authors' experience. The current study aimed to review the available anesthesia for patients suffering from NMDs. The search process resulted in the detection of relevant articles using valid keywords on electronic databases, including Embase, PubMed, Scopus, Web of Science, and Cochrane Library. Subsequently, 19 articles published between 2009 to 2022 were identified as eligible for this review.
Results: When anesthetizing a patient with NMD, special attention should be paid to preoperative evaluation, medical-history taking, risk of difficult intubation or cardiac incidents, respiratory insufficiency, and frequent pulmonary infections. It is also necessary to keep in mind that these patients are at risk of prolonged paralysis, hyperkalemia, rigidity, malignant hyperthermia, cardiac arrest, rhabdomyolysis, or even death.
Conclusions: Problems of anesthesia in patients with NMDs arise from the nature of the condition itself and the interaction of anesthetics and muscle relaxants with anticholinesterase drugs used in therapy. Each patient's individual risk should be assessed before anesthesia. Therefore, it is important (and even necessary before major surgery) to perform a thorough preoperative examination to not only determine perioperative risk but also to ensure optimal perioperative follow-up.

Keywords: Humans, Anesthesia, Neuromuscular Diseases, Anesthetics, Muscles

1. Context

Neuromuscular diseases (NMDs) are considered a broad term that encompasses a range of conditions that impair muscle function, directly or indirectly subject to being pathologies of the peripheral nervous system or neuromuscular connections. The respiratory muscle weakness in NMDs leads to respiratory failure and subsequent death. The weakness of respiratory muscles initially causes hypoventilation during sleep, leading to daytime respiratory failure. Weakening of the bulbar muscles results in difficulty with speech and swallowing, often complicated by recurrent regurgitation. Diagnostically, it is important to determine whether the underlying disease is reversible (e.g., Guillain-Barré syndrome (GBS)), stable or slowly progressive (e.g., post-polio syndrome or myotonic dystrophy (DM)), or rapidly progressive.

The NMDs occur in both children and adults. Typical symptoms include muscle weakness, reduced ranges of motion in joints, spinal deformities, and respiratory disorders. Patients might report difficulties occurring during daily activities, such as walking, climbing stairs, getting up from a chair, getting up from the floor, and lifting upper extremities. Motor activities might be accompanied by fatigue. In some diseases, with a more severe course, it is difficult to change positions in bed, lift the head when lying down, sit up from a lying position, and move the limbs.

The NMDs are rare, indicating that many specialists in the healthcare system do not have enough knowledge about them in practice. Patients with NMDs need special attention before, during, and after anesthesia. Due to the nature of these diseases, it can be challenging for anesthe-

siologists to provide good and appropriate pain medications, symptom management, and other necessary techniques that are implemented to anesthetize the patient properly.

The NMDs are a group of heterogeneous diseases whose common and major characteristic is a decrease in muscle strength (1). They can be divided into three categories, namely prejunctional disorders, junctional disorders, and postjunctional disorders. Prejunctional disorders include motor neuron diseases (e.g., amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA)), peripheral neuropathies (e.g., GBS, chronic inflammatory demyelinating polyneuropathy (CIDP), and inflammatory processes), and hereditary neuropathies (e.g., Charcot-Marie-Tooth (CMT) disease and Friedreich's ataxia (FA)). Junctional disorders consist of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS). At last, postjunctional disorders are characterized by muscular dystrophies (MDs) (i.e., Duchenne MD, Becker MD, and Emery-Dreifuss MD) and congenital myopathies (i.e., central core disease (CCD) and multicore disease). This classification is widely used in the literature because, in each category, the diseases show similar pathologic processes. Therefore, this can be helpful in understanding the mechanism and managing anesthesia pertaining to a certain category of NMDs (2). There is also another classification of NMDs that was created by the Muscular Dystrophy Association in July 2018 (Table 1) (3).

2. Evidence Acquisition

This study was based on the available literature and the authors' experience. The current study aimed to review the available anesthesia for patients suffering from NMDs. The search process resulted in the detection of relevant articles using valid keywords on electronic databases, including Embase, PubMed, Scopus, Web of Science, and Cochrane Library. Subsequently, 19 articles published from 2009 to 2022 were identified as eligible for this review. During the preliminaries, MeSH words were used. The search terms "neuromuscular diseases" and "anesthesia" or "anesthesiology" were also used. Initially, a list of titles and abstracts of all the articles on the searched databases was provided by two researchers and reviewed separately to detect and select relevant titles. Subsequently, the related articles were independently included in the research process. Special attention was also paid to the clinical approach of the topic; accordingly, this article will be helpful not only for anesthesiologists but also for doctors from a variety of specialties. However, it is unfortunately impossible to find any article that describes such a variety of disease groups in much detail in one place. Therefore, although the topic is not new, the present holistic approach and the inclusion of useful tables in the article make it a helpful resource for many doctors. This study pays considerable attention to the latest publications and the fundamentals of anesthesiology.

3. Results

3.1. Clinical Manifestations of Neuromuscular Diseases

There are several categories of NMDs. The categories given focus mainly in this article are MDs, myotonic syndromes, congenital myopathies, and mitochondrial myopathies. The MDs are inherited conditions that cause muscle weakness, leading to a level of instability worsening with time. Some MDs include Duchenne MD, Becker MD, Emery-Dreifuss MD, and Limb-girdle MD. Duchenne MD and Becker MD are, for the most part, similar to each other as they are both characterized by a high risk of rhabdomyolysis, cardiomyopathy, respiratory weakness, recurrent pneumonia, exercise intolerance, and muscle weakness. However, only Duchenne MD manifests with additional spinal deformities. Emery-Dreifuss MD also presents with a risk of rhabdomyolysis, cardiomyopathy, muscle weakness, and spinal deformities; however, other symptoms could include arrhythmias and the risk of sudden cardiac death. Another manifestation that has not been mentioned when it comes to MDs occurs in Limb-girdle MD. Including the risk of rhabdomyolysis, cardiomyopathy, arrhythmias, and muscle weakness, it also presents with dysarthria (Table 2).

The second group of NMDs discussed is myotonic syndromes. They are rare genetic conditions characterized by myotonia or the inability to relax voluntary muscles after effort. One example from this category, which is described in this article, is myotonia congenita which presents with an occasional risk of rhabdomyolysis and myotonia/spasms (Table 3).

The CCD, multi/minicore disease, and King-Denborough syndrome (KDS) all fall into the next discussed category, which is congenital myopathies. Congenital myopathies are usually present at birth; however, their onset might also appear during infancy or even early childhood. In all three of the aforementioned congenital myopathies, some manifestations include malignant hyperthermia (MH) susceptibility, risk of rhabdomyolysis, muscle weakness, and spinal deformities. Both central core and multi/minicore diseases occasionally present with difficulty swallowing, although only the latter commonly presents with additional ophthalmoplegia. The KDS, in addition to all the aforementioned symptoms, manifests with ptosis, which makes it easier to differentiate it from the other two diseases (Table 4).

Table 1. Classes of Neuromuscular Diseases

Class	Diseases
Muscular dystrophies	Becker MD; Congenital MDs; Duchenne MD; Emery-Dreifuss MD; Facioscapulohumeral MD; Limb-girdle MD; Myotonic dystrophy; Oculopharyngeal MD
Motor neuron diseases	Amyotrophic lateral sclerosis; Spinal-bulbar muscular atrophy; Spinal muscular atrophy
Ion channel diseases	Andersen-Tawil syndrome; Hyperkalemic periodic paralysis; Paramyotonia congenita; Myotonia congenita; Potassium-aggravated myotonia
Myopathies	Congenital myopathies; Distal myopathies; Endocrine myopathies; Metabolic myopathies; Inflammatory myopathies; Myofibrillar myopathies; Scapuloperoneal myopathy
Mitochondrial diseases	Friedreich's ataxia; Mitochondrial myopathies
Neuromuscular junction diseases	Myasthenia gravis; Lambert-Eaton myasthenic syndrome; Congenital myasthenic syndromes
Peripheral nerve diseases	Charcot-Marie-Tooth disease; Giant axonal neuropathy

Abbreviation: MD, muscular dystrophy

Table 2. Clinical Manifestations in Muscular Dystrophies [a]

Myopathy	Duchenne MD	Becker MD	Emery-Dreifuss MD	Limb-girdle MD
Risks				
MH susceptibility	-	-	-	-
Risk of rhabdomyolysis	++	++	+	+
Cardiac				
Cardiomyopathy	++	+	++	+
Arrhythmias	-	-	++	+
Sudden cardiac death	-	-	+	-
Lungs				
Respiratory weakness	++	++	-	-
Recurrent pneumonia	++	++	-	-
Neurology				
Ataxia	-	-	-	-
Dysarthria	-	-	-	++
Ocular				
Ophthalmoplegia	-	-	-	-
Ptosis	-	-	-	-
Other				
Difficulty swallowing	-	-	-	-
Musculoskeletal				
Exercise intolerance	++	++	-	-
Muscle weakness	++	++	++	++
Myotonia/spasm	-	-	-	-
Spinal deformities	++	-	+	-

Abbreviations: MH, malignant hyperthermia; MD, muscular dystrophy
[a] ++ Common; +- occasional; – not reported

Table 3. Clinical Manifestations in Myotonic Syndromes [a]

Myopathy	Myotonia Congenita
Risks	
MH susceptibility	-
Risk of rhabdomyolysis	+
Cardiac	
Cardiomyopathy	-
Arrhythmias	-
Sudden cardiac death	-
Lungs	
Respiratory weakness	-
Recurrent pneumonia	-
Neurology	
Ataxia	-
Dysarthria	-
Ocular	
Ophthalmoplegia	-
Ptosis	-
Other	
Difficulty swallowing	-
Musculoskeletal	
Exercise intolerance	-
Muscle weakness	-
Myotonia/spasm	++
Spinal deformities	-

Abbreviation: MH, malignant hyperthermia
[a] ++ Common; +- occasional; - not reported

The last group of NMDs discussed in this article are called mitochondrial myopathies, which are a group of genetic diseases manifesting an impaired oxidative metabolism. The present article pays attention to a few of them, namely Kearns-Sayre syndrome (KSS), Leber's disease, maternally-inherited Leigh disease (MILS), mitochondrial DNA depletion syndrome (MDS), mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), and mitochondrial neurogastrointestinal encephalopathy (MNGIE), their various manifestations, and, most importantly, risks for developing various symptoms. For example, the risk of cardiac manifestations is most prominently observed in KSS; however, it can also manifest in other diseases in the form of cardiomyopathies, such as MELAS and MNGIE, and as arrhythmias in Leber's disease and MELAS. Lung manifestations are only prominently noted in MILS in the form of respiratory weakness. Neurological manifestations are predominant in KSS and MILS, manifesting as ataxia. Neuropathy can be observed mainly in MNGIE.

There are also other neurological manifestations present, such as epilepsy, which can be observed in MDS and MELAS, and dysarthria in MDS. There can also be ocular complications, such as ophthalmoplegia, mainly noticed in KSS, MILS, and to a lower degree in MNGIE. Ptosis is also prominent in KSS and MNGIE. The risk of rhabdomyolysis is similar in all the stated diseases. Musculoskeletal manifestations can present as exercise intolerance in MELAS and muscle weakness mainly in MDS and MNGIE and, to a lesser extent, in all the other mentioned diseases. Other complications can involve difficulty swallowing, which is present in MILS, MDS, and MNGIE. Kidney impairment can manifest in KSS and MILS, and liver impairment is present in MDS and MNGIE (Table 5).

3.2. Preoperative Evaluation

Preoperative evaluation continues to play an imperative role in significantly reducing the risks of anesthesia in surgery. A comprehensive preoperative evaluation consists of effective history-taking, paying attention to outpatient medications, and evaluations in cardiology, pulmonology, and neurology (4). It should also include the assessment of the neurological disease and associated issues of the disease (5). The diagnosis of the disease is critical, as various locations (i.e., prejunctional, junctional, and postjunctional) of the disease can have varying effects and alter therapy (2). The evaluation can then further be expanded to include a laboratory workup (including creatinine kinase, arterial blood gasses, basic metabolic panel, and myoglobin), pulmonary function tests or chest X-ray, and electrocardiography (4). Particular NMDs can also predispose individuals to a condition known as MH, which requires special attention as it causes a hypermetabolic state after exposure to succinylcholine and inhaled anesthetics. Therefore, it is imperative to have an early evaluation, suspicion, and diagnosis of this complication, in addition to an early administration of dantrolene, to drastically decrease the mortality from MH (5).

3.2.1. Medical History

Medical history characterizing patient knowledge of exact diagnosis, any underlying diseases, and disease duration is an integral part of establishing the course of further actions, such as choosing the right anesthetic procedure and imperative monitoring techniques (2). It is important to pay attention to the duration and severity of the disease and any general physical restrictions the patient might possess (1). Other information which needs to be also obtained concerns neurological status (i.e., cranial nerve involvement) and involvement of other organs

Table 4. Clinical Manifestations in Congenital Myopathies [a]

Myopathy	Central Core Disease	Multi/Minicore Disease	King-Denborough Syndrome
Risks			
MH susceptibility	++	+	++
Risk of rhabdomyolysis	++	++	++
Cardiac			
Cardiomyopathy	-	-	-
Arrhythmias	-	-	-
Sudden cardiac death	-	-	-
Lungs			
Respiratory weakness	-	++	-
Recurrent pneumonia	-	-	-
Neurology			
Ataxia	-	-	-
Dysarthria	-	-	-
Ocular			
Ophthalmoplegia	-	++	-
Ptosis	-	-	++
Other			
Difficulty swallowing	+	+	-
Musculoskeletal			
Exercise intolerance	-	-	-
Muscle weakness	+	+	++
Myotonia/spasm	-	-	-
Spinal deformities	++	++	++

Abbreviation: MH, malignant hyperthermia
[a] ++ Common; +- occasional; - not reported

(e.g., the heart and lungs) (2). For example, Duchenne MD and Becker MD are both X-linked recessive diseases and are usually identified promptly during childhood, usually with comorbidities relating to proximal muscle weakness. However, in these diseases, there is also hindered respiration due to inspiratory and expiratory muscle weakness and chest wall contractures (5). Therefore, it is imperative to inquire about systemic involvement and symptoms, such as dyspnea, tachypnea at rest, or orthopnea (1). Cranial nerve involvement or bulbar symptoms can be found mainly in pre-junctional diseases. This can manifest as muffled speech and dysphagia and predominantly affects individuals with SMA, GBS, and ALS (2).

Concurrent data about recurrent infections, particularly pneumonia or persistent swallowing, can be apprehensive for the involvement of throat muscles or cranial nerves and can be an increased risk of aspiration (1). This is also typical in patients with the previously mentioned disorders (i.e., SMA, ALS, and GBS) and those with advanced-stage myopathies (i.e., MD and Duchenne MD) (2). Such information and data collection about signs and symptoms, especially concerning current respiratory infections, will decide the elective nature of operations and, therefore, must be performed before each surgery (1). Some neurodegenerative diseases might be associated with the onset of dysphagia and dysmotility, which in turn results in a full stomach even if patients have not consumed any meals in the recommended time before surgery. Therefore, some studies indicate that it might be helpful to perform a gastric ultrasound to assess the volume of gastric content to choose the best method of anesthesia (6).

3.2.2. Blood Test Results

As stated earlier, a thorough preoperative evaluation should be carried out with the workup, including various aspects of laboratory tests (4). However, except in a

Table 5. Clinical Manifestations in Mitochondrial Myopathies [a]

Myopathy	Kearns-Sayre Syndrome	Leber's Disease	Maternally-inherited Leigh Disease	Mitochondrial DNA Depletion Syndrome	Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes	Mitochondrial Neurogastrointestinal Encephalopathy
Risks						
Risk of rhabdomyolysis	+	+	+	+	+	+
Cardiac						
Cardiomyopathy	++	-	-	-	+	+
Arrhythmias	++	+	-	-	+	-
Lungs						
Respiratory weakness	-	-	+	-	-	-
Neurology						
Epilepsy	-	-	-	+	+	-
Ataxia	++	-	++	-	-	-
Dysarthria	-	-	-	+	-	-
Neuropathy	-	-	-	-	-	++
Ocular						
Ophthalmoplegia	++	-	++	-	-	+
Ptosis	++	-	-	-	-	++
Other						
Difficulty swallowing	-	-	++	++	-	++
Kidney/liver impairment	K	-	K	L	-	L
Musculoskeletal						
Exercise intolerance	-	-	-	-	++	-
Muscle weakness	+	+	+	++	+	++

Abbreviations: K, kidney; L, liver
[a] ++ Common; +- occasional; - not reported

few cases for patients with NMDs, no additional or specific laboratory values are necessary. The evaluation of creatinine kinase and myoglobin does not contribute to indicating the severity of the disease, although they are typical biomarkers used to show pathological processes in muscles (2). It is observed that in patients with Duchenne MD, creatinine kinase is only marginally elevated, especially if the disease is advanced. This is because a sizable amount of the muscle has already undergone a transformation into fibrotic tissue (2, 4). Nevertheless, it is a possible indication for preoperative evaluation to check the levels of myoglobin and creatinine kinase. This is performed to possibly establish a base value of these biomarkers to allow the assessment of the kinetics of any perioperative rhabdomyolysis (1). In individuals suffering from junctional disorders, such as MG, LEMS, and MD, the evaluation of serum electrolyte levels, such as calcium, magnesium, potassium, and phosphate, is recommended (2). It is also required to keep in mind the difficulties in temperature control and blood glucose regulation due to reduced muscle mass (7, 8).

3.2.3. Cardiac Risk

The heart consists mainly of muscle tissue and its innervating nervous tissue. Neuropathies can damage the cardiac conduction system, and myopathies can weaken and injure the heart's musculature (1). If there is any defect in one or both tissues, this might lead to serious complications during or after surgery (2). Therefore, special attention to cardiac risks must be given to all patients

who present with NMDs. It has been found that patients with Duchenne MD, Emery-Dreifuss MD, Limb-girdle MD, and DM almost always present with cardiac manifestations as the disease progresses. Patients with FA (i.e., a hereditary neuropathy) and Becker MD often show cardiac myopathies. In FA and MD, disorders in the conducting system of the heart have been observed. It is common for such patients to suffer from conduction blocks, ventricular tachycardia, extrasystoles, and changes in the ST segment. In order to examine the patient before surgery and identify possible cardiac risks, it is recommended to carry out echocardiography and 24-hour echocardiography. It is usually not possible to conduct a physical stress test in patients with NMDs because these patients will not be able to perform such tests due to their disabilities (2).

3.2.4. Pulmonary Risk

The first thing that needs to be evaluated to identify possible pulmonary risks in NMDs during anesthesia is the airways. The risk of difficult intubation might be increased due to possible changes in the thorax, mandible, and cervical spine, as such changes can occur due to the course of the disease. These changes include a decrease in mobility and musculoskeletal malfunction or malposition. Factors that can increase the risk of restrictive lung disease and, consequently, cor pulmonale are muscle weakness (central or obstructive) apnoea, swallowing impairment, spinal deformities, and facial dysmorphism (9). Computed tomography of the chest can identify scoliosis and other changes (e.g., thymoma in myasthenia) that can lead to a modification of the shape of the trachea. Other changes (e.g., macroglossia in Duchenne MD) should be evaluated by an ear, nose, and throat specialist. If there is an increased risk of a difficult airway, healthcare professionals should proceed based on official guidelines to manage such circumstances (1).

Additional factors that show an elevated pulmonary risk are a higher risk of respiratory insufficiency and frequent pulmonary infections, for the diagnosis of which it is necessary to undergo a physical examination, pulse oximetry, blood gas analysis, lung function testing, and an X-ray of the chest. However, the results of these diagnostic tests depend on the disease and the type of planned surgery (2). It is required to be aware that the prediction of any pulmonary risk, which is based on a chest X-ray, cannot be taken for a hundred percent. Additionally, other diagnostic tests need to be evaluated, although previously taken images should still be checked for any visible signs of tracheal deviation or recurrent aspirations (1).

Recurrent aspirations are common in NMDs, such as ALS, SMA, GBS, and CMT disease; the reason for aspiration in the aforementioned diseases is mainly malfunctioning of cranial nerves, and the reason for aspiration in Duchenne MD and DM would be a decrease in strength of throat muscles. Such patients with the above-mentioned diseases also have a higher risk of aspiration in the perioperative setting due to previously mentioned reasons (2). It is important to also note that patients might have certain anatomical issues, such as macroglossia or progeny, or even deficient control of his/her own tongue and its movements and swallowing. This, in turn, can cause difficulties in intubation or ventilation at the time of general anesthesia and can lead to acute respiratory failure caused by the obstruction of the tongue or inhalation during procedural sedation (10).

3.3. Intraoperative Management

When discussing intraoperative management, it is required to consider various aspects, including the type of anesthetic procedure, later choice of medication used during the procedure, additional monitoring, and concomitant factors, such as heat management. As will be described further on, volatile anesthetics are safe in patients with prejunctional disorders and can even be beneficial in junctional disorders. However, they are contraindicated in postjunctional disorders. Opposite to that statement stands muscle relaxants, as they can act differently in these groups of diseases. On the other hand, opiates are harmless for patients with any NMDs (2).

3.3.1. Anesthetics

When it is assumed to have an NMD, it is heavily suggested to use trigger-free anesthesia. The main risk in patients with this kind of condition is developing MH or rhabdomyolysis. However, the only absolute contraindication for the administration of volatile anesthetics is postjunctional disorders. Patients who are at the highest risk of rhabdomyolysis after using volatile agents are those with myopathies. The mechanism behind it is not entirely understood yet; however, it is suspected that volatile anesthetics interact with disturbed muscle cell membranes.

In a patient who suffers from DM (i.e., one of the MDs), it is required to be aware that the complications that can arise perioperatively are not proportional to the severity of the disease. This means that even in mild cases, severe complications might arise. Aa s result, it is always essential to consider if the surgery is necessary at all and, if yes, whether regional anesthesia can be used instead of general anesthesia. To be able to apply safe anesthesia and avoid complications, such as aspirations of stomach contents, cardiac arrhythmias that can lead to death, or medication-induced respiratory depression in patients who suffer from DM, it is essential to be aware that certain

medications or circumstances can activate muscle contraction with abnormal, prolonged relaxation. Such triggers can be hypothermia, certain medications, mechanical or electrical stimuli, potassium, and shivering. Myotonic dystrophy patients are exquisitely sensitive to the respiratory depressant effects of anesthetic medications. Therefore, it is important to be prepared with appropriate treatment and management options, such as mechanical ventilators. In DM patients, rapid sequence induction with cricoid pressure is recommended. All patients with DM should be evaluated thoroughly prior to surgery. It is recommended that all DM patients undergo 12-lead echocardiography, thorax radiography, and baseline echocardiography to avoid severe complications that can lead to death (11).

The risk of developing MH after volatile anesthesia is only connected to CCD and KDS. Other myopathies show no risk, and it has not been proven to date. Prejunctional and junctional disorders are not associated with damage in the muscle itself; therefore, volatile agents can be used in patients with these conditions. There are multiple cases of using both propofol and volatile anesthesia in patients with ALS, SMA, CMT disease, GBS, and MG with no further problems. It is important to consider their muscle-relaxing properties in the cases of MG and LEMS, as using muscle relaxants additionally is then not necessary (2).

When it comes to nitrous oxide, it is associated with good analgesic potency. Laughing gas can be used in various scenarios as an addition to balanced anesthesia and as total intravenous anesthesia (TIVA). The major advantage that nitrous oxide has over other volatile agents, such as sevoflurane, desflurane, isoflurane, and enflurane, is that it does not trigger MH or rhabdomyolysis. Special care should be provided for patients who previously suffered from cardiac damage. In those cases, the negative inotropic effect of laughing gas can cause further deterioration in cardiac function. This effect is the main reason nitrous oxide should not be the first line for anesthesia, especially when it comes to patients with myopathies. The administration of nitrous oxide to patients with neuropathies also has to be considered, as the possibility of worsening the condition is not entirely absent, from a pathophysiological perspective at least. However, the issue has not been thoroughly researched yet.

In the case of using laughing gas in patients with CMT and its connection to aggravating neurological symptoms, there are still speculations about whether it does or does not exist (2). For anesthesia induction, etomidate, thiopental, and propofol have all been used safely. However, using agents with a short beta half-life seems logical to minimize the possibility of prolonged postoperative mechanical ventilation. Safe and effective anesthesia using propofol and remifentanil for TIVA has been described in the medical literature. Neostigmine should not be used in MD patients because it might trigger myotonia, and opioids should only be used with extreme caution due to their respiratory depressant effects.

Another important issue to note is using etomidate in the induction of general anesthesia. It is an intravenous, short-acting, nonbarbiturate hypnotic agent and is preferred for induction as it only causes a minimal amount of blood pressure drop, which ultimately makes it viable for various procedures in anesthesia. However, it might have a disinhibitory effect on the specific regions of the nervous system that are responsible for the extrapyramidal motor activity and, therefore, might cause a significant incidence of myoclonus during incidence (12). This is an undesirable side effect, occurring in about 50 - 80% of cases. However, the mechanism of this reaction is unclear. Nevertheless, a variety of drugs, such as rocuronium, benzodiazepines, and opiates, can be used before the induction of this general anesthesia as it helps prevent myoclonus (13). Recent studies indicate that remimazolam might be a useful drug in the future due to its circulatory stability and the possession of an antagonist (14, 15).

3.3.2. Muscle Relaxants and Reversals

The general rule in anesthesia for patients with NMDs is to use drugs from this group only if necessary. Using muscle relaxants in patients with muscle disease might lead to experiencing severe complications, such as prolonged paralysis, hyperkalemia, rigidity, MH, cardiac arrest, rhabdomyolysis, or even death. For this reason, in such cases, caution should be exercised because the administration of depolarizing muscle relaxants (e.g., succinylcholine) can result in the release of large amounts of potassium ions from muscle cells into the bloodstream, causing a brief muscle contraction before relaxation. This sudden increase in blood potassium concentration can cause life-threatening cardiac arrhythmias. Succinylcholine should be avoided in all patients with NMDs. Non-depolarizing muscle relaxants (e.g., vecuronium, atracurium, cisatracurium, or mivacurium) do not cause muscle contractions, and their administration does not entail this risk. However, the affected muscles become more sensitive to non-depolarizing muscle relaxants; therefore, drug doses should be carefully selected.

Previous studies have shown that it is possible to use succinylcholine in MG, as those with this disease are in some way resistant to the drug. It was also found that mivacurium and atracurium are the best muscle relaxants for such patients. Nevertheless, their duration of action will also be prolonged. This is why it is necessary to give in the reduced doses (10 - 20% of recommended dose) and

to closely monitor the degree of neuromuscular block. It should also be noted that train of four (i.e., a test used to detect the level of neuromuscular blockade by the stimulation of peripheral nerves followed by provoked muscle contractions) measurements in patients with MG might be unreliable; neuromuscular conduction disturbances might be selective in nature (i.e., differing greatly in individual muscles).

As for the reversal of skeletal muscle relaxation, the response to classical agents is highly unpredictable and, in extreme cases, can lead to a cholinergic breakthrough. Therefore, the agent of choice for the reversal of neuromuscular blockade induced by steroidal skeletal muscle relaxants (e.g., rocuronium and vecuronium) is sugammadex, whose action is not impaired by acetylcholinesterase inhibitor (16). Some anesthesiologists intubate patients with NMDs without muscle relaxation; nevertheless, it results in difficult intubation and is a risk factor for laryngeal morbidity.

3.3.3. Regional Anesthesia

Procedures conducted under regional anesthesia are usually considered a good alternative to procedures with general anesthesia. Patients who suffer from junctional and postjunctional disorders have no contraindications to having procedures performed under both central and peripheral regional anesthesia. This lack of risk is because these conditions are not associated with nerve involvement. However, prejunctional disorders are associated with neuronal function disruption; therefore, regional anesthesia is not recommended in these cases. In 1937, Critchley raised concerns about performing regional anesthesia in a publication. He observed the deterioration of neurological symptoms in patients with GBS and multiple sclerosis (MS) when conducting the procedure. The proposed cause of GBS is inflammation by autoantibodies with the consecutive destruction of the myelin layer of the nerves, which makes GBS a peculiar case of inflammatory disease. Regional anesthesia should similarly be discussed in cases of MS as a demyelinating disease.

Epidural anesthesia and peripheral blocks do not cause complications for patients with neurological symptoms; however, spinal anesthesia should be avoided in these cases. There are a couple of publications on prejunctional diseases (i.e., motor neurons and neuropathies) that prove no connection between successful central and peripheral regional anesthesia and worsening neurological symptoms. The disorders reviewed in those reports are CMT, ALS, SMA, Duchenne MD, Limb-girdle MD, MD, and CCD. Patients with neuropathies are impervious to the nerve stimulator. In various studies, it has been discussed that some CMT patients with probable well-advanced neuropathy are prone to the stimulation of the sciatic nerve, albeit only with very high currents. After the procedure, the advanced neuropathy works in these patients' favor as the dosages of painkillers can be decreased. The MD can be characterized by muscle spasms caused by cold mechanical irritation or stress. Their mechanism can be described as the disruption of ion channels' function directly on the muscle membrane; therefore, they could not be prevented by regional anesthetics. In the future, intravenous regional relief might be provided for those patients (2).

3.3.4. Choice of Anesthetic Technique

Table 6 shows the choice of the anesthetic technique, depending on the kind of NMD. Patients with MH myopathy (i.e., MH connected with myopathy) can receive regional anesthetics and TIVA but no volatile anesthetics. Patients with non-MH myopathy can receive all three kinds of anesthetics, and patients with mitochondrial myopathy can receive regional anesthetics and volatile anesthetics; however, TIVA should be avoided. Instead, ketamine can be used as an alternative.

Table 6. Choice of Anesthetics in Neuromuscular Diseases

Kind of Neuromuscular Disease	Regional Anesthetics	Total Intravenous Anesthetics	Volatile Anesthetics
MH myopathy [a]	+	+	-
Non-MH myopathy	+	+	+
Mitochondrial myopathy	+	- (Ketamine can be used as an alternative.)	+

Abbreviation: MH, malignant hyperthermia
[a] Malignant hyperthermia connected with myopathy

3.4. Postoperative Monitoring

Postoperative monitoring includes ensuring access to an intensive care unit (ICU) with the possibility to ventilate the patient and 24-hour monitoring. Outpatient anesthesiology is only recommended in special cases (17). Data for postoperative monitoring in patients with NMDs did not exist. Therefore, there are no general recommendations on how to handle such cases. As a result, decisions on how to handle such patients should be based on the pathophysiology of the disease, its severity, the surroundings with the required equipment, and the experiences of healthcare professionals.

Particular attention should be given to the involvement of cranial nerves and a decrease in cardiopulmonary functioning (2). In patients with NMDs, a decrease in cardiopulmonary functioning is usually observed. Therefore,

a reduction in postoperative stress to decrease oxygen consumption can be beneficial. In order to achieve a decrease in postoperative stress, it can be crucial to avoid MH; this is a congenital condition in which the patient is prone to release too much calcium out of the mitochondria after contact with anesthetic gasses which leads to the activation of muscle metabolism, increased oxygen consumption, acidosis, rhabdomyolysis, hyperkalemia, death (17), and shivering. Shivering is known to be a cause of myotonic reactions in MD patients. Adequate pain management to reduce postoperative stress is as important as controlling normothermia. For each patient, there should be individual pain management, with broad medication therapy and all kinds of regional anesthesia. However, it is important to keep in mind that different NMDs can have different effects on pain medication. For example, acetaminophen, which is used in muscle dystrophies, is known for a higher risk of toxicity (2).

3.4.1. Outpatient Procedures

Outpatient procedures are not followed based on a diagnosis of NMDs. One of the most important factors to be considered is the involvement of cranial nerves in the disorder. Patients who suffer from peripheral neuropathies are generally less affected. In patients with cranial nerve involvement, there is an increased risk of aspiration; therefore, those individuals require additional inpatient monitoring. To summarize, patients with muscular disorders, motor neuron disorders, and junctional disorders always depend upon inpatient monitoring which adds to the conclusion of not performing outpatient surgery (2).

3.4.2. Intensive Care Unit

It is hard to determine if postoperative monitoring needs to be carried out in an ICU. Patients who suffer from MG can be easily managed in a regular unit postoperatively, depending on the level of experience of their caregivers. Experience is of much importance in the matter of decision-making. Usually, when there is less experience, the chance of patient transfer to the ICU after the procedure becomes higher. When it comes to other NMDs, the stage of the disease needs to be determined before deciding upon a postoperative care method. For example, young patients with Duchenne MD do not require intensive medical monitoring as they are at the early stage of the disease. The symptoms include only slight peripheral muscle weakness, and they do not suffer from cardiopulmonary deficits. However, intensive medical monitoring should be introduced in adolescent patients with Duchenne MD as more symptoms appear due to the disease progression, such as respiratory limitations, dysphagia, cardiomyopathies, and prolonged neuromuscular blockade, after muscle relaxants administration. Intensive medical monitoring should also be induced in other diseases, such as MD or GBS. Patients with the former condition are susceptible to malignant cardiac arrhythmias and mitochondrial diseases, which can lead to severe lactic acidosis; however, those suffering from the latter are at greater risk of fulminant ascending paralysis. Therefore, the ICU should be in charge of monitoring these cases (2).

3.4.3. Postoperative Ventilation and Recovery Room

Ventilation can lead to a reduction in the strength of the respiratory muscles; therefore, it should be avoided, particularly in patients with NMDs, as the diaphragm can be affected by these diseases. Prophylactic postoperative ventilation is also not indicated, and the aim is for the earliest possible extubation, even if it is not particularly possible in specific cases due to the limitations of the respiratory system in patients suffering from NMDs (e.g., ALS, SMA, GBS, FA, Duchenne MD, and MD).

In terms of predictions for necessary postoperative ventilation, there is no definitive answer. However, in any case, the possibility of having postoperative ventilation must be presented to patients, particularly in cases of patients who are preoperatively impaired in terms of the respiratory system. The ultimate goal, as stated previously, is for the earliest possible extubation (2, 18). Regarding recovery room care, all patients are provided with proper monitoring, even those with only minor procedures performed. Proper care, monitoring, and experienced help are provided despite the severity of the disease or problem (1).

3.5. Special Features

3.5.1. Pregnancy

Choosing the proper anesthesia techniques in pregnant women who suffer from NMDs can be even more challenging than choosing proper anesthesia for patients with NMDs but without pregnancy. It is essential to include knowledge about the interactions of NMD with pregnancy and vice versa and which effects can be shown on the fetus. It is important to know that, especially in diseases from the neuropathy group (i.e., MS, CMT, and CIDP) and MG, worsening clinical symptoms can occur during pregnancy. In women who suffer from myopathies, especially MD and Limb-girdle MD, the patient can expect worsening muscle strength during pregnancy (2).

Furthermore, for NMDs that belong to the autoimmune category (e.g., myasthenia), it is especially known that pregnancy can worsen the course of the disease for the mother. It can also be nearly impossible for the mother to give birth in a natural way due to muscle weakness and

bleeding complications, especially in patients with CMT and MD (2). A cesarean section is almost always necessary. During cesarean section (or any other necessary surgeries), succinylcholine cannot be used under any circumstances. Magnesium should also be avoided due to the potential worsening of muscle weakness. Neuraxial blockade or other regional anesthesia techniques might be used. It is important to check whether the disease will have any hereditary components so that it might affect the newborn. With autoimmune diseases, it is essential to be aware that autoantibodies from the mother can reach the unborn child through fetal circulation, and such newborns might show symptoms after birth. Appropriate treatment is necessary until the autoantibodies from the mother are eliminated from the newborn's circulation (1). Additionally, neonates with NMDs require careful monitoring for complications in the post-partum period (19).

4. Limitations

This review has potential limitations. The most significant of these limitations is that this is not a systematic review. In addition, the number of NMDs is huge, and a large proportion of them is very rare; therefore, there is not enough information on them. As a result, further studies are required in this regard.

5. Conclusions

When a patient with MD undergoes general anesthesia, various serious problems can occur. Problems of anesthesia in patients with NMDs arise from the nature of the condition itself and the interaction of anesthetics and muscle relaxants with anticholinesterase drugs used in therapy. Each patient's individual risk should be assessed before anesthesia. Therefore, it is important (and even necessary before major surgery) to perform a thorough preoperative examination to not only determine perioperative risk but also to ensure optimal perioperative follow-up. Careful preoperative assessment and management of patients suffering from NMDs decrease postoperative complications. The choice of anesthetic technique should be based on a cautious assessment of the balance of benefits and risks. Moreover, the patient should be monitored especially closely during surgery. It is also necessary to be aware of the consequences of the actions and how to counteract them.

Footnotes

Authors' Contribution: Study concept and design: P. R. and L. S.; acquisition of the data: L. S., K. P., S. H., and N. J.; analysis and interpretation of the data: L. S., S. H., and N. J.; drafting of the manuscript: P. R., L. S., K. P., S. H., and N. J.; administrative, technical, and material support: P. R.; study supervision: P. R. and K. P.

Conflict of Interests: K. P. and P. R. are employed by Voivodal Specialist Hospital in Olsztyn.

Funding/Support: None of the authors received any funding or support related to this work.

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