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MUSCULAR DYSTROPHY - HOPEFUL FUTURE !

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ABSTRACT

Muscular dystrophy refers to a group of genetically determined, progressive disorders with distinctive genotype and phenotype. Muscular dystrophy weakens musculoskeletal system and affects locomotion. Duchene muscular dystrophy (DMD) is the most common muscular dystrophy with X-linked recessive inheritance and characterized by severe muscle wasting resulting in muscle degeneration with early confinement to wheel chair and premature death (around 20 years). The disease is caused by mutation in DMD gene present on short arm of X chromosome at Xp21which codes for cytoskeleton protein "dystrophin". *DMD* is present since birth, but manifests between 3-5 years of age. Progressive weakness of proximal limb muscles (especially leg) and pelvis is observed. Gower's sign is positive. Becker's muscular dystrophy (BMD) is clinically same as DMD but is less severe. The dystrophin produced is in insufficient amount or altered in size which causes instability of sarcolemma. Limb girdle muscular dystrophy may have autosomal dominant or autosomal recessive inheritance and known as sacroglycanopathies. Emery-Dreifuss muscular dystrophy is associated with mutations in genes at Xp28. Congenital muscular dystrophy is associated with hypotonia and weakness of proximal muscles at birth or in few months after birth. Facioscapulohumeral dystrophy witnesses near puberty. In myotonic dystrophy smooth muscles, skeletal muscles, neurological, endocrinal and ocular involvement is observed. Physiotherapy, cycling and walking to be encouraged with avoidance of immobilization. Orthopedic braces are used to improve mobility. Though muscular dystrophy is rare but morbid condition, use of corticosteroids and other modalities like genetic interventions and prenatal diagnosis showed some hope. Despite giving all modalities of treatment patients of dystrophy ultimately meet their fate.

Key Words: Duchene muscular dystrophy(DMD), Becker's muscular dystrophy (BMD), Dystrophin.

INTRODUCTION

Muscular dystrophy refers to a group of genetic ally determined, progressive disorders each with unique genotypic and phenotypic features. Muscular dystrophy weakens musculoskeletal system and affects locomotion. Common clinical features of the muscular dystrophies include delayed development of motor milestones, defective locomotion, frequent falls, fatigue, difficulty in climbing up and running, difficulty in getting up from floor, imbalance, waddling gait, weakness of pelvic girdle muscles, scoliosis (3-dimensional sideways deviation of spinal axis), muscle wasting, spasm of pelvic girdle muscles, ocular symptoms like drooping of eye lid, muscle atrophy and recurrent pulmonary infections.

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Muscle dystrophies are genetically classified as

1. ***X-linked recessive-*** Duchene muscular dystrophy, Becker's dystrophy, Emery –Dreifurs muscular dystrophy.
2. ***Autosomal recessive-*** Limb girdle muscular dystrophy (LGMD 2A-H), Congenital muscular dystrophy.
3. ***Autosomal dominant-*** LGMD 1A-C, Facioscapulohumeral dystrophy, mytotonic dystrophy.

Duchene muscular dystrophy (DMD) is the most common fatal genetic disorder diagnosed in childhood, with a sex-linked inheritance pattern of one in 3500 live

male births. (Emery E, 1995). This is X-linked recessive severe muscle wasting disorder resulting in degeneration of muscles with early confinement to wheel chair and premature death (around 20 years) and named after French neurologist *"*Guillaume Benjamin Amand Duchenne*"*. X-linked recessive disorder affects males and females are carriers, but can be diseased if one normal allele is lost as in turner's syndrome. The disease is caused by mutation in DMD gene present on short arm of X chromosome at Xp21. The gene codes for a 427 kDa cytoskeleton protein "dystrophin" localized to inner aspect of sarcolemma. DMD gene is one of the largest (>2000kb) human genes identified. Most common mutation is deletion which affects 60% individuals. 5% have duplication and rest 35% possess point mutations. Dystrophin is a component of dystrophin-glycoprotein complex which stablizes sarcolemma. This complex forms a linkage between cytoskeleton of each muscle fiber and extracellular matrix. Expression of dystrophin is seen in skeleton muscle, smooth muscle, peripheral nerves, brain and various other tissues. Deficiency of dystrophin allows extra calcium to penetrate sarcolemma which leads to mitochondrial dysfunction and cell death. Repeated cell death and regeneration ultimately leads to exhaustion of cell in DMD. In a study it was shown that the genetic causation of DMD was established by localization of candidate complementary DNAs (cDNAs) to the short arm of the X chromosome (Xp band 21.2) (Monaco AP *et al.*, 1986), which led to full characterization of the 2.5 Mb DMD locus and corresponding 427-kDa dystrophin protein as observed in a study (Hoffman EP *et al.*, 1987). In a study in 1987 it was observed that the sheer size of the resulting 14-kb dystrophin messenger RNA transcript served to explain how one-third of DMD cases arise from spontaneous new mutations (Koenig H *et al.*, 1987).

Becker's muscular dystrophy (BMD) is a clinically similar but less severe form of myopathy affecting 1/30,000 males (Koenig *et al.*, 1989). This X-linked recessive disorder presents with later onset and slow progression. BMD is named after a German doctor "Peter Emil Becker*"*. This is caused by mutations in DMD gene present on short arm of X chromosome at Xp21. The dystrophin produced is in insufficient amount or altered in size which causes instability of sarcolemma. A study showed that intragenic deletions appear to be the most common gene defect leading to DMD or BMD (Forrest SM *et al.*, 1987). On the basis of analysis of a limited set of deletions, Monaco AP and others proposed that DNA deletions resulting in clinically less severe BMD bring together the exons which maintain the translational reading frame of mRNA. These deletions should allow the production of an internally deleted dystrophin protein which may be at least partially functional. Conversely, deletions resulting in the more severe DMD bring together exons that disrupt the translational reading frame, which should result in the production of a severely truncated molecule. (Monaco AP *et al.*, 1988). Subgroup of patients between DMD and BMD who are considered as intermediates are known as outliers. Limb girdle muscular dystrophy (LGMD) is the muscular dystrophy which may have autosomal dominant or autosomal recessive inheritance and known as sacroglycanopathies. LGMD 2A-H is autosomal recessive in inheritance pattern and LGMD-1 shows autosomal dominant inheritance. Mutations in sarcoglycan genes or SG-genes (excluding ε-SG) leads to deficiency of sarcoglycans by damaging whole sarcolgycan complex. Emery-Dreifuss muscular dystrophy (EDMD) is an X-linked recessive muscular dystrophy in which mutations in the genes at Xp28 are seen at the end of long arm of X chromosome. The affected gene codes for emerin protein. Congenital muscular dystrophy (CMD) is associated with hypotonia and non progressive weakness of proximal group of muscles at the time of birth or in few months after birth. Facioscapulohumeral dystrophy (FSHD) witnesses near puberty. In myotonic dystrophy smooth muscles, skeletal muscles, neurological, endocrinal and ocular involvement is observed.

MATERIAL AND METHODS

A review study

Observations

DMD is present since birth, but manifests between 3-5 years of age. Child presented with clumsy and waddling gait on even surface and may fall during walking or running. The child experiences fatigue, frequent falls, difficulty in standing, running, jumping, climbing up stairs and getting up while playing. Progressive weakness of proximal limb muscles (especially leg) and pelvis is observed with loss of muscle mass. *Meryon's sign* is positive i.e child slips when lifted from under arms. By the age of 4-5 years calf muscles get hypertrophied. Patient is unable to raise the hand above the shoulder (e.g combing hair) which indicates weakness of shoulder girdle. Eventually weakness is experienced in upper limbs, neck and other areas of the body. Walking on forefoot and toe walking occur as an adaptation to weakness of knee extensors. Gower's sign named after "*William Richard Gowers"* is positive. This sign is diagnostic of DMD in which the patient turns to one side, supports his weight on arms, lifts the trunks and stands up as if walking on his own body. The characterstic distribution of pseudohypertrophied (calf muscles, glutei muscles, deltoid, tongue muscles, brachioradialis, serrati anterior) and hypertrophied muscles (pectoralis major, supraspinatus) is diagnostic. Delayed learning and impairment of cognitive functions is observed. Child presents with mental retardation and impaired speech. With further progression of the disease muscle wasting occurs. Muscle mass gets replaced by fibrofatty tissue and gets atrophied. By the age of 10 years orthopedic braces are required for walking and

patient gets confined to wheel chair by 12 years of age. Patient is predisposed to severe chest infections by 16-18 years. The patient presents with aspiration of food, sudden vomiting, abdominal pain, gastric dilatation and distension. Usually death occurs by age of 20 years. Severe pulmonary infections are the most common cause of death in DMD patients. Dilated cardiomyopathy, arrhythmia, congestive cardiac failure are cardiac sequalae of the disease. Emery A observed that the clinical course of DMD is progressive; muscle weakness by age 5 years eventually leads to loss of independent ambulation by the middle of the second decade and death during the third decade, primarily as a result of respiratory or cardiac complications. (Emery E, 1995). In *BMD* gradually progressive muscle weakness, toe walking, calf muscle hypertrophy, frequent falls and positive gower's sign are observed. Patients of BMD encounter the difficulties around 5-15 years of age. Patients have reduced life span, but survive up to 30-40 years. Mental retardation can also occur, but not as severe as in DMD. Koenig and others in 1989 classified patients as DMD or BMD depending on severity of muscle weakness. The age when patients became permanently wheelchair bound was the main clinical parameter used for classification, but for young patients the progression of muscle weakness was used. Patients wheelchair bound by age 13 years, as well as ambulatory patients between 8 and 13 years of age and with severe muscle weakness typical of DMD, were classified as DMD. BMD patients were those who remained ambulatory past the age of 15 years (Koenig *et al.*, 1989).

Creatinine phosphokinase (CPK) is increased around 20-100 times normal. CPK is elevated in earlier stages of the disorder due to leakage of CPK from the muscle fibers as a result of damage to sarcolemma. In a study it was observed that the affected individuals can be diagnosed at birth on the basis of elevated serum creatine kinase (CK), a biochemical marker of muscle necrosis, prior to visible difficulty in walking between 1 and 3 years of age.(Bushby K *et al*, 2010). Electromyography showed myogenic pattern. Reduced amplitude and duration of motor unit potential with increased frequency of polyphasic potential is seen. Muscle biopsy shows diffuse areas of necrosis and regeneration. Ultimately fatty tissue replaces the degenerated muscle. Involvement of Xp21 is detected by genetic studies. The mutations are more common in the initial and middle segment of the gene i.e mutations are not uniform over the gene. Absence of dystrophin can be shown by immunocytochemical staining muscle with dystrophin antibodies. Prenatal testing is done in fetus i.e is by chorionic villus sampling *(*11-14 weeks), aminocentesis (after 15 weeks), ultrasound scan (16 weeks) and fetal blood sampling (18 weeks). Western blot depicts alteration in molecular weight and quantity of dystrophin molecule. Lowered mutation rate is observed in mutation analysis in case of BMD as compared to DMD. In a study it was found that the combination of genomic deletion analysis and direct dystrophin analysis should give maximal diagnostic and prognostic accuracy, even before the onset of any clinical symptoms (Hoffman AP *et al.*, 1988). It was observed that in the future, routine detection of deletions could be carried out by the powerful technique of polymerase chain reaction (PCR) amplification (Saiki RK *et al.*, 1988).

LGMD is characterized by variable degree of muscle weakness in limb girdle. Hypertrophy of calf muscles is seen often. CPK levels are more in autosomal recessive form as compared to autosomal dominant form. Diagnosis can be confirmed by muscle biopsy. *EDMD* is characterized by weakness in proximal muscles of upper limb (scapulohumeral) and distal muscles of lower limb (peroneal muscles). In *CMD* neurological involvement is predominantly observed. Signs of dystrophy (increased endomyosial and perimyosial connective tissue with variation in fiber size) are seen in muscle biopsy. Western blot technique depicts absence of merosin. *Fukumaya CMD* is mainly seen in Japan and is characterized by seizures, mental retardation, cardiomyopathy and ophthalmological involvement. Before 10 years of age most of the patients become bed-ridden and maximum meet death by 20 years. *FSHD* is associated with involvement of facial muscles, shoulder girdle and proximal arm muscles. Weakness of scapular muscles leads to winging and elevation of scapula. Weakness of peroneal muscles and anterior tibial muscles causes foot drop. Patient of *myotonic dystrophy* presents with muscular weakness, stiffness, mental retardation, tented upper lip and cataract. Neonate faces difficulty in sucking and swallowing with delay in development of motor milestones. Eventually immunodeficiency and respiratory distress develop.

DISCUSSION

After diagnosing the type of dystrophy, physiotherapy, cycling and walking to be encouraged. Prolonged rest and immobilization to be discouraged. Orthopedic braces are used for active walking and to improve mobility. Exercise therapy is advised to reduce the contracture and deformity. Respiration is maintained by respiratory exercises, ventilators and antibiotics (for pulmonary infections). It is preferable to avoid fatty food to prevent obesity as obese persons are difficult to treat. Psychosocial support is a must. Corticosteroids like prednisolone (0.75mg/kg/day) slows progression of disease by 2-3 years and increases strength. Beta-2 agonists may be given to enhance the strength, but they do not alter progression of disease. Some researchers found that although standards of care are improving, with better quality of life and prolonged survival, there is no cure for DMD (Bushby K *et al.*, 2010). In a study it was observed that long-term corticosteroid treatment purportedly extends functional ability for up to 2 years (DeSilva S *et al.*, 1987) by modifying cellular events, including inflammation and

Ca^{2+} homeostasis; however, their relative nonspecificity also causes unfavorable effects such as weight gain and loss of bone density as observed in a study (Moxley RT *et al.*, 2005) and in a study in 2012 it was found that delivery of exogenous functional dystrophin is an attractive prospect to benefit all DMD patients (given the inconsequential nature of the endogenous mutation), and gene replacement is traditionally divided into viral and naked (nonviral) categories. (Perkins KJ and Davies KE, 2012). A study showed that a compensatory approach aimed at restoring components of the DAPC (discriminant analysis of principal component) involves increasing levels of utrophin, the autosomal paralogue of dystrophin. (Love DR *et al.*, 1989). In a study it was found that the utrophin-based up regulation therapy increases the ability to circumvent immunological challenges that accompany introduction of functional dystrophin protein; in principle, effectiveness for all DMD patients, regardless of gene defect (Fisher R *et al.*, 2001). In BMD, in addition to physical activity and prednisolone, intravenous immunoglobulin may be given for long term use, but high cost may be the limiting factor especially in developing countries. Anti myotonic drugs like phenytoin, procainamide, quinine can be given in myotonic dystrophy to decrease myotonia.

CONCLUSION

Though muscular dystrophy is a rare but morbid condition, use of corticosteroids and various treatment modalities like genetic interventions, prenatal diagnosis showed some hope. Despite all the modalities of treatment the patients with dystrophy ultimately meet their fate. Even then quality of life can be improved to great extent by various kinds of treatment plans.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

REFERENCES

Bushby K et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol*. 2010; 9(1): 77–93.

DeSilva S, Drachman DB, Mellits D, Kuncl RW. Prednisone treatment in Duchenne muscular dystrophy. Long-term benefit. *Arch Neuro*. 1987; 44(8): 818–22.

Emery A.Muscular dystrophy - the facts. *Neuromuscul dis*. 1995; 5(6): 521.

Fisher R et al. Non-toxic ubiquitous over-expression of utrophin in the mdx mouse. *Neuromuscul Dis.* 2001; 11(8): 713–21.

Forrest SM et al. Effective strategy for prenatal prediction of Duchenne and Becker muscular dystrophies. *Lancet.*1987; 2: 1294-7.

Hoffman EP et al. Dystrophin characterization in muscle biopsies from Duchenne and Becker muscular dystrophy patients. *New Eng J Med*. 1988; 318: 1363- 8.

Hoffman EP, Brown RH Jr, Kunkel LM. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. *Cell*. 1987; 51(6): 919–28.

Koenig et al. The molecular basis for Duchene versus becker muscular dystrophy: Correlation of severity with type of deletion. *Am J Hum Genet*. 1989; 45: 498-506.

Koenig M, Hoffman EP, Bertelson CJ, Monaco AP, Feener C, Kunkel LM. Complete cloning of the Duchenne muscular dystrophy (DMD) cDNA and preliminary genomic organization of the DMD gene in normal and affected individuals.*Cell*.1987; 50(3): 509–17.

Love DR et al. An autosomal transcript in skeletal muscle with homology to dystrophin.*Nature*. 1989; 339(6219): 55–8.

Monaco AP, Bertelson CJ, Liechti-Gallati S, Moser H, Kunkel LM. An explanation for the phenotypic differences between patients bearing partial deletions of the DMD locus. *Genomics*. 1988; 2: 90-5.

Monaco AP, Neve RL, Colletti-Feener C, Bertelson CJ, Kurnit DM, Kunkel LM. Isolation of candidate cDNAs for portions of the Duchenne muscular dystrophy gene. *Nature*. 1986; 323(6089): 646–50.

Moxley RT et al. Practice parameter: corticosteroid treatment of Duchenne dystrophy: report of the quality standards subcommittee of the american academy of neurology and the practice committee of the child neurology society. *Neurology*. 2005; 64(1): 13–20.

Perkins KJ, Davies KE. Recent advances in Duchene muscular dystrophy. *Degenerative neurological and neuromuscular disease.* 2012; 2: 143-64.

Saiki RK et al. Primer directed enzymatic amplification of DNA with a thermostable DNA polymerase. *Science*. 1988; 239: 487-91.