Myopathies: Muscular Dystrophy

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Introduction

Myopathies are a heterogeneous group of diseases characterized by a primary structural or functional impairment of the skeletal muscle cell. They are unrelated to any disorder of innervation or neuromuscular junction. The most common symptom is muscle weakness with possible impact on respiratory, cardiovascular, and also other systemic manifestations. Among the inherited myopathies, distinction is made between muscular dystrophies, congenital myopathies, metabolic and mitochondrial myopathies, and channelopathies. Acquired myopathies can be subdivided into inflammatory, toxic, or myopathies associated with systemic diseases.

With an uncommon, but non-rare, disease, multidisciplinary care in early pregnancy is essential to ensure a good outcome to a woman with myopathy and her newborn.

This chapter does not have the ambition to address all the different types of myopathies, but only the most encountered in anesthetic consultation.

Muscular Dystrophies

Muscular dystrophies are a heterogeneous group of inherited diseases characterized by progressive and symmetrical skeletal muscular weakness.

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Myotonic Dystrophy or Steinert Disease

Definition

Steinert disease is the most frequent muscular dystrophy in adults, also known as myotonic dystrophy type 1 (MD 1). MD 1 affects distal skeletal muscles, whereas another form with similar symptoms, myotonic dystrophy type 2 (MD 2), is mainly proximal. Both forms are autosomal dominant diseases: trinucleotide repetition on chromosome 19 for MD 1 and tetranucleotide repetition on chromosome 3 in MD 2. The severity of the disease is directly correlated to the size of this unstable genetic repetition. The anticipation phenomenon in MD 1, i.e., increased clinical severity and earlier age of onset in the next generation, is caused by the expansion of the trinucleotide repeat.

Prevalence

MD 1 prevalence is estimated at 1 per 8000–10,000 people worldwide. Classically, the age of onset is 15–30 years of age (even older for MD 2), with slow progression; thus, multiple severity states can be seen during pregnancy [1].

Symptoms

Muscle weakness and myotonia (delay in muscle relaxation after cessation of voluntary contraction) are the principal features. Both MD affect the smooth muscles, heart (conduction disorders, arrhythmias), eyes (cataract), endocrine system (diabetes, hypogonadism, dysthyroidism, adrenal insufficiency), gastrointestinal system (dysphagia, hypokinesis, gallstones), and central nervous system (hypersomnia, hypoventilation, neurobehavioral abnormalities) [2, 3]. Known triggers of myotonia are hypothermia, shivering, succinylcholine, and unpredictable neostigmine [4–6]. To prevent myotonic crisis, these factors should be avoided and the patient kept warm by increasing the operating or delivery room temperature, cautious body temperature monitoring, and warming systems (forced-air blanket, warmed IV fluids), along with trying to reduce shivering as much as possible (Table 108.1). General anesthesia (GA) and non-depolarizing neuromuscular blockade are not ableto relieve the abnormal muscle contraction.

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Table 108.1 Triggers of myotonic crisis and its prevention

Triggers of myotonic crisis	Prevention
Hypothermia	Warm – Delivery room temperature – Forced-air blanket – Warmed IV fluids
Shivering	Warm the patient Anti-shivering medication
Succinylcholine	Contraindicated
Neostigmine	Contraindicated

Table 108.2 Obstetric risks associated with MD 1 compared to the general population

Complication	Frequency (%)
Preterm delivery[a]	19–31
Polyhydramnios[a]	17
Placenta previa	9–11
Hemorrhage	Frequency unknown
Instrumental delivery	15
Non-vertex presentation	35
Caesarean section	37

[a]With congenitally affected fetus

Interaction with Pregnancy

Effect of Pregnancy on Myotonia

1. Since there is no prospective data, it is hard to confirm the influence of pregnancy on the course of the disease. Nevertheless, symptoms seem to remain stable in parturients with MD 1; at least there are no temporary or lasting changes reported. In contrast, a retrospective study suggests pregnancy might hasten the onset of MD 2 [7].
2. In the presence of muscle weakness, an undiagnosed muscular dystrophy should be kept in mind as a differential diagnosis. Depending on the age of onset or the progression course of the myopathy, except for limb-girdle muscular dystrophy (LGMD) (see section "Limb-Girdle Muscular Dystrophy (LGMD)"), parturients can be asymptomatic, and the disease can be revealed by pregnancy or during delivery.

Effect of Myotonia on Pregnancy

1. Pregnant women with MD 1 are at higher risk for obstetric complications [1, 2, 8]. Please see Table 108.2.
2. The risk of postpartum hemorrhage is increased due to the potentially prolonged labor and uterine atony [2, 4, 9].
3. Preeclampsia could be slightly increased, although it has not been further studied [8, 9].

Diagnosis and Testing

1. Congenital myotonic dystrophy (CMD) is the most severe form of myotonic dystrophy and is almost always passed to the child by an affected mother, who can be undiagnosed or nearly asymptomatic. Due to the anticipation phenomenon, it is not unusual to diagnose a mild MD 1 in a mother following the birth of her newborn with CMD. No congenital form of MD 2 is known.
2. CMD should be suspected if polyhydramnios and reduced fetal movement are observed during pregnancy. At birth, the affected newborns are usually severely hypotonic with facial muscle weakness and swallowing difficulties. The latter can lead to aspiration, and, with the association of respiratory muscle weakness and failure of central respiratory drive, CMD newborns are at high risk of respiratory insufficiency with a high mortality rate. When they survive, speech and motor developments are delayed, and clinical features of MD 1 appear earlier than in the adult form. Their life expectancy is around 30 years, mainly shortened by cardiac causes [2, 5, 9].
3. Prenatal testing is possible when the diagnosis of MD 1 has been confirmed by molecular genetic testing in the parents.
4. A multidisciplinary evaluation is required, including a specific anesthetic consultation early enough before the due date or even in preparation for pregnancy in some cases, so that additional tests can be ordered according to the anamnesis and the clinical characteristics of the thorough physical exam. A multidisciplinary team, including obstetricians, anesthesiologists, neonatologists, physiotherapists, cardiologists, and lung specialists, should closely follow up these patients over the pregnancy.
5. There may be cardiac and pulmonary involvements, scoliosis, and respiratory compromise.
6. An electrocardiogram (ECG) is essential to assess cardiac conduction abnormalities. Further evaluations, such as Holter ECG and echocardiogram, may be warranted to assess the increased cardiac involvement in this population [10].
7. Likewise, pulmonary function tests, at best during pre-pregnancy counselling, may reveal underlying ventilatory muscle pathology, at which point arterial blood gases may be useful.

Anesthetic Management: General Principles for All Myotonias

1. During labor and delivery, close cardiac monitoring to rapidly detect any cardiac incident is more than recommended, with at least a 5-lead ECG.
2. Regarding the higher percentage of postpartum hemorrhage, an updated blood crossmatch should be performed, and a second peripheral IV access should be installed in case volume expansion or blood transfusion is needed.

3. Neuraxial analgesia
   (a) Early epidural analgesia is recommended during labor. Parturients suffering from musculoskeletal disorders have a heightened sensibility to the respiratory depressant effects of opioids, analgesics, and general anesthetic agents; neuraxial anesthesia is also preferred if caesarean delivery (CD) is performed.
   (b) To prevent or reduce respiratory complication, lower doses of opioids should be used [11].
   (c) Neuraxial anesthesia has been successfully reported in various cases as a safe technique in this population, respecting the usual contraindications. Starting the epidural at an early stage of labor would leave time to assess its effectiveness and assure semi-urgent caesarean delivery under neuraxial anesthesia if needed.
   (d) If associated scoliosis is known or suspected, assessing the spine and the epidural space distance by ultrasound can help to optimize neuraxial placement.
   (e) For CD, spinal anesthesia should not be considered as the first option if the respiratory state is severely compromised.
   (f) Neither platelet dysfunction nor altered coagulation is associated with myopathy, but advanced stage of muscular disease can impair mobility, putting parturients at higher risk of thrombosis in addition to the hypercoagulability state at the end of pregnancy. According to these circumstances, one should make sure to have a multidisciplinary consensus for antithrombotic prevention and prophylaxis. Early mobilization by a physiotherapist may help parturients recover faster and take care of their baby normally.

      If muscular weakness is present and regional anesthesia is planned, a thorough neurological consultation may be considered to document predelivery status.
4. General anesthesia (GA)
   (a) As an emergency CD can happen at any time, if regional anesthesia fails, is difficult, or contraindicated, GA will be performed, keeping in mind the possible complications, most of those occurring postoperatively.
   (b) Due to the increased risk of adverse reactions to anesthetic agents and opioids, short-acting drugs are preferable, as well as drugs' titration, to minimize their respiratory and cardiac depression effects, accelerate recovery, and reduce postoperative respiratory failure [11].
   (c) All usual precautions apply to avoid aspiration with GA: due to the weakness of the pharyngeal and diaphragm muscles in myopathic patients and the impaired oesogastric motility.
   (d) For rapid sequence induction (RSI), succinylcholine is strictly contraindicated (see below the risk of hyperkalemia). It can lead to myotonic crisis in patients with myotonic disorders, sustained total body rigidity, and loss of airway access (mask ventilation, intubation), rhabdomyolysis, severe *hyperkalemia*, and hyperkalemic cardiac arrest in all myopathies
   (e) As an alternative to succinylcholine for RSI, high dosage (0.9–1.2 $mg.kg^{-1}$) of rocuronium provides a quick (less than 60 s) and deep neuromuscular blockade, but prolonged. Case reports show fast and successful reversal with sugammadex (8–12 mg/kg). High dosage of sugammadex is required to reverse the deep blockade and avoid respiratory adverse events [12].
   (f) Non-depolarizing muscle relaxants are allowed, but to anticipate the postoperative muscle weakness, they should probably be used at a lower dose. Nonetheless, neuromuscular monitoring is mandatory to avoid any residual blockade and impaired respiratory function.
   (g) In myopathic patients, volatile anesthetics can induce rhabdomyolysis and therefore *hyperkalemia* [13]. Thus, halogenated anesthetics are contraindicated in these patients, even though inhalation anesthesia could be shortly used in special circumstances (e.g., difficult venous access) as long as the anesthesiologist is prepared to treat an acute rhabdomyolysis and its complications.
      - In addition, halogenated anesthetics are myocardial depressants, which associated with the underlying cardiac condition of these patients could worsen their hemodynamic status.
      - In MD 1, halogenated anesthetics should moreover be avoided as they are uterine-relaxing agents and could exacerbate postpartum hemorrhage by uterine atony.
   (h) The susceptibility to *malignant hyperthermia (MH)* in muscular dystrophies does not exclude a higher risk than in the general population, so that clinicians should err on the side of caution and exclude the use of succinylcholine and halogenated anesthetics [14].
      - *MH* is linked to mutations of the ryanodine receptor gene with a clear increased risk in central core and minicore diseases, but not so well-documented in all other myopathies [3, 5, 15]. Due to mutational locus reasons, hypokalemic periodic paralysis is theoretically at higher risk of *MH*. The literature remains uncertain about a possible susceptibility to *MH* for patients with myotonia congenita [14].
      - In order to take all the precautions and avoid *MH*, the anesthetic team should be informed of patients with muscular disease at their arrival in the labor unit so as to place a new breathing circuit after

flushing the anesthetic machine with fresh O_2. If avoidance of volatile anesthetic agent is necessary, GA should be maintained by a total intravenous (IV) perfusion of propofol and remifentanil under mechanical ventilation. Nitrous oxide can be used but should be avoided in case of cardiac involvement. In addition, having dantrolene readily available in the operating room area is a safe precaution.

(i) Myotonic crisis and postoperative weakness have been described with neostigmine for patients with MD. Reversal of neuromuscular blockade with acetylcholinesterase inhibitors is unpredictable and so should be avoided [5, 11]. This is why anesthesiologists have to weigh the benefits of reversing a residual blockade and avoiding a few hours of postoperative ventilation against lowering the risk of inducing myotonia.

Other Muscular Dystrophies

Duchenne and Becker Muscular Dystrophies or Dystrophinopathies

1. Duchenne and Becker muscular dystrophies are X-linked recessive inherited disorders, caused by a mutation of the dystrophin gene, and so they are called dystrophinopathies.
2. The usual clinical presentation is a progressive, symmetrical, and proximal pelvic girdle muscle weakness with calf pseudohypertrophy and waddling gait.
3. Main systemic manifestations are dilated cardiomyopathy and scoliosis with severe respiratory impact.
4. These diseases are rather similar, except patients with Becker muscular dystrophy have milder symptoms, lower incidence (1/36,000 males), and a later onset. Duchenne myopathy is the most common and most severe form of childhood muscular dystrophy with an incidence of 1/3600 males.
5. Women can be carriers of this dystrophin defect and be asymptomatic aside from pregnancy. The diagnosis must be suspected if a mild muscle weakness is associated with elevated creatine kinase (CK). In 50% of women carriers, family history is missing. Pregnant women carriers must undergo an electrocardiogram and echocardiography to assess subclinical cardiac abnormalities; apparent correlation does not exist with the skeletal-muscle involvement [9].
6. Please see the section on Anesthetic Management for additional recommendations.

Limb-Girdle Muscular Dystrophy (LGMD)

1. The principal feature of this muscular dystrophy is the limbs' progressive muscular weakness.
2. Its frequency is 1 in 15,000 with a mainly autosomal recessive mode of inheritance (90%).
3. There is a broad range of clinical symptoms, severity, and age of onset, from childhood through adulthood, due to variable genetic disorders. At the adult stage, the weakness is more proximal, involving pelvic and shoulder girdles, leading to mobility restriction and eventually to being chairbound [1].
4. Cardiac involvement is rare, and respiratory involvement is inconstant [1].
5. According to the studies, 25–54% of women with LGMD experience a muscular weakness exacerbation during pregnancy [1, 3, 9, 15]. Parturients are also at higher risk for breech presentation [1, 9, 15] and are more likely to deliver by caesarean section.
6. Please see the section on Anesthetic Management for additional recommendations.

Facioscapulohumeral Muscular Dystrophy

1. Facioscapulohumeral muscular dystrophy is a rare autosomal dominant disorder due to a deletion on chromosome 4, with an incidence of 4 per million.
2. The characteristic form is a slow progressive weakness of the facial expression and arm muscles, with scapular winging that begins during adolescence. Involvement of the lower limbs usually appears later in the course of the disease.
3. Supraventricular arrhythmias occur occasionally.
4. In a retrospective study of 38 affected women, half were diagnosed at the time of pregnancy [3]. Conflicting data exist in the literature regarding the incidence of operative deliveries or preterm labor, but all agree that worsening of the symptoms appears in about 25% of pregnancies [1, 3, 15].
5. Please see the section on Anesthetic Management for additional recommendations.

In conclusion, several specific aspects have to be considered in pregnant women with muscular diseases: cardiac and pulmonary involvements, potential scoliosis and its respiratory impact, anesthetic agents' hypersensibility, risk of rhabdomyolysis, and severe *hyperkalemia*, as well as *malignant hyperthermia* in some myopathies with all the precautions it implies.

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