INTRODUCTION

Duchenne muscular dystrophy (DMD) is the most common childhood muscular dystrophy, with an incidence of approximately one in 3500 live male births. Patients with DMD suffer from progressive degeneration of skeletal, cardiac and smooth muscle beginning at 3–5 years of age. The progression of muscle weakness is rapid, resulting in a failure to walk by adolescence and eventual death from respiratory failure before the end of the third decade. Dilated cardiomyopathy occurs in over 50% of patients by 15 years of age. Although many of these patients undergo anesthesia and surgery without complication, perioperative adverse events are not uncommon ***(Almenrader, 2006).***

Patients with Duchenne muscular dystrophy suffer from a progressive deterioration in muscle secondary to a defect in the dystrophin gene. The patients with duchenne muscular dystrohy have associated difficult airway anatomy in the form of macroglossia and limited mobility of mandible and cervical spine. These patients are at an increased risk of developing extreme hyperthermia, rhabdomyolysis and hyperkalemic cardiac arrest when exposed to halogenated inhalational anaesthetics and depolarizing muscle relaxants ***(Hayes et al., 2008).***

Anaesthesia for children known to have muscular disorders is a challenging balance between meeting anaesthetic

and analgesic requirements, while avoiding excessive suppression of neuromuscular, cardiovascular and respiratory systems. It is possible that the greatest challenge lies in managing the patient who may develop a catastrophic reaction to a chosen anaesthetic. Preoperative vigilance may raise suspicion, and intraoperative vigilance lead to early diagnosis and management, with possible avoidance of adverse outcome. Postoperative observation is essential ***(Gray, 2013)***.

Preoperative evaluation in patients with DMD should include a detailed work-up of their pulmonary function, which includes measurement of forced vital capacity, maximum inspiratory pressure, maximum expiratory pressure, and peak cough flow. Preoperative training with assist devices should be considered based on their pulmonary function. Complete cardiac evaluation should be undertaken before any surgical procedure and a dobutamine stress test should be considered if any abnormalities of cardiac function are present. Medical therapy of any cardiac dysfunction should be optimized before any surgery ***(Birnkrant et al., 2007)*.**

AIM OF THE WORK

The goal of this essay is to study Perioperative anesthetic management in patients with Duchenne muscular dystrophy and the strategies employed to prevent complications associated with anesthesia.

CHAPTER ONE
PATHOPHYSIOLOGY OF DUCHENNE MUSCULAR DYSTROPHY

Duchenne muscular dystrophy (DMD), an X-linked disorder and the most common muscular dystrophy, has an incidence of one in 5000 boys and presents in early childhood with proximal muscle weakness ***(Moat et al., 2013)***.

The defect is located on the short arm of the X chromosome at the Xp21 region, which contains the gene for the large protein Dp427, also known as *dystrophin*. Dystrophin is a large protein, found on the cytoplasmic surface of skeletal muscle cell membranes; it regulates the integrity of the sarcolemma, the membrane enclosing the striated muscle fibers ***(Hopkins, 2010)***.

The dystrophin gene is 2500 kilobases long with more than 70 exons. Dystrophin is distributed not only in skeletal, cardiac and smooth muscle but also in the brain. Because of the large size of the dystrophin gene, spontaneous new mutations are common and account for one third of new cases ***(Dalakas et al., 2003)***.

The most common form of mutation is a deletion within the gene (65% to 70% of patients with DMD and more than 80% of those with Becker muscular dystrophy (BMD).

Duplication and point mutations are responsible for the rest. In addition, hot spots also appear in the first 20 exons and in the central region of the gene (exons 45 to 55) where deletion and duplication are likely to occur ***(Dalakas et al., 2003)***.

Female patients with DMD have been reported with the 45,X and 46,XX karyotypes. The disease mechanism for the female 46,XX karyotype is thought to be preferential loss of the paternal X chromosome by postzygotic nondisjunction and manifestation of the DMD gene from the maternal X chromosome in muscle cells ***(Dalakas et al., 2003)***.

Dystrophin is responsible for the maintenance of muscle membrane integrity, despite the fact that it accounts for only approximately 0.002% of the protein in striated muscle. Dystrophin plays an important role in sarcolemmal stability and muscle membrane integrity. A cytoskeletal protein links intracellular actin to a group of cell membrane proteins called the *dystrophin-associated protein complex*. This complex, in turn, links via laminin to the extracellular matrix. In DMD, not only is dystrophin absent, but an abnormal expression of the dystrophin-associated protein complex is evident ***(Allen &Whitehead, 2011)***.

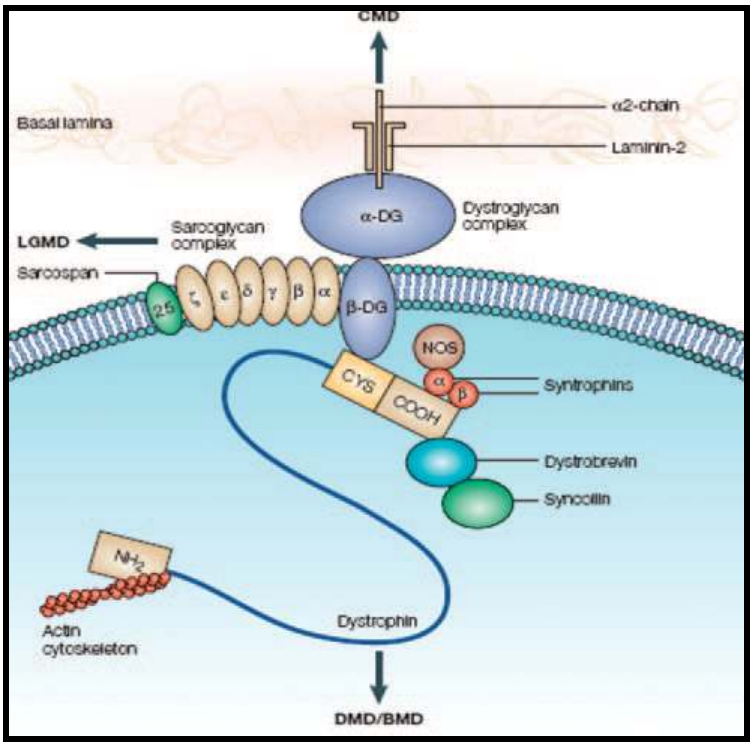

Figure (1): Schematic representation of the organization of the dystrophin-glycoprotein complex (DGC). Various muscular dystrophies (MD) result from defects in the muscle DGC. DMD results from a complete deficiency of dystrophin, whereas a partial deficiency leads to BD ***(Khurana & Davies, 2003)***

Normal Muscle Physiology

The propagation of an action potential down a motor nerve fiber produces depolarization of that fiber and release of acetylcholine (ACh) at the neuromuscular junction. When two molecules of ACh interact with the ACh receptor, the channel opens, allowing sodium to enter the cell and potassium to flow out. This initiates a wave of depolarization along the muscle cell membrane or sarcolemma. The propagated depolarization

wave spreads internally via transverse tubules that abut onto the sarcoplasmic reticulum (SR). The SR is an internal cellular wall of the transverse tubule contains the dihydropyridine (DHPR) receptor, a voltage-dependent calcium channel that interacts with the calcium-sensitive ryanodine receptor (RYR), the footplate between the transverse tubule and the SR. Within a voltage window, calcium is released from the SR into the sarcoplasm through RYR type 1 (RYR1). Increased calcium in the sarcoplasm also induces further calcium release from the SR ***(Melzer and Dietze, 2001)***.

Furthermore, when calcium has been depleted from the SR, a process known as store-operated calcium entry (SOCE) allows calcium entry into the sarcoplasm from the extracellular milieu ***(Zhao et al., 2006)***.

Excitation-coupled calcium entry (ECCE) refers to the process by which extracellular calcium enters the sarcoplasm through the plasma membrane after depolarization. The RYR has influence on both SOCE and ECCE ***(Lyfenko and Dirksen, 2008)***.

Type 1 RYRs are found in all skeletal muscle, smooth muscle, neurons, and B lymphocytes. Type 2 RYRs are found in cardiac muscle, brain, and some hematopoietic cells. Type 3 RYRs are found in skeletal and smooth muscle and to a lesser extent in the brain. The function of RYR1 is modified by other proteins and by the redox state of the cell ***(Protasi et al., 2009)***.

Calcium released from the SR combines with troponin, allowing cross-bridges to form between actin and myosin filaments and muscle to contract. When the wave of depolarization ceases, calcium ions dissociate from troponin and are removed from the sarcoplasm by adenosine triphosphate (ATP), requiring calcium pumps in the SR and other organelles. Thus, coupling of the excitation of the muscle membrane and contraction of the muscle cell entails changes in intracellular calcium concentration. Calcium increase in the sarcoplasm also initiates the breakdown of ATP and metabolic processes that support the energy needed for muscle contraction (e.g., glycolysis) ***(Protasi et al., 2009)***.

Properties of DHPR and RyR1

DHPR is major component of the transverse tubular membrane. It contains α_1, α_2/δ, β, and γ subunits, forming an L-type channel protein that is the receptor for certain Ca^{2+} channel blockers such as dihydropyridines. The $\alpha 1$ subunit forms the Ca^{2+} ion channel, the voltage sensor for channel gating and the DHPR binding site. It is comprised of 4 repeat domains connected by large cytoplasmic loops. The functions of the other subunits are less-well defined, although it is known that the β subunit is required for targeting the DHPR to the tubular membrane ***(Protasi et al, 2002)***.

Although the α_1 subunit mediates slow (L)-type Ca^{2+} inward currents, it has been known since the 1970s that Ca^{2+} entry through the Ca^{2+} channel is a late event in excitation–

contraction coupling. This is in marked contrast to heart muscle, which has led to the conclusion that the voltage sensor of the α_1 subunit, not the Ca^{2+} channel function, is the key component in excitation– contraction coupling of skeletal muscle. Although the precise mechanism for excitation–contraction coupling remains unknown, current concepts suggest that membrane depolarization causes a conformational change in the DHPR that opens the SR Ca^{2+}release channel. This precedes the slower opening of the L-type Ca^{2+} channel ***(Protasi et al, 2002)***.

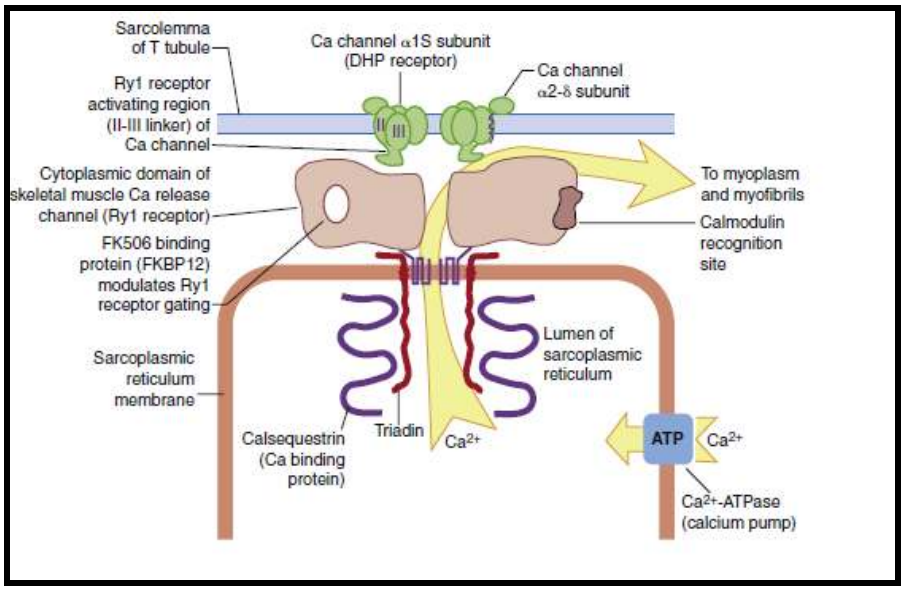

Figure (2): Schematic representation of the triadic junction of skeletal muscle shows the junctional foot protein (ryanodine [Ry1] receptor) and its associated proteins. In skeletal muscle, the α1S-subunit of the dihydropyridine receptor (DHPR) participates in excitation-contraction coupling. These physical links transmit essential signals across the narrow gap of the triadic junction that activate the Ry1 receptor and release Ca2+ from the sarcoplasmic reticulum ***(Pessah et al., 1996).***

Electron microscope studies reveal that the RYR1 and α_1 subunit of DHPR have a highly specific spatial association in skeletal muscle. Clusters of 4 evenly spaced particles (tetrads) representing DHPRs are positioned in the sarcolemma such that each particle is located immediately above 1 of the four RyR1 subunits. However, DHPR tetrads are associated with only every second subunit of RyR1, suggesting that not all release channels are directly coupled to DHPRs. Release channels that are not opposed by tetrads are most likely activated by Ca2+ release channels via Ca2+-induced Ca2+ release (CICR). Available evidence suggests that there is a direct physical coupling between the II and III loops of the α_1 subunit of the DHPR and multiple cytoplasmic regions of the RYR1 ***(McCarthy, 2000)***.

RYR1 belongs to intracellular Ca2+ channel superfamily that includes two other RYR isoforms. All three isoforms have tissue-specific expression and share a high degree of homology (70%). The name ryanodine receptor came from its affinity to bind to the plant alkaloid of the same name ***(Meissner, 2002).***

A hallmark of the disease at its early stages is increased membrane permeability and leakage of intracellular components, including creatine phosphokinase out of the cell and extracellular ions (including calcium into the cell). Traditionally, the absence of dystrophin has been thought to render the sarcolemma fragile and susceptible to rupture with contraction and that this accounts for the increased membrane permeability. Recently, however, this mechanism has been

called into question, and evidence has suggested that the disease alterations in channel function in the early stages lead to an increase in intracellular calcium, which activates proteases and reactive oxygen species ***(Lerman, 2011)***.

Untreated boys become wheelchair dependent by 12 years of age and die in their late teens; however, advances in management have significantly improved life expectancy and quality of life ***(Eagle et al., 2007)***.

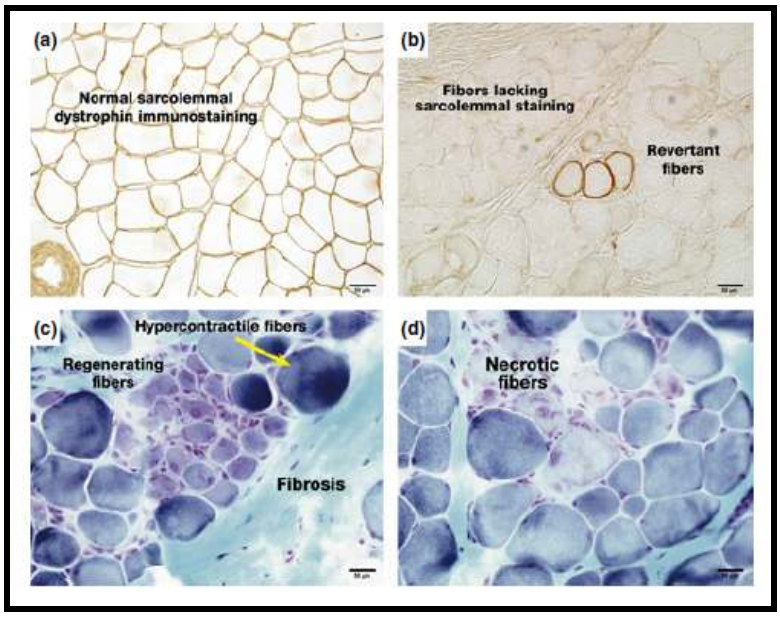

Figure (3): Dystrophin rod domain immunostain from a control muscle shows a normal sarcolemmal immunostainingpattern. (b) Dystrophin immunostain from a Duchenne muscular dystrophy (DMD) specimen shows the complete absence of sarcolemmal staining in muscle fibers, except for three dystrophin-positive (revertant) fibers, which is characteristic of DMD . (c,d) Sections from a DMD musclespecimen. Note the clusters of regenerating fibers with more basophilic & larger nuclei, (panel c), necrotic fibers with pale cytoplasm and indistinct nucleus (panel d), and hypercontracted fibers (panels c and d) ***(Segura et al.,2013)***.

Diagnosis of DMD

The aim of care around diagnosis is to provide an accurate and prompt diagnosis, allowing initiation of appropriate interventions, continuing support and education, and minimising the length and impact of a potentially protracted diagnostic process. Diagnosis should be done by a neuromuscular specialist who can assess the child clinically and can rapidly access and interpret appropriate investigations in the context of the clinical presentation. Family follow-up and support after diagnosis will often be augmented by support from geneticists and genetic counselors ***(Bushby et al., 2010).***

When to suspect DMD

Suspicion of the diagnosis of DMD should be considered irrespective of family history and is usually triggered in one of three ways: (1) most commonly, the observation of abnormal muscle function in a male child; (2) the detection of an increase in serum creatine kinase (CK) tested for unrelated indications; or (3) after the discovery of increased transaminases (aspartate aminotransferase and alanine aminotransferase, which are produced by muscle as well as liver cells) ***(Parsons et al., 2004)***.

The diagnosis of DMD should thus be considered before liver biopsy in any male child with increased transaminases. Initial symptoms might include delayed walking, frequent falls,

or difficulty with running and climbing stairs. Although DMD is typically diagnosed at around 5 years of age, the diagnosis might be suspected much earlier because of delays in attainment of developmental milestones, such as independent walking or language; such delays have been documented prospectively by following patients with DMD identified by newborn screening ***(Parsons et al., 2004)***.

Screening With Creatine Kinase (CK)

CK is a good screening test for muscle disease in clinical practice because levels rise in conditions with active muscle fiber necrosis and injury. In DMD patients, CK levels are usually very elevated and are between 5000 and 150 000 IU/L (normal is less than 200 IU/L). Reversible causes of elevated CK include drugs, trauma, crush injury, recent bacterial/viral infections, and hypothyroidism. However, the CK elevation in these circumstances rarely approaches that of DMD. Newborn screening using CK levels is not done routinely, and such screening has been restricted to research settings because of limited data on the impact of early diagnosis and initiation of (steroid) therapy in DMD ***(Kemper & Wake, 2007).***

Clinical Features

Infant boys with DMD are often asymptomatic. Although the clinical manifestations may be present by the end of the first year, first symptoms are usually noted during the toddler and

preschool years (2-5 years). In spite of increased awareness, there is an average delay of 2.5 years from the onset of symptoms, and mean age of definitive diagnosis is 5 years ***(Ciafaloni et al., 2009)***.

Affected children usually present with gait problems (waddling, toe walking, and lordotic posture), calf hypertrophy, positive Gower's sign (difficulty arising from the floor, spreading their legs, and using their hands to climb up their thighs to help them to an upright position), and difficulty climbing stairs. Approximately 60% of patients will have pseudohypertrophy of the calves, and 30% will have macroglossia ***(Bushby et al., 2010)***.

Pediatricians should be aware of the importance of having preschoolers get up from a sitting position on the floor, walk, and run so as to detect early signs of muscle weakness. Motor status may appear to plateau between 3 and 6 years; deterioration begins between 6 to 8 years. Affected children lose the ability to climb stairs and rise from the floor and also develop Achilles tendon contractures. They may be able to self-propel for some time and maintain posture, but lordosis and scoliosis become obvious. Between ages 9 and 12 years, the majority of DMD patients become wheelchair bound. Upper limb function is preserved until a later period ***(Bushby et al., 2010)***.

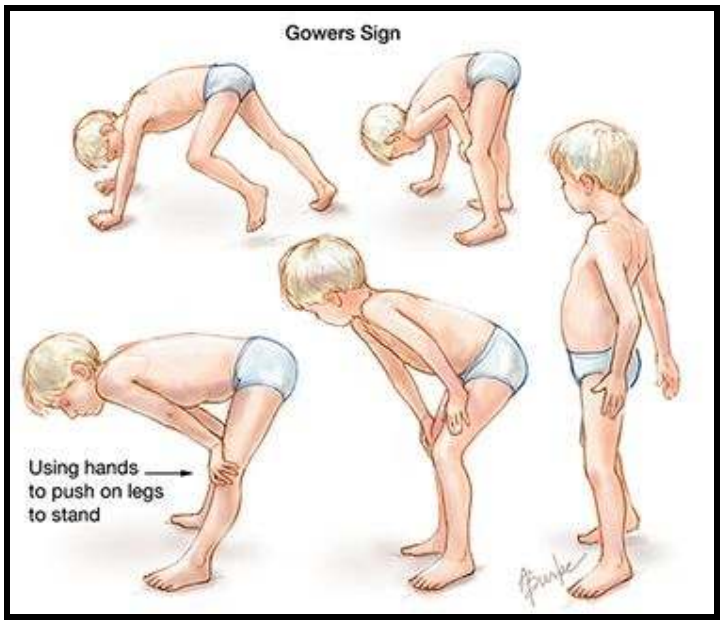

Figure (4): Gowers' sign ***(Punnoose et al., 2011)***.

Decreased pulmonary function as a result of respiratory muscle weakness and chest deformity (kyphoscoliosis), along with respiratory infections, predisposes to respiratory failure ***(verma et al., 2010)***.

Additionally, they are vulnerable to upper airway dysfunction and sleep apnea ***(Lerman, 2011)***.

Cardiomyopathy occurs in nearly all patients with DMD. Dystrophin is present in cardiac muscle cells, and the degeneration of cardiomyocytes results in fibrosis. This fibrosis initially affects the posterobasal segment of the left ventricle, which leads to increased myocardial wall stress and a progressive decrease in left ventricular systolic function that