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A Review of Duchenne Muscular Dystrophy: a progressive muscle degeneration

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ABSTRACT:

Duchenne muscular dystrophy is a neuromuscular ,x linked inherited disorder occur dueto mutation in dystropingene. It is mainly occur due to progressive muscle wasting and weakness .It mainly causes degeneration in skeletal and cardiac muscle due to the absence of dystrophin protein . The molecular diagnostic of duchenne muscular dystrophy contains a deletions/duplications analysis which was mainly done by quantitative technique includes microarray-based comparative genomic hybridization (array-CGH)and Multiple Ligation Probe Assay MLPA. Traditional methods for detection of point mutations and other sequence variants require high cost

Keywords: dystrophin; molecular diagnosis and DMD therapy.

INTRODUCTION:

The most world wide , prevalent and a neuromuscular disorder is duchenne muscular dystrophy which was affect up to birth[1]. It is caused by dystrophin gene mutation and on the X chromosome mutation so at birth clinical signs are not present .[2] The average age of diagnosis is usually at four years, when the first symptoms appear [3]. The disease was progresses very quickly and the life expectancy has also been significantly extended by using corticosteroid treatment and higher standards of medical care such asartificial respirators, but the use of this lead to die for cardiac and respiratory complications .[4] DMD patients was develop a severe cardiomyopathy that generally manifests at about 10 years and the prevalent in most patients was by 20 years of age[5]. Becker muscular dystrophy (BMD) is the milder form of dystrophinopathy, with an incidence of one in 18,518 male births. BMD typically presents later than DMD, between the ages of 5 and 15 years and the severity or course was varies among in patients.[6]Dystrophin gene was the largest gene described in human and it contain a full length messenger RNA is mainly seen in skeletal and cardiac muscle, and also, in small amounts, in the brain. The DMD gene produces three full-length isoforms, through it has three independent promoters, in brain, muscle, and Purkinje cerebellar neuron, but many other isoforms are mainly generated by alternative splicing events [7]. In healthy muscle, the dystrophin protein is seen on the intracellular surface of the sarcolemma it made assembly with the dystrophin-associated glycoprotein complex (DGC), presents on plasma membrane of myofibers (8). The dystropin associated complex is mainly formed by(dystroglycan, sarcoglycan, and neuronal nitric oxide synthase).[9] The important function of dystrophin in the muscle is stabilizes the fibers during contractions by binding to F-actin with N-terminal domain and to β-dystroglycan with C-terminal domain,and acting as abridging and anchoring protein .(10) DMD disease ismainly associated with mutations as deletions (65%), duplications (6%–10%), small mutations (10%), or other smaller rearrangements that mainly interrupt the open reading frame of RNA. [11]Due tothese mutations lead to a loss of dystrophin protein expression resulting in a severe muscle wasting, respiratory and cardiac failure and death before the age of 30 [12].

EPIDEMIOLOGY

These are x linked disorder which are affecting up to 5,000 in 1 and to in 6,000to 1 live male births5–7. The prevalence of DMD is low level than 10 cases per 100,000 males and seems to be the sameand between the regionsof 6–8. By the prevalence of DMD is less than 8 cases of per 100,000 live in male births is 7.[10]

DMD has made an improvement of time; france astudy found that the median lifebirth rate was 25.77 years for those born before 1970 and 40.95 years for those born after 1970 DMD in females is rare (<1 per million) and is low cases reported of individuals with Turner syndrome10–12.[11]

DIAGNOSIS:

Diagnosis of muscular dystrophies requires a medical history, particularly the distribution of weakness, age of onset, family history, and diseasespecific features[13]. A physical examination needs to document the distribution of weakness and atrophy (face, distal, or proximal or specific muscle groups), the presence of contractures and other specific features such as myotonia.[14] These findings together with investigations such as serum creatinine phosphokinase, electromyography, and muscle biopsy may direct testing toward a specific genetic diagnosis[15]

PATHOGENESIS

Formation of dystropin associated protien complex

Duchenne muscular dystrophy (DMD) can be explained by a one mechanism the disease can account for various symptoms in different systems. Muscle tissue is mainly for contraction and forms movement of body , pumping blood and ventilation. Contraction activity generated a mechanical stress that if not managed properly, will affect the muscle. The failure to management of muscle activity-induced mechanical stress which constituteted a theme in pathogenesis of DMD. Several lines are the proof tosuggested the main involvement of activity of muscle in the initated and progressed form of muscle disease in DMD.. Dystrophin expression patterns and it associated protein complex (DAPC) composition is the point to the important activity of muscles.The important is dystropin which help in the interaction of cell membrane and matrix.The correlation of genotype and phenotype is mainly gene mutation ,pathology and dysfunction.,the cells are correlated with this. The calcium and magnesium mainly it deposited in muscle cell during in DMD , due to deposition in cells lead an decrease in the level of magnesium[32]

Effect of calcium influx

In this mainly an acute membrane damage which lead to calcium influx and it deficiency also associated to proteins .Then the dendric cell lead to connective tissue changes they are grouped together to necrosis. And then regeneration in ,alternative linkages lead to failure in

regeneration ,deficiency in associated proteins lead to defect in myofibrin and ecm linkage .There is defect in synapse stabilization ,then mainly calcium influx lead to loss in it homeostatsis and in filteration in macrophage produce toxic effects,dendric cell and mast cell also lead to this loss of calcium.The calcium influx is in the presence of adenyl cyclase lead to energy and mitochondrial function and it metabolism[32]

Death of muscle fibres

The Dystropin is mainly made linkage to the cytoskeleton of muscle fibres in underline basal lamina,Dystropin absence permitting to more amount of calcium to sarcolemma leading to dysfunction in mitochondria. It gives the amplication of calcium signals and is reactive in oxygen induced species and lead to the production of ros.Then lead to death in cell . Damaging to sarcolemma also producing death in the cell then that muscle fibres are replaced with connective tissues[31]

MANAGEMENT:

Glucocorticosteroid

The gold standard therapy ofDMD progression is based on corticosteroids, it was the first therapy in 1974 and tested in several trials to get the optimal dose, age of initiation and frequency [16]. At present, the corticosteroids are the only pharmacologic agents which has provenbenefits, but are associated to several adverse effects (weight gain nervous system disturbance, gastrointestinal symptoms, metabolic disorders, osteoporosis with increased risk of vertebral fractures).[17] The two corticosteroids mainly used in DMD treatment are Prednisone/Prednisolone and Deflazacort, an oxazoline derivative of prednisolone, administered by two common regimens: daily and intermittent.[18] The three regimens in most common use are 0.75 mg/day prednisone, 0.9 mg/kg/day deflazacort, and 0.75 mg/kg/day prednisone for 10 days on and 10 days off .[19] Both drugs have been equally effective in the short-term treatment trials (six months to two years), which is mainly improving muscle strength and function and presenting adverse effects not considered clinically severe .[20] and a general amelioration of quality of life, have been observed after treatments for longer than two years with prednisone or deflazacort [21]. The mechanisms of action of corticosteroids in DMD, although not yet completely known. Prednisone and prednisolone show an anti-inflammatory effect[22]

Cardiac care management

It includes mainly DMD associated cardiac insufficiency can be treated with ACEinhibtors and beta blockers ACE provides a prophylactic and it delay onset of cardic symptoms,treatment of DMD cardiac manifestation including mainly the early investigation of the symptoms related arrhythmias and insufficiency can be assessed by diagnosing every year. This investigation made should be included a physical examination,mainly electrocardiography, echocardiography or, when possible, MRI of cardiac. After the onset of these cardiac symptoms, the frequency of examination should increased at the discretion of the cardiologist[23,28]

Gene Therapy

A Important management for most muscular dystrophypatients is the gene therapy here a therapeutic gene is injected to cardiac muscle and skeletal muscle mainly for the, restoreation of the protien called dystrophin. The dystrophin gene, , is large than a adeno-associated recombinant virus , the s vector for the selection of DMD gene is the iinjectability due to it can persistence in the muscle and pathogenicity is the absence. Due to this , a -size reduced dystrophin version based on this , in DMD patients, a dystrophin leads a phenotype mild has been developed [29,30]

Cell therapy

Cell based-therapies is mainly to made acure andit replace dystrophin and stem cells is the approached management of DMD and confident regenerationof mucle for their capacity to self made and differentiate into various cell types [31]

Neurodevelopmental and neuropsychological management.

For the treatment of neuropsychological disorders in patients with DMD.Patients with DMD patient has a great incidence of cognitive impairment, an attentioncompared to other population,hyperactivity disorder, autism spectrum disorder, anxiety and obsessive-compulsive

disorder is seen. A neuropsychological investigation is made should be is considered for the diagnosis of DMD but is important when concered about arise of developmental progress . Educational support may be required and as a results of test for neuropsychological , which are increased and performed as part of care. The treatment of hyperactivity disorder or other behavioural or psychiatric problems is based on the symptoms and followed a guidelines for the management of these disorders in the general population. A research for improving the knowledge of these DMD and mainly to made a guidelines to monitor identify and treat the manifestations is important as they have a major effect on outcome and quality of life of both the families.of patients[30]

Respiratory Care

During DMD mainly there is obstruction in airway and a cough is produced that can managed by giving a care to respiration. Here a positive pressure is giving in this and maintain adequate ventilation[29]

Orthopediac management

Due to DMD muscle weakness and it function is loss ,osteoporosis can be developed this all can be managed by this therapy[31]

Endocrine management

Due to this mainly an adrenal insufficiency and deficiency of endocrine hormone this all cand managed by using this therapy insufficiency here mainly it provide a replacement therapy and provide adequate growth[32]

Gastrointestinal management

The main aim is to provide fluid balance and provide nutrition in DMD condition all may be developed as a complication such as fluid imbalance and loss in nutrition[28]

CONCLUSION

Duchnee muscular dystrophy is a neuromuscular disorder caused due mutation in dystropin gene .The standard golden treatments Include glucocorticoids,such as prednisolone show anti-inflammatory effect and also certain orthopediac ,gastroinstestinal ,repiratory care,endocrine therapies and gene therapy can be done

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