Duchene muscular dystrophy (DMD) is a neuromuscular inherited disease which deal with X-linked occurs due to mutations in the dystrophin gene. The characterisation achieved by progressive muscle weakness in all over the body specially in legs and arms and wasting due to the absence of dystrophin protein which further causes degeneration of different types of muscles such as skeletal and cardiac. Gene mutation is one of the major causes for Duchenne muscular dystrophy located in cytoskeletal protein dystrophin. The diagnosis can be start up with careful review of the physical condition, history and examination of body organs and developmental delay, proximal weakness in muscles, and elevated biochemical compound serum creatine kinase, plus other confirmatory test like muscle biopsy or genetic testing. To improve the life expectancy of patient the early use of exercises, diet & nutrition management and other supportive strategies has been implemented. Moreover, uncontrolled condition can be treated with gene therapy with the use of plasmids or viruses, mutation and short DNA fragments can be corrected, oligonucleotides are first line treatment for exon skipping of mutations. Myoblasts or stem cells replacement therapy can be apply to reproduction of muscles.

**Keywords:** Duchene muscular dystrophy, dystrophin, gene mutation, muscles wasting and stem cell.

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**INTRODUCTION**

DMD is a disease which currently affecting 1 in 3600-6,000 in newborn baby (boy) associated with X-chromosome. Disease firstly characterized by weakness in the muscles. It is abnormal gait so it’s indicating through positive Gowers sign.\(^1\) Similar symptoms also seen in calf muscle disorder (posterior compartment of leg) and examined by the serum creatinine kinase level. Generally DMD disease patient show effects around in 5-6 years of age and after this year symptoms become more severe. DMD has been mostly affect on cardiac muscles or Respiratory systems but its effect commonly watched in boys.\(^2,3\) After 13 years of age patient usually stopped walking and if condition is not treat on time then both cardiac system and Respiratory system get infected and dysfunction.\(^1,2\) DMD is a genetically and muscular atrophy progressive disease. Prevalence of diseases estimate in population is 1.8-4.8 per 100,000.\(^4,5\)

DMD is mostly common observe in childhood age of patient. However, found in new born baby also and abnormalities are attached with X-chromosomes. Generally cause by mutation in the protein specifically at X-chromosomes on dystrophin gene.\(^6\) Dystrophin is a rod shaped cytoplasm protein. Present within innar surface area of muscle membrane. Some symptoms like delayed the speech, patient never running properly, weakness of hip, shoulder gridles muscle lead and pseduohypertroph of calf muscle in this disease.\(^7\)

DMD & BMD both are mostly common inherited and neuromuscular disease and denoted with gene expressed by Xp21. Dystrophin gene deletatin are found in 55% of patient with BMD and 65% of Patients of DMD,
respective.8 Identification carried by performing Genetic testing through PCR (polymerase reaction) and other Dystrophin level estimated tests.9 Muscle biopsy demonstrates the degenerating muscle fibers are present in the form of clusters. These necrotic fibers placed nearby macrophages and another one is CD4 lymphocytes cells.60 Figure 3.

CAUSES

Duchenne muscular dystrophy is caused by completely absence of dystrophin protein in muscle and found in sarcolemma of muscle fibers and it's divided in 4 parts i.e. The Cerminal domain- it's common for joints others proteins in membrane it’s called the dystroglycan complex, The Rod domain, The Cystein rich domain and N terminal domain.11,12 These all types of domains bind with actin and postulated that dystrophin is essential to transudate of the contractile required to outside of cell matrix. Additionally, DMD caused by muscle fibers or completely absence of cytoplasm protein and further lead to damage to mechanical scleroma or loss of calcium level in body or loss of the muscle fibers.13,14

Figure 1: Numbers of theory which further develops DMD in patient.

PATHOGENESIS:-

There are mainly three types of theories for define the pathogenesis of Duchenne muscular Dystrophy. The cumulative evidence suggested that abnormal microvascualur and muscle surface is mostly common but not yet proven.

The vascular theory –

Firstly in 1996 a theory revived and suggested that adequate blood flow might account for generation of Dystrophy muscle. Found that slowed circulation in arm to tongue in patients can occur by Duchenne muscular Dystrophy.15 (As per figure 1) Some new suggestion that abnormalities of catcholamine metabolism due to oxidation in platelets and platelets report showing abnormal and uptake serotonin also. In fluorescence observe the dystrophy muscles accumulation of catecholamine observe by ceroscopy. Other examination depicts Muscle lesions, ischemia at chronic stage.16

The Neurogenic Theory

The muscle Dystrophy pathogenesis firstly cleared within last half in 19th century. Some other patient with DMD disease went from post-martam pathology and there report shows burnt of anatomical changes in spinal cord which reveal the“ spinal muscle Atrophy”.17 The dystrophies was separate by another myopathies the basis of heritable transmission. Regarding these all reasons Neurogenic theories to be fading but this type of issue in not closed.18 In muscle dystrophies generally affected on metabolic disorder of hypothyroidism of spinal cord in the deficiency of vitamin B12 and then cause the pernicious anemia, this principle also cleared at the same time.19

Membrane and muscle disease

These both types of theories (Neurogenic and vascular) is still required some special technique to understand pathogenesis and to perform other biomedical tests and genetics test to clear the concept.20,21 These type of different technique identify the abnormalities occurs in biochemical changes and all genetic problems related to protein abnormality. DMD genetic disease are caused due to an anomalous protein or abnormality of protein in side our body.22,23

Duchenne Dystrophy

Previous observation recognized abnormality of biochemical in Duchenne Dystrophy increased excretion of creatinine, there was no overt abnormality of metabolic patterns within muscle. So mechanism of the abnormality not fully elucidated. Suggest that there is decrease value of creatinine in muscle with degenerative condition such as amyotrophic lateral sclerosis but there is impaired “trapping “ inside the cells compound in Dystrophy muscle.24-26 In DMD serum enzymes and proteins arise from muscle which further increased serum activity and decreased in muscle.27

Figure 2: List of path physiological reasons to cause DMD diseases.

PATHOPHYSIOLOGY

Muscle fiber Necrosis:-

Mechanical Hypothesis- Early estimation of muscle Dystrophy (as Delta lessons) and decreased level of muscle enzymes in DMD patient with sample of muscle fibers.28 Dystrophin is a type of protein present in muscles in the form of protein complex. (Figure 2) In view of absence, any one type of protein in muscle leads to muscle membrane loss integrity of the fibers. This research has led to the emergence of the exercise and important implications for managed.29,31

Calcium Hypothesis:-

Certainly, it is a critical aspects of muscle function documentation of calcium accumulation and fibers in muscle Biopsies of DMD patients. As concern with pathophysiology, the increase influx of deficiency of Dystrophin membrane has been demonstrate in DMD patient.32,33

Vascular Hypothesis:-

DMD is early affected in clusters and necrotic fiber’s play important role of the Muscle vasculature in pathophysiologic hypotheses postulated. However structural studies have revealed no blood vessealmalaties observed.34,35 Nitric oxide is present in skeleton muscle and production started in muscle cells by the isform which
leads to floating freely in cytoplasm and slowly reduced.36,37

**Gene Regulation Hypothesis:-**
Play vital role in membrane stabilization and in DMD involved the complex of protein and in other process such as mechanism of transduction muscle activity related gene expression.38 Dystrophin associated and make the complex related to absence of Dystrophin proteins result in various genes. Interestingly the injection of stem cells into Dystrophin deficiency muscle is not only partially dystrophin protein complex but also restores physiology gene expression.39

**Tissue Remodeling:-**

Tissue remodelling based on the several observation and put emphasis on secondary features of Dystrophin deficiency, for instant – Null mutation of Dystrophin produce early onset action like progressiveness of disease in body.40,41 (Figure 2) For DMD treatment anabolic steroidsis counted as good since it protecting muscle mass. Other medicines like Methandrostenolone or Norethandrolone cause initial gives modest improvements but accompanied by androgenic side effects.42,43

**Inflammatory Hypothesis:-**

In DMD patients consistently exhibit inflammatory changes in muscles. That cases activities the numerous components of chronic inflammatory response including cytokine and cytokine signaling, Leukocyte adhesion, cell types specific markers and complement system activation.44-46 In DMD most commonly used drug is corticosteroids and provide the anti inflammatory effects. Deflazacort an oxazoline derivate of drenisolone, these also give similar effect but with observing loss in weight gain.47

**Diagnosis, Management and Treatment:-**

DMD diagnosed of care and provide an accurate and prompt diagnosis, allow the initiation and appropriate interventions continuing support and education and minimize the length. Diagnosis should be done by neuromuscular specialist. Mention all parameters in figure no. should be followed to diagnose the disease. Similarly many points are there to manage and treatment of DMD also given to cure this disorder.48-50

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**General Parameters:** family History, observation abnormal muscle functions, creatine kinase test, biopsy, Screening test and Gower’s sign.

**Neuromuscular and skeletal assessment:** Clinical evaluation of strength function and ROM (Range of Motion).

**Physical Examination:** abnormal gait, clumsiness, flat feet, late walking, Weakness in hip muscles, sway back, belly stick out, foot drops, Knee bend back, Shoulder and arms held back, week butt, Thick lower leg muscles, tight heel cord, tip toe contractures, poor balance, fall often intervals, week and thin thighs, poor muscles in sit-ups.

**Laboratory test for DMD and BMD:** serum creatine, Creatinine kinase, AST, ALT, Ca, Vit D, Dystrophin protein, Chromosomal study and PCR.

**Confirmation of the diagnosis:** Blood Testing, Dystrophin mutations test, Genetic testing, PCR and further tissue processing.

**Psychosocial management:** psychosocial difficulties, if observed in DMD should be treated with the same effective evidence-based interventions.

**Respiratory management:** monitoring of Respiratory muscle function, assisted coughing and subsequent day time ventilation.

**Cardiac management:** cardio exercise, Walking regularly or jogging, low cholesterol contain diet in take, A proactive strategy of early diagnosis.

**Bone health and osteoporosis management:** Maximising bone mineralization, dietary intake Ca and Vit D, Physical activity. Bisphosphonate therapy, some cases steroid dose equivalences used, prescription of osteoporosis therapy, mitigating osteoporosis progression, medicine like deflazacort and antiresorptive therapy.

**Diet and nutrition:** take prenisone, low-calorie diet under special cases, diet high in fluids and fiber, More dietary calcium and vitamin D

**Drugs:** Glucocorticoids like prednisone and deflazacor, Immunosupression like azathiprine, Vitamin D tablets or capsules. Anti-inflammatory drugs: Givinostat, Fluvocoid, Antiobiotic drugs: Losartan and Lisinopril. Treatment of muscle ischemia drugs: Phosphodiesterase 5 inhibitors i.e. tadafali and sildenafil.

**Exon Skipping:** uses synthetic antisense oligonucleotide sequences to correct specifically dystrophin gene mutations. Exon 53, Exon 51, Exon 45 & Exon 44.

**Surgery:** Sciosis surgery correct the sciosis in order of spinal instrumentation and prevented further deformity. Foot Surgery: surgery correct for various foot deformities.

**Nanoparticles as Delivery System for DMD Therapy:** Liposomes and polylactide.

**Cell Therapy:** replace dystrophin for a potential cure e.g. Mesangioblasts & myogenic vessel-associated stem/progenitor cells.

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**Figure 3:** The table depicts the possible diagnosis for DMD disease, the various parameters need to follow before comes to any conclusion of result. Further, the different ways to taken as a part of management of disease which have lists of techniques to provide relaxation of symptoms and management of DMD. At the last the different approaches to cure the DMD somehow cannot cure the diseases completely but initial diagnosis can help to reduce the further development of disease in body.
CONCLUSION

Early recognition and precise genetic diagnosis will allow for individualized therapeutic options for DMD. Even though there is presently no cure, respiratory intervention and other supportive strategies as outlined in the current standard of care for DMD have led to improved survival and better health-related quality of life for many affected individuals. New emerging treatments will depend on the appropriate use of clinical end points and sensitive surrogate outcome measures such as muscle MRI and circulating biomarkers to detect meaningful changes in disease progression.

REFERENCES: