Muscular Dystrophy Syllabus

Much of the following is reproduced from material contributed by the author to
Smith's Anesthesiology for Infants and Children (8th edition); Eds. Davis PJ, Cladis FP, Motoyama EK. (2011), Pub. Elsevier. Chapter 36 Systemic Disorders

Phil G. Morgan, MD

Introduction.

First, we will give a general overview of the generation of muscle contraction in a normal cell. Skeletal muscle contraction is accomplished by the generation of a neuronal action potential that terminates at the neuromuscular synapse. The neuronal action potential (AP) stimulates sodium channels in the neuronal axon that propagates the signal along the axon. As the AP reaches the end of the axon, voltage gated calcium channels are activated which allows the influx of calcium into the neuron. This influx of calcium, in turn, stimulates the release of a neurotransmitter, acetylcholine, from the nerve terminal into the synapse. The acetylcholine binds to receptors on the cell surface of the postsynaptic cell, the muscle in this case. Binding of the acetylcholine to its receptors allows influx of sodium into the muscle, generates a new AP that propagates a transmembrane signal that spreads along the membrane of the cell.

The AP is carried from the cell surface into the interior of the cell by a series of invaginations of the cell membrane known as T-tubules. These structures allow for transmembrane electrical depolarizations to be carried deeply within the cell where they would otherwise not be generated. At the ends of the T-tubules the sodium currents are again replaced by calcium currents, resulting from the activation of a voltage gated calcium channel known as the dihydropyridine receptor. These calcium currents, in their turn, stimulate larger calcium release from the sarcoplasmic reticulum through a calcium-sensitive calcium channel, the ryanodine receptor. These larger fluxes of calcium stimulate movement of the actin-myosin filaments, an ATP requiring step (and therefore dependent on functioning mitochondria). The filaments are attached to the surface of the muscle and the surrounding matrix through a variety of proteins, most notably dystrophin. Movement of the filaments is transduced into shortening of the cell (muscle contraction) by the connection to the cell surface and surrounding matrix. Relaxation is accomplished by reuptake of the intracellular calcium primarily back into the sarcoplasmic reticulum. This reuptake is energy requiring and dependent on ATP-dependent calcium pumps. Since reuptake of calcium is energy requiring, it is dependent on mitochondrial function and ATP generation. Loss of this energy source is the cause of rigor mortis.

Muscle Disease

One can then divide muscle diseases into four general groups: muscular dystrophies, myotonic syndromes, mitochondrial myopathies, and myasthenic syndromes. We will discuss each of these categories separately (concentrating on the dystrophies) and discuss their clinical implications. The underlying pattern of defects in molecular action leads to defective muscle contraction. An overview of muscle diseases is given below:

1. ***Myasthenic syndromes*** affect transmission of the action potential from the motor neuron to the muscle cell. This generally involves a disruption of the signal carried by the neurotransmitter, acetylcholine, across the synaptic cleft. The molecular changes may affect release of the

neurotransmitter, acetylcholine, or its action at the postsynaptic receptor. These syndromes will not be discussed further here.

2. ***Myotonic syndromes*** affect transmission of the action potential along the muscle membrane and are generally caused by abnormalities in sodium, chloride or potassium channels. These changes cause a prolonged depolarization of the muscle membrane which leads to prolonged contraction of the muscle. A subgroup of these syndromes also causes muscle degeneration and are termed ***myotonic dystrophies***.

3. ***Mitochondrial myopathies*** are (as their name implies) caused by abnormalities in mitochondrial function. Since mitochondria are important for supplying ATP in most tissues (most importantly nerve and muscle), the symptoms often involve the nervous system as well as muscle. The lack of ATP in muscle leads primarily to weakness and wasting of muscle. This is a very complex and diverse group of diseases with an equally wide range of clinical implications.

4. ***Muscular dystrophies*** result from the dissociation of contractile force from the muscle to the surrounding connective tissue. The actin-myosin filaments in the muscle cell contract but they are no longer adequately connected to the cell membrane or the surrounding tissue. As a result there is the equivalent of electromechanical dissociation, *i.e.* the electrical signal from the muscle cell membrane is not translated into effective mechanical force.

Myotonias.

Myotonia is a temporary, involuntary contraction of muscle fibers due to transient hyperexcitability of the surface membrane (Miller G., 1989). In general, the myotonias may be thought of as a family of channelopathies mostly affecting muscle (Jurkat-Rott K and others 2002; Rosenbaum HK & Miller JD. 2002). The abnormalities in the channels leads to prolonged depolarization in the membrane once an AP is generated and leads to prolonged or increased release of calcium into the cell. This, in turn, leads to prolonged stimulation of the actin-myosin contractile apparatus of the muscle cell. The persistent contracture of the skeletal muscle generally occurs after muscle stimulation but may be triggered by other stimuli such as cold, pain or stress. A classic finding in patients with myotonia is the inability to easily relax after a firm handshake.

Two forms of myotonia (myotonia congenita and Becker's disease) result from defects in the *same* skeletal muscle chloride channel (termed ClC-1) (Pusch M., 2002; Renner DR & Ptacek LJ.,2002; Jurkat-Rott K and others 2002). Myotonia congenita (Thomsen's disease) is an autosomal dominant disease, presenting in childhood associated with a normal life expectance and minimal symptoms (Grunnet M, and others. 2003). Becker's disease, not to be confused with Becker muscular dystrophy, is an autosomal recessive form of this channelopathy, appearing in childhood also (Pusch M., 2002). In addition, some mutations in this chloride channel cause a variant of dominant myotonia with a milder phenotype, myotonia levior (Ryan A. and others, 2002; Farbu E, and others, 2003). These myotonic diseases are nonprogressive and do not have a dystrophic component, *i.e.* there is no deterioration of the muscle over time. Other, more mild, myotonias result from abnormalities in sodium or potassium channels on the muscle cell membrane. These include paramytonia congenital (sodium channel), hyperkalemic periodic paralysis (sodium channel) and hypokalemic periodic paralysis (calcium, sodium or potassium channels) (Jurkat-Rott K and others 2002).

Anesthetic Considerations. As noted above, myotonic contractions may be precipitated by stress, cold and pain. Thus, these triggering factors must be aggressively avoided during the perioperative period for these patients. Regional anesthesia and neuromuscular blockade (NMB) ***do not reverse*** the contractions since they act upstream from the molecular causes of the syndrome.

Succinylcholine has been noted to precipitate contractions, as have NMB reversal agents. These contractions have been most notable in the occurrence of masseter spasm after the use of succinylcholine but can also involve other muscles and lead to extreme difficulty with positive pressure ventilation as well as intubation (Farbu E. and others, 2003). For these reasons, the use of succinylcholine is discouraged in patients with myotonia. If an episode of myotonia occurs during anesthesia, volatile anesthetics, quinine, or procainamide can be used for relaxation. Since the myotonias occur as the result of abnormal ion channels, great care must be taken to keep electrolytes normal at all times. While myotonic syndromes may have symptoms in common with malignant hyperthermia (especially muscle contracture following the administration of succinylcholine), they are not associated with true MH.

Myotonic dystrophy (Steinert muscular dystrophy) is the most common form of myotonia (Anderson BJ & Brown TC, 1989). This disease is a form of muscular dystrophy and includes congenital myotonic dystrophy. Myotonic dystrophy is discussed here instead of with other muscular dystrophies because its presentation is different, more resembling the myotonias than the dystrophies.

Recently, it has been shown that myotonic dystrophy actually includes two different molecular diseases (Ranum LP & Day JW, 2002). Myotonic dystrophy type 1 results from alterations in the human dystrophica myotonica-protein kinase gene (DMPK) (Amack JD, Mahadevan MS, 2004). The precise mechanism by which this mutation causes the disease is not clear at present but the dystrophy results from abnormal development of the muscle cells (Martorell L and others, 2004; Wansink DG & Wieringa B, 2003). However, the myotonia probably is the result of abnormal phosphorylation of sodium channels resulting in delayed inactivation following channel opening (Lee HC and others, 2003). The prolonged channel activation causes prolonged muscle contraction. The changes in the protein kinase gene are in the promoter or starting region of the gene and are the result of duplications in short repetitive sequences (CTG triplets). The number of repetitive sequences are often increased in the offspring compared to an affected parent. As a result, each successive generation tends to exhibit a more severe form of the disease. Myotonic dystrophy type 2 has a clinically diverse presentation including myotonia, proximal muscle wasting, endocrine, cardiac and cerebral abnormalities. Myotonic dystrophy 2 also results from expansion of a sequence in the promotor of a gene, but the gene is separate from that causing DM1 and codes for a probable transcription factor, ZNF9 (Finsterer J., 2002; Liquori CL and others, 2003). The precise physiologic changes leading to myotonic or dystrophic changes are not known. In both disease states, the abnormalities result from abnormal RNA species that disrupt normal development of the cells (Mankodi A & Thornton CA, 2002).

Anesthetic Considerations. Production of muscle relaxation can be very difficult in these patients. As with the other forms of myotonia discussed above, cold, stress, pain and succinylcholine can precipitate myotonia. Additionally, since this is a dystrophy with muscle wasting, succinylcholine can elicit a hyperkalemic response and should be avoided. Unlike the other myotonias, myotonic dystrophy leads to deterioration of the muscle fibers, affects tissue other than skeletal muscle, and is associated with weakness and hypotonia in the infant and child. Paradoxically, however, the patients can trigger a myotonic episode as well. These patients can have profound respiratory depression, severe cardiac conduction abnormalities, cardiomyopathy, developmental delay, dysphagia and decreased gastric motility. Muscle relaxants must be used with great care, if at all, in these patients. Smaller doses are probably necessary and a neuromuscular blockade monitor is advised. As with other myotonias, reversal agents may induce myotonia. Since respiratory depression is notable in these patients, the respiratory status is potentially fragile

when any narcotic or general anesthetic is used. Thus, their care presents challenges involving several physiologic systems. White and Bass recently presented a thoughtful review involving the anesthetic care of patients with myotonic dystrophy (White RJ & Bass SP, 2003). Myotonic dystrophy is also commonly thought to be associated with MH. However, as with the above myotonias, while this syndrome shares features with MH, it is not associated with true MH.

Mitochondrial Myopathies.

An increasingly large list of disease syndromes are associated with mitochondrial dysfunction. The more commonly seen mitochondrial syndromes are Leigh disease, Kearns-Sayre syndrome, and Leber hereditary optic neuropathy. However, mitochondrial dysfunction is also associated with unnamed myopathies and encephalopathies and with symptoms of failure to thrive. Recently mitochondrial abnormalities have been shown to be involved with some forms of autism and Parkinson's disease. It is clear that the presentation of mitochondrial disease may be quite varied.

Mitochondria are the principal source of energy metabolism within cells, especially those of nerve and muscle. Within mitochondria reside the enzymes responsible for the Krebs cycle, fatty acid β-oxidation and, most importantly, oxidative phosphorylation. Mitochondria contain the enzymes that metabolize glucose, fatty acids and amino acids to generate NADH and succinate that, in turn, are used as electron donors for the electron transport chain. By passing electrons down the electron transport chain (complexes I-IV), a proton gradient is generated across the mitochondrial inner membrane (dotted arrows) and electrons are donated to oxygen to generate water. The proton gradient is then used to drive an ATP synthase (complex V). The coupling of electron transfer to phosphorylation is known as oxidative phosphorylation and is overwhelmingly the major source of ATP and other high energy phosphate bonds supplying energy to the cell. ATP is necessary both for actin-myosin filament contraction and for reuptake of calcium by ATP-dependent calcium pumps into the sarcoplasmic reticulum.

Mitochondrial complexes are composed of groups of proteins ranging from just a few (complex II) to over 40 (complex I). In addition, the dehydrogenases, membrane transporters, and structural proteins raise the number of functional proteins in the mitochondria into the hundreds. It is a common mistake to group all mitochondrial diseases together as similar entities. However, it is possible to have a mutation in any of the mitochondrial proteins and the resulting functional changes can be dramatically different. In addition, mitochondria in different tissues can be quite varied in their activity. The differences between tissues in sensitivity to mitochondrial function (and the varied inheritance pattern discussed above) give rise to different symptoms even within members of a family carrying identical mutations. It is dangerous to imply that, because an anesthetic technique was successful in a few patients with mitochondrial disease, that the technique is safe for all patients with mitochondrial dysfunction.

Muscle and nerve cells are uniquely dependent on the energy delivered by these mitochondria. Mutations in mitochondrial proteins are causative for striking clinical features in those two tissues including myopathy, cardiomyopathy, encephalopathy, seizures and cerebellar ataxia. Of course, cardiac muscle and the central nervous system are also the two main targets of general anesthetics. Thus, particular care must be taken when exposing such a patient to these agents. Since motor neurons may be affected, a hyperkalemic response to succinylcholine may be seen. Lastly, MH is thought to be associated with some forms of mitochondrial myopathies, but the nature of this relationship is unclear (Fricker RM and others, 2002; Keyes MA and others, 1996).

Anesthetic Considerations. The perioperative period is a time during which a patient may be exposed to periods of stress. Under conditions of stress this may lead to inadequate ATP levels to meet demand. Shivering due to hypothermia probably represents the greatest threat to these patients. However, hyperthermia and stress from untreated pain also represent serious risks. The failure for ATP production to meet metabolic demands inevitably leads to a lactic acidosis, often of profound significance. To avoid such problems great care must be taken to keep patients normothermic during surgical cases and to adequately treat postoperative pain. Postoperative pain represents a particularly troublesome problem since narcotics can compromise respiratory status further.

Mitochondrial patients may become acidemic due to high levels of lactate as a result of hypovolemia. Prolonged preoperative fasting should be avoided in these patients. If fasting is necessary, then intravenous fluids should be started with glucose added to avoid anaerobic metabolism. Cyanide inhibits the respiratory chain, so sodium nipride should probably be avoided. For similar reasons, tourniquets should be avoided if possible. It is not clear what hematocrit is adequate in these patients, but it is probably wise to keep them closer to normal levels than other patients. Lastly, while mild levels of hypotension are commonly used in many patients to avoid blood loss, such an approach is less desirable in patients with mitochondrial disease. These patients are probably less able to compensate for decreased oxygen delivery.

Unfortunately, essentially every general anesthetic studied has been shown to depress mitochondrial function. The most notable of these are the volatile anesthetics and propofol. It is reported that these agents only significantly depress mitochondria at doses higher than their clinical concentrations. However, recent studies have shown that even at dose commonly used in the operating room, anesthetics cause a significant depression of mitochondria from normal patients (Miro O and others, 1999; Morgan PG and others, 2002; Wolf A and others, 2001). Since both propofol and volatile anesthetics primarily inhibit complex I function, patients with complex I-specific defects may have increased susceptibility to these drugs.

In general, regional anesthesia is well tolerated by patients with mitochondrial myopathies. This tolerance is in spite of data indicating that local anesthetics, especially bupivicaine, are capable of potently depressing mitochondrial function. Fortunately, most neural blockade uses doses of anesthetic that are well below the doses necessary for mitochondrial effects. However, one must be vigilant that these drugs are also capable of such effects, especially on the heart. Despite this risk, however, due to the low doses commonly used, regional anesthesia represents a valuable mode of treatment. Ideally, such blocks avoid the exposure of the CNS and cardiac muscle to potentially toxic side effects. Not all cases can be done with regional anesthesia, especially in children. However, consideration should be given to this approach when possible.

From an anesthesiologist's point of view, the primary complications of mitochondrial myopathies include respiratory failure, cardiac depression, conduction defects and dysphagia. All of the general anesthetic agents are known to directly inhibit mitochondrial function and may add to preoperative problems. However, each of the commonly used anesthetics has been used successfully when caring for patients with mitochondrial disease. It may be that as the different types of mitochondrial disease are better defined, preferences for an anesthetic in certain cases may become clear. However, such a recommendation cannot be made at the present time. What is clear is that these patients must be monitored more closely than other patients when using a general anesthetic and that great care must be exercised to document that the effects of the anesthetics are largely gone before assuming that the patient can ventilate adequately.

Conclusions: At the present, we do not have the perfect anesthetic for patients with mitochondrial myopathies. When possible, consideration should be given to the use of local

anesthetics in small amounts. When a general anesthetic is necessary, probably each of the general anesthetics in use has its place. At present it is not possible to eliminate one group as less safe than others. What is clear is that these patients must be monitored more closely than other patients. The advent of the bispectral index (BIS) monitor may allow us to monitor their depth of anesthesia more closely and thus expose these patients only to the minimum amount of drug necessary to carry out the surgical procedure.

Muscular Dystrophy.

At least five forms of muscular dystrophy are clinically relevant for anesthesiologists (Farrell PT, 1994). These include Becker, Duchenne, Facioscapulohumeral, Emery-Dreifuss, and Limb-girdle muscular dystrophies. These entities vary greatly in severity of presentation; however, many of their indications for anesthesiologists are similar (Kerr TP and others, 2001; Schmidt GN and others, 2003). ***Duchenne muscular dystrophy*** (DMD) is an X-linked disorder resulting from deletion mutations in the dystrophin gene resulting in a complete lack of dystrophin in skeletal muscles. The defect is present in about 1/3500 live births with the onset of disease often before school age and progressing to wheel chair dependence by the second decade of life. Dystrophin is a large protein which helps anchor the contractile components (the actin-myosin filaments) to the cell membrane and indirectly to the surrounding extracellular matrix. Loss of this protein leads to profound muscle weakness and eventual respiratory insufficiency (Muntoni F and others, 2003; Finsterer J & Stollberger C, 2003). Other, less global, changes in this same gene cause ***Becker muscular dystrophy*** (BMD) and the related disease, ***X-linked dilated cardiomyopathy***. Cardiomopathy is occasionally seen in female heterozygote carriers of the mutation.

Dystrophin is also found in cells other than skeletal muscle and has an apparent role in organizing protein complexes in the membrane and stabilizing the membrane. Absence of the protein leads to membrane instability which causes eventual muscle cell deterioration. Associated defects seen in patients with DMD and BMD dystrophies include cardiomyopathy, cardiac conduction defects and, occasionally, mild mental retardation. The presence of the protein in other cell types provides an explanation for the involvement of the nervous system in affected patients.

Dystrophin also is important in organizing the post-synaptic acetylcholine receptors (Muntoni F and others, 2003). In its absence, abnormalities occur both in the types of receptors and in their number and location. In the absence of dystrophin there is also an increase in expression of acetylcholine receptor subunits as well as changes in interacting proteins (Chen YW and others, 2000). The membrane instability coupled with changes in acetylcholine receptors may explain the sensitivity of the muscle to succinylcholine and volatile anesthetics.

Anesthetic Considerations. The main anesthetic implications of DMD and BMD are related to the profound myopathies. As would be expected in patients with muscle weakness, significant postoperative respiratory insufficiency can result from either disease. Cardiac muscle and conduction are also involved and drugs that further depress cardiac function, or which increase the likelihood of arrhythmias, should be avoided. All patients with DMD or BMD should receive a full cardiology evaluation and PFTs prior to any surgery. Lastly, dysphagia is common and gastric motility may be decreased requiring expedient control of the airway. The association of malignant hyperthermia with DMD and BMD appears to be coincidental only.

Both DMD and BMD patients can have rhabdomyolysis and hyperkalemia in response to succinylcholine; thus succinylcholine is contraindicated in these patients. It is unclear whether volatile anesthetics alone can cause rhabdomyolysis in these patients. Other forms of congenital muscular dystrophy exist that also involve other proteins necessary for attaching the contractile

machinery to the extracellular matrix. While this is a heterogeneous group of mutations, it is probably best to treat these patients as if they had DMD. These are discussed below.

Other Dystrophies. More than 30 different forms of congenital muscular dystrophy are now known, and are caused by defects in a wide array of components of the basement cell membrane and extracellular matrix (Engvall E, Wewer UM, 2003). These are not discussed in detail as their clinical implications are similar to each other. Examples are the absence of laminin, or a related protein merosin, which give rise to similar forms of congenital dystrophies. These often have profound effects both on skeletal muscle and the nervous system.

The most common remaining dystrophies, ***Facioscapulohumeral*** (FSH), ***Emery-Dreifuss*** (ED), and ***Limb girdle muscular dystrophy*** (LG) are much milder in their presentations (Emery AE, 2002). FSH is one of the most common muscular dystrophies, but the molecular basis of FSH is unknown. FSH is the most benign muscular dystrophy usually with little respiratory involvement (Fitzsimons RB, 1999). However, the neck, face and scapular stabilizing muscles are often weak, and the ability to raise the head may be of little use in determining respiratory muscle strength. Importantly, these patients may lose the ability to swallow well and therefore be unable to protect their airway during emergence from anesthesia.

Emery-Dreifuss dystrophy may result from multiple causes. The most common form of ED usually has its onset in the teenage years and results from mutations in emerin, an inner nuclear membrane protein which interacts with laminin (part of the nuclear matrix) and transcription regulators. These patients have cardiac conduction defects, cardiomyopathy, contractures (positioning problems) and often a fusion of C3-C5 resulting in a less mobile neck (difficulty during intubation) (Aldwinckle RJ & Carr AS, 2002; Shende D & Agarwal R, 2002). Limb-girdle dystrophy results from mutations in several proteins (at least 11 known), such as α-sarcoglycan, which associate with dystrophin. LG is associated with some respiratory muscle weakness and significant cardiac conduction abnormalities. At least some cases of LG result from a defect in a protein which interacts with muscle cell membrane and is implicated in membrane repair (Capanni C and others, 2003).

Anesthetic Considerations. There is little experience in the literature on the interaction of anesthetics with LG dystrophy (Pash MP and others, 1996). In all three forms of muscular dystrophy, succinylcholine should be avoided as hyperkalemia can result. MH is **not** reported in these three milder forms of muscular dystrophy. Thus, though not universal, the recurring themes with muscular dystrophy are to avoid succinylcholine, to watch for respiratory depression, and to avoid cardiac depressants and arrhythmiagenic drugs.

It is important to note that anesthetic complications have been reported in most of these forms of muscular dystrophy (Farrell PT, 1994). These episodes most commonly result from a hyperkalemic episode and sudden cardiac arrest may occur. Such events can occur in patients who are still in a subclinical stage of their disease and in whom the crisis may be the first manifestation. For this reason, many clinicians reserve their use of succinylcholine in all children to only those cases in which there exists a specific indication for their use.

References.

Aldwinckle RJ, Carr AS. The anesthetic management of a patient with Emery-Dreifuss muscular dystrophy for orthopedic surgery. Can J Anaesth. 2002 May;49(5):467-70.

Amack JD, Mahadevan MS. Myogenic defects in myotonic dystrophy. Dev Biol. 2004 Jan 15;265(2):294-301.

Anderson BJ, Brown TC. Congenital myotonic dystrophy in children--a review of ten years' experience. Anaesth Intensive Care. 1989 Aug;17(3):320-4.

Bolton P, Peutrell J, Zuberi S, Robinson P. Anaesthesia for an adolescent with mitochondrial encephalomyopathy-lactic acidosis-stroke-like episodes syndrome. Paediatr Anaesth. 2003 Jun;13(5):453-6.

Capanni C, Sabatelli P, Mattioli E, Ognibene A, Columbaro M, Lattanzi G, Merlini L, Minetti C, Maraldi NM, Squarzoni S. Dysferlin in a hyperCKaemic patient with caveolin 3 mutation and in C2C12 cells after p38 MAP kinase inhibition. Exp Mol Med. 2003 Dec 31;35(6):538-44.

Chen YW, Zhao P, Borup R, Hoffman EP. Expression profiling in the Muscular Dystrophies: Identification of Novel Aspects of Molecular Pathophysiology. J Cell Biol. 2000; 151:1321-1326.

Clausen T. Na+-K+ pump regulation and skeletal muscle contractility. Physiol Rev. 2003 Oct;83(4):1269-324.

Dresner DL, Ali HH. Anaesthetic management of a patient with facioscapulohumeral muscular dystrophy. Br J Anaesth. 1989 Mar;62(3):331-4.

Engvall E, Wewer UM. The new frontier in muscular dystrophy research: booster genes. FASEB J. 2003 Sep;17(12):1579-84.

Emery AE. The muscular dystrophies. Lancet. 2002 Feb 23;359(9307):687-95.

Farbu E, Softeland E, Bindoff LA. Anaesthetic complications associated with myotonia congenita: case study and comparison with other myotonic disorders. Acta Anaesthesiol Scand. 2003 May;47(5):630-4.

Farrell PT. Anaesthesia-induced rhabdomyolysis causing cardiac arrest: case report and review of anaesthesia and the dystrophinopathies. Anaesth Intensive Care. 1994 Oct;22(5):597-601.

Finsterer J, Stollberger C. The heart in human dystrophinopathies. Cardiology. 2003;99(1):1-19.

Finsterer J. Myotonic dystrophy type 2. Eur J Neurol. 2002 Sep;9(5):441-7.

Fitzsimons RB. Facioscapulohumeral muscular dystrophy. Curr Opin Neurol. 1999;12(5):501-11.

Fricker RM, Raffelsberger T, Rauch-Shorny S, Finsterer J, Muller-Reible C, Gilly H, Bittner RE. Positive malignant hyperthermia susceptibility in vitro test in a patient with mitochondrial myopathy and myoadenylate deaminase deficiency. Anesthesiology. 2002 ;97(6):1635-7.

Froemming GR, Ohlendieck K. The role of ion-regulatory membrane proteins of excitation-contraction coupling and relaxation in inherited muscle diseases. Front Biosci. 2001 Jan 1;6:D65-74.

Grunnet M, Jespersen T, Colding-Jorgensen E, Schwartz M, Klaerke DA, Vissing J, Olesen SP, Duno M**.** Characterization of two new dominant ClC-1 channel mutations associated with myotonia. Muscle Nerve. 2003 Dec;28(6):722-32.

Jurkat-Rott K, Lerche H, Lehmann-Horn F. Skeletal muscle channelopathies. J Neurol. 2002 Nov;249(11):1493-502.

Kerr TP, Duward A, Hodgson SV, Hughes E, Robb SA. Hyperkalaemic cardiac arrest in a manifesting carrier of Duchenne muscular dystrophy following general anaesthesia. Eur J Pediatr. 2001 Sep;160(9):579-80.

Keyes MA, Van de Wiele BV, Stead SW. Mitochondrial myopathies: an unusual cause of hypotonia in infants and children. Paediatr Anaesth. 1996;6(4):329-35.

Lee HC, Patel MK, Mistry DJ, Wang Q, Reddy S, Moorman JR, Mounsey JP. Abnormal Na channel gating in murine cardiac myocytes deficient in myotonic dystrophy protein kinase. Physiol Genomics. 2003 Jan 15;12(2):147-57.

Liquori CL, Ikeda Y, Weatherspoon M, Ricker K, Schoser BG, Dalton JC, Day JW, Ranum LP. Myotonic dystrophy type 2: human founder haplotype and evolutionary conservation of the repeat tract. Am J Hum Genet. 2003 Oct;73(4):849-62.

Mankodi A, Thornton CA. Myotonic syndromes. Curr Opin Neurol. 2002 Oct;15(5):545-52.

Martorell L, Gamez J, Cayuela ML, Gould FK, McAbney JP, Ashizawa T, Monckton DG, Baiget M. Germline mutational dynamics in myotonic dystrophy type 1 males: allele length and age effects. Neurology. 2004 Jan 27;62(2):269-74.

Miller G. Myopathies of infancy and childhood. Pediatr Ann. 1989 Jul;18(7):439-53.

Miro O, Barrientos A, Alonso JR, Casademont J, Jarreta D, Urbano-Marquez A, Cardellach F. Effects of general anaesthetic procedures on mitochondrial function of human skeletal muscle. Eur J Clin Pharmacol. 1999 Mar;55(1):35-41.

Morgan PG, Hoppel CL, Sedensky MM. Mitochondrial defects and anesthetic sensitivity. Anesthesiology. 2002 May;96(5):1268-70.

Muntoni F, Torelli S, Ferlini A. Dystrophin and mutations: one gene, several proteins, multiple phenotypes. Lancet Neurol. 2003 Dec;2(12):731-40.

Pash MP, Balaton J, Eagle C. Anaesthetic management of a parturient with severe muscular dystrophy, lumbar lordosis and a difficult airway. Can J Anaesth. 1996 Sep;43(9):959-63.

Pusch M. Myotonia caused by mutations in the muscle chloride channel gene CLCN1. Hum Mutat. 2002 Apr;19(4):423-34.

Ranum LP, Day JW. Myotonic dystrophy: clinical and molecular parallels between myotonic dystrophy type 1 and type 2. Curr Neurol Neurosci Rep. 2002 Sep;2(5):465-70.

Renner DR, Ptacek LJ. Periodic paralyses and nondystrophic myotonias. Adv Neurol. 2002;88:235-52.

Rosenbaum HK, Miller JD. Malignant hyperthermia and myotonic disorders. Anesthesiol Clin North America. 2002 Sep;20(3):623-664.

Ryan A, Rudel R, Kuchenbecker M, Fahlke C. A novel alteration of muscle chloride channel gating in myotonia levior. J Physiol. 2002;545(Pt 2):345-54.

Schmidt GN, Burmeister MA, Lilje C, Wappler F, Bischoff P. Acute heart failure during spinal surgery in a boy with Duchenne muscular dystrophy. Br J Anaesth. 2003 ;90(6):800-4.

Shende D, Agarwal R. Anaesthetic management of a patient with Emery-Dreifuss muscular dystrophy. Anaesth Intensive Care. 2002 Jun;30(3):372-5.

Wansink DG, Wieringa B. Transgenic mouse models for myotonic dystrophy type 1 (DM1). Cytogenet Genome Res. 2003;100(1-4):230-42.

White RJ, Bass SP. Myotonic dystrophy and paediatric anaesthesia. Paediatr Anaesth. 2003 Feb;13(2):94-102.

Wolf A, Weir P, Segar P, Stone J, Shield J. Impaired fatty acid oxidation in propofol infusion syndrome. Lancet. 2001 Feb 24;357(9256):606-7.