Stem Cell Therapy
& other Recent Advances in
Muscular Dystrophy

Dr. Alok Sharma

Co-Authors :
Dr. Prerna Badhe, Dr. Nandini Gokulchandran, Dr. Guneet Chopra,
Dr. Mamta Lohia, Pooja Kulkarni

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(100 Case Reports)

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Stem Cell Therapy & Other Recent Advances in Muscular Dystrophy

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Aaron Ciechanover
Nobel Prize winner in Chemistry in 2004

"In basic science versus clinical medicine,
there is a problem of time scale.
In science, unrevealing secrets takes a lot of time but meanwhile,
patients are suffering and even dying and
therefore we need to find intermediate solutions for their problems."

From President Obama's Speech on Stem Cell Policy Change, March 9, 2009

President Barack Obama

"There is no finish line in the work of science.
The race is always with us - the urgent work of giving substance to hope
and answering those many bedside prayers,
of seeking a day when words like "terminal" and "incurable"
are finally retired from our vocabulary"

This Book is Dedicated to
all our Patients and their Families
and Caretakers

Preface

Over the last 150 years or so, the evolution of modern medicine, has had several success stories. From the wiping killer diseases like small pox off the face of the planet to reducing former killer diseases such as tuberculosis and the plague to treatable conditions, from advanced intervention and surgical techniques in cardiac conditions that have prevented many deaths to microsurgery for the brain, spine, eyes, ears and other organs that have given relief from suffering of many debilitating conditions, all of us are able to live better lives today due to the availability of many drugs and surgical procedures.

There are however still some conditions that modern medicine had not been able to touch. Curing them was a distant dream even giving symptomatic relief or palliation was not possible. Many of these diseases were referred to as incurable neurological conditions. One such disease is Muscular Dystrophy. The tragedy of the muscular dystrophies was that it is a slowly progressive condition that over several years results in limb weakness reducing a normal human being to a wheelchair and later a bedridden existence. Limb contractures and scoliosis that occurred often result in a painful day to day existence. In the most common form of the muscular dystrophy , Duchene Muscular Dystrophy, death followed at the age of 20-25. The mental and emotional agony of parents watching their child slowly progress painfully to a certain death is indescribable. Many mothers had watched their brothers go through this and then having to watch their sons also go through the same agony over 15-20 years is something none of us in the medical profession can understand. DMD children are most often very cute, remarkably intelligent and have a very non complaining and positive attitude to life. Watching these courageous kids wither away slowly over several years was bad enough. Being told my multiple doctors that absolutely nothing could be done for them made things so much worse.

But all this is now about to change. The development of regenerative medicine with the availability of cellular transplantation in the form of Stem Cells has given us the first major breakthrough in the management of Muscular Dystrophy. No longer do we have to turn away these patients with the advice that "nothing can be done". Despite the availability of stem cell therapy the majority of treating physicians are still not recommending these patients for this therapy. Their argument is that "there is not enough evidence available". In today's world of evidence based medicine this argument is justified. However for once we should look at this from the patients and their families point of view. It will take several years before class 1 evidence will be available in the form of prospectively randomized controlled muiltcentric studies. What do the patients do till then ?

What if instead of looking at evidence based medicine we looked at practice based evidence. What is there was enough practice based evidence to show that this was a

completely safe therapy and had a reasonable degree of effectiveness. This book was written for this purpose. Although at the time of publishing this book, we have treated over 200 patients of muscular dystrophies, we are presenting in this book a summary of 100 patients detailing their clinical presentation, improvements after stem cell therapy both in symptoms, signs as well in their investigations. We believe that with this large body of evidence there is no need to wait till multicentric trials are done and class 1 evidence collected. Ethically this is in complete accordance with the World Medical Associations " WMA Declaration of Helsinki" which states that " In the treatment of a patient , where proven interventions do not exist or have been ineffective, the physician, may use an unproven intervention if in the physicians judgment if offers hope of saving life, re-establishing health or alleviating suffering. "

In this book we have attempted to put together and summarize all the basic science and clinical research that has been done all over the world as well as share our own clinical results. Based on this we can now make a reasonable conclusion that the treatment of Muscular Dystrophy with adult stem cells combined with an aggressive rehabilitation program is a safe and effective form of therapy in slowing down/halting the progression of the disease and in producing functional and neurological improvements in the patients.

To all the patients, their families, caretakers, therapists and doctors who have this question in their mind " Can Muscular dystrophy be treated", the answer all these years may have been no, but now, based on the evidence we have, we can say with a profound confidence :- "*Yes we can*".

Dr. Alok Sharma

The Impossible Dream

To dream the impossible dream,
to fight the unbeatable foe,
to bear with unbearable sorrow,
to run where the brave dare not go.

To right the unrightable wrong,
to love pure and chaste from afar,
to try when your arms are too weary,
to reach the unreachable star.

This is my quest,
to follow that star --
no matter how hopeless,
no matter how far.

To fight for the right
without question or pause,
to be willing to march into hell for a
heavenly cause.

And I know if I'll only be true to this
glorious quest
that my heart will be peaceful and calm
when I'm laid to my rest.

And the world will be better for this,
that one man scorned and covered with scars
still strove with his last ounce of courage.
To reach the unreachable stars.

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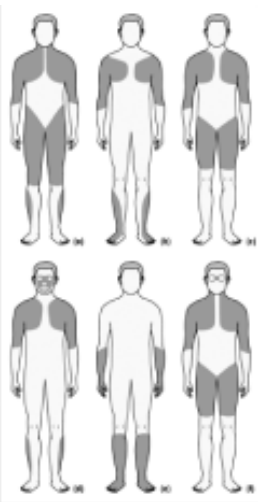
1

Introduction And Clinical Features

Muscular dystrophies are a group of clinically and genetically heterogeneous myopathic disorders that primarily affect striated muscles throughout the body. These myopathies are caused by mutations in genes that encode for structural proteins that link the cytoskeleton of muscle fibers to the extracellular matrix. The absence of functional proteins results in destabilization of the muscle membrane, increased muscle fragility and degeneration, and progressive muscle wasting. (1)

There are many forms of muscular dystrophy, some noticeable at birth, known as congenital muscular dystrophy while other forms develop in adolescence such as Becker muscular dystrophy. Regardless of the exact timing of onset, some muscular dystrophies lead to mobility impairment.



Distribution of predominant muscle weakness in different types of dystrophy: (a) Duchenne-type and Becker-type, (b) Emery-Dreifuss, (c) limb girdle, (d) facio-scapulohumeral, (e) distal, and (f) oculopharyngeal ***(Emery AEH. The muscular dystrophies. BMJ 317 : 991)***

TYPES

There are nine major types of muscular dystrophies. This group of genetically distinct disorders shares clinical and pathological characteristics but varies in age of onset, rate of progression, distribution of weakness, severity, inheritance pattern, and molecular defect.

They are majorly classified as follows

1. ***Early (Childhood) onset***
   a. DMD
   b. BMD
   c. Congenital
   d. Emery Dreifuss
2. ***Youth/adolescent-onset MD***
   a. Fascioscapulohumeral
   b. Limb Girdle
3. ***Adult Onset MD***
   a. Distal
   b. Myotonic
   c. Oculopharyngeal

1. Duchenne muscular dystrophy (DMD)

It is one of the most common and a rapidly-worsening form of muscular dystrophies, affecting 1 in 3,600 male births.(2) It is an X-linked recessive disorder caused by mutations or deletions in the dystrophin gene on the X chromosome (Xp21) leading to almost no dystrophin protein production.

Although dystrophin mutations represent the primary cause of DMD, it is the secondary processes involving persistent inflammation and impaired regeneration that aggravate the disease progression. (3) This results in chronic inflammation and severe skeletal muscle degeneration, where the extent of muscle fibrosis contributes to disease severity. Elevated numbers of inflammatory cells are known to be present at the sites of muscle injuries to interact with cytokine and growth factor signaling. (4-6) It is evident that dystrophic muscles undergo increased oxidative stress and altered calcium homeostasis, which may contribute to myofiber loss by triggering both necrosis and apoptosis. (7) In humans, DNA-fragmentation and expression of apoptosis- related proteins indicate that apoptosis plays a role in muscle degeneration in muscular dystrophies. (8)

Clinical Presentation

Duchenne muscular dystrophy is the commonest serious muscle disorder in children. Although Duchenne muscular dystrophy is an inherited disease, and present from the initial stages of fetal development, there is no physical indication at birth that

the baby is anything less than perfectly formed. It is rare for any delay in development to be noticed in the first year of life. Problems are usually not evident until eighteen months to four years of age. On average a diagnosis is not made until the child is five, although with increasing awareness of the problem, some boys are diagnosed earlier. At least half of affected boys do not walk until eighteen months of age or later. Over the first few years of life these children have difficulty in climbing and getting up from the floor. The common symptoms include:

- Impairment of balance, resulting in frequent falls
- Pseudohypertrophy- loss of muscle mass (wasting), with the degenerating muscles fibres being replaced by fat and connective tissue making the muscle (especially calf) appear larger.

  Most involved muscles: Adductor magnus in legs

  Relatively spared muscles: Gracilis & Sartorius
- Gowers' sign
- Difficulty walking, running and jumping, due to weak leg muscles
- Waddling gait
- Scoliosis
- Increased creatinine phosphokinase levels
- Muscle contractures of achilles tendon and hamstrings impair functionality because the muscle fibers shorten and fibrosis occurs in connective tissue.
- Muscle wasting begins in the legs and pelvis, then progresses to the muscles of the shoulders and neck, followed by loss of arm muscles and respiratory muscles.
- Cardiomyopathy is common, but the development of congestive heart failure or arrhythmias is only occasional.
- Most deaths occur due to pneumonia, diaphragm muscle weakness or cardiac complications.

2. Becker Muscular Dystrophy

It is also known as Benign pseudohypertrophic muscular dystrophy which is an X-linked recessive inherited disorder characterized by slowly progressive muscle weakness of limbs. It affects about 1 in 30,000 males.

Becker muscular dystrophy (BMD) is allelic to Duchenne muscular dystrophy (DMD) and shows a more heterogeneous clinical picture than DMD and has a milder course. DMD patients lack functional dystrophin, whereas BMD patients havepartially functional or not enough dystrophin protein.

Patients with very low levels of dystrophin (<20%) often have an intermediate phenotype. Thus, the presence of partially functional dystrophin is sufficient to ameliorate the DMD phenotype, leading to the milder presentation seen in BMD. (9)

Clinical Presentation

The symptoms of BMD usually appear in late childhood to early adulthood. Though the progression of symptoms may parallel that of DMD, the symptoms are usually milder and the course more variable.

Common symptoms of Becker muscular dystrophy include:

- Leg weakness, unsteadiness, and contractures. Muscle weakness may be especially prominent in quadriceps or hamstrings
- Waddling Gait
- Pseudohypertrophy
- Scoliosis may occur, but is usually milder and progresses more slowly.
- Cardiomyopathy, occurs more commonly in BMD. Problems may include arrhythmias and congestive heart failure.
- Respiratory weakness also occurs, leading to the need for mechanical ventilation.

3. Limb-Girdle Muscular Dystrophy

Limb-girdle muscular dystrophy (LGMD) also known as Erb's muscular dystrophy is an autosomal class of muscular dystrophy. The term "limb-girdle" is used to describe these disorders because the muscles most severely affected are generally those of the pelvic and shoulder girdle muscles. Prevalence for all forms of LGMD range from one in 14500 to one in 123000. (10, 11) LGMDs transmitted by autosomal dominant inheritance are designated as LGMD type 1, and those transmitted by autosomal recessive inheritance are designated as LGMD type 2. The autosomal dominant forms tend to be less severe than the autosomal recessive. The dominant forms of LGMD can arise by a new mutation in the affected person. (12)

Clinical Presentation:

Each type of LGMD has a different range of symptoms. The symptoms can even vary between individuals with the same type of LGMD. The age of onset of symptoms can occur from infancy to adulthood.

The most common symptoms of LGMD are

- Muscle weakness and deterioration involving the muscles around the hips and shoulders.
- Waddling gait due to weakness of the hip and leg muscles.
- Difficulties in rising from a chair and difficulties in climbing stairs are common.
- Eventually, walking may become impossible and lead to resorting to a wheelchair.
- Enlargement or a decrease in size of the calf muscles can also be seen.
- Some individuals with LGMD also experience contractures and muscle cramps.
- The limited mobility associated with LGMD can result in muscle soreness and joint pain.

- Lifting heavy objects, holding the arms outstretched, and reaching over the head can become impossible because of weaknesses in the shoulder muscles.
- Some individuals with LGMD may eventually have difficulties in swallowing and feeding themselves.
- Sometimes the back muscles can become weakened and result in scoliosis.
- LGMD can occasionally result in a weakening of the heart muscles and/or the respiratory muscles. Some people may experience cardiomyopathy.
- A weakening of the muscles necessary for respiration can cause breathing difficulties.

4. Facioscapulohumeral Muscular Dystrophy

Facioscapulohumeral muscular dystrophy, (FSHMD, FSHD or FSH), which is also known as Landouzy-Dejerine, is the third most common genetic disease of skeletal muscle, an autosomal dominant disorder with incidence of 1 in 20,000.(13) . FSHD is due to deletions of a repetitive element on 4q35 known as D4Z4. (14) There is an inverse relationship between clinical severity and age of onset and the residual repeat size, with the smallest repeats causing the most severe phenotypes (15,16). Intrafamilial clinical variability is a common feature in FSHD. (17) Monosomy of 4q does not cause FSHD, suggesting that the FSHD-associated deletion leads to a deleterious gain of function.

Clinical Presentation

The clinical phenotype is known to be distinctive. Symptoms usually commence in the second or third decade for most affected patients. (18)

- FSHD is characterized by onset of weakness in an initially restricted and characteristic distribution, starting with facial weakness, followed sequentially by scapular fixator, humeral, truncal, and lower-extremity weakness.
- The most common initial symptom is difficulty reaching above shoulder level related to weakness of the scapular fixators.
- The clinical severity is wide ranging, from asymptomatic individuals to individuals who are wheelchair-dependent.
- Symptomatic respiratory weakness occurs in only about 1% of affected individuals.
- The most common extramuscular manifestations in FSHD are mild high-frequency hearing loss and asymptomatic retinal telangiectasias, occurring in 75% and 60% of affected individuals, respectively.
- Rarely, in severely affected individuals, the retinal vascular abnormalities can cause potentially catastrophic retinal exudation leading to retinal detachment (Coat's syndrome).
- Cardiac involvement, manifesting as a predilection to atrial arrhythmias, is seen in about 5% of patients, few of whom require treatment.

5. Oculopharyngeal Muscular Dystrophy

Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant disorder characterized by slowly progressive ptosis, dysphagia, and proximal limb weakness. (19) Muscle histology in affected individuals typically reveals abnormality such as variability in fibre size, an increase in endomysial fibrosis, and cytoplasmic basophilic rimmed vacuoles.

Clinical Presentation

The symptoms of OPMD usually start in the fifth or sixth decade, with a slowly progressive course; eventually, beyond the age of 70, all patients are symptomatic

The main symptoms are:

- Ptosis and dysphagia due to weakness of the levator palpebrae and pharyngeal muscles. Muscles around the eyes can also be affected (external ophthalmoplegia). This additional muscle weakness leads to a decreased range of motion of the eyes causing problems such as difficulty gazing upwards and double vision (diplopia).
- Characteristic face with progressive facial muscle weakness
- Progressive weakness of throat muscles
- Progressive limb muscle weakness
- Weakness and atrophy of the tongue can be observed in the vast majority of patients.
- Consecutive aspiration pneumonia, together with malnutrition or even starvation, is the leading causes of death in patients with OPMD.

6. Emery- Dreifuss Muscular Dystrophy

Emery-Dreifuss muscular dystrophy (EDMD) is inherited either as an autosomal dominant form or an X-linked recessive disorder. The two forms are clinically very similar with a predominance of the X-linked form. (20) Prevalence is estimated at 1 in 300,000. Usually manifest after age 20 and may lead to sudden death and ischemic accidents due to embolism. (21,22) The genes known to be associated with EDMD are EMD which causes X linked recessive EDMD and LMNA which causes autosomal dominant EDMD (AD-EDMD) and autosomal recessive EDMD (AR-EDMD)

Clinical Presentation

Emery-Dreifuss muscular dystrophy (EDMD) is a relatively benign form of dystrophy, with onset in early childhood and thereafter relatively slow progression that is characterized by

- Early contractures of the Achilles tendons, elbows and postcervical muscles.
- Slowly progressive muscle wasting and weakness with a distinctive humeroperoneal distribution in the early stages of the disease,
- Cardiomyopathy with life threatening conduction defects (23)

  Cardiac involvement is the most serious and important aspect of the disease.

It usually becomes evident as muscle weakness progresses, but may exceptionally occur before there is any significant weakness. In almost all those affected by the disorder there is some evidence of cardiac involvement by age of 30 years.

7. Congenital Muscular Dystrophy

The congenital muscular dystrophies (CMDs) are clinically and genetically heterogeneous group of inherited muscle disorders. This group of conditions is thought to be among the most common of autosomal recessive neuromuscular disorders. (24)

The main CMD subtypes, grouped by involved protein function and gene in which causative mutations occur, are laminin alpha-2 (merosin) deficiency (MDC1A), collagen VI-deficient CMD, the dystroglycanopathies (caused by mutations in POMT1, POMT2, FKTN, FKRP, LARGE, and POMGNT1), SEPN1-related CMD (also known as rigid spine syndrome, RSMD1) and LMNA-related CMD (L-CMD). Several less known CMD subtypes have been reported in a limited number of individuals. Cognitive impairment ranging from intellectual disability to mild cognitive delay, structural brain and/or eye abnormalities, and seizures are found almost exclusively in the dystroglycanopathies while white matter abnormalities without major cognitive involvement tend to be seen in the laminin alpha-2-deficient subtype. (25)

Clinical Presentation

Muscle weakness typically presents from birth to early infancy. The main symptoms are:

- Hypotonia and muscle weakness at birth or during infancy. Affected children may present with poor or decreased gross motor development.
- Delay or arrest of motor milestones
- Joint contractures, spinal deformities, and respiratory compromise.
- The central nervous system, eye, and connective tissue may also be involved.

8. Myotonic Muscular Dystrophy

Myotonic dystrophy (MD) is the most common form of adult-onset muscular dystrophy. It affects at least 1 in 8,000 people worldwide. There are currently two known types of MD; myotonic dystrophy type 1 (MD1), also known as Steinert disease and myotonic dystrophy type 2 (MD2), commonly referred to as PROMM or proximal myotonic myopathy. (26)

Clinical Presentation

- It affects the skeletal, smooth and cardiac muscle causing nervous system abnormalities, ocular diseases and endocrine disorders.
- Cardiac involvement is an integral part of the disorder, and it is mainly represented by conduction abnormalities, arrhythmias and, less frequently, heart failure progressive muscle wasting and weakness.
- People with this disorder often have prolonged muscle contractions

(myotonia)

- Affected people may have slurred speech or temporary locking of their jaw and difficulty in swallowing
- Cataracts
- Premature balding may occur in some males, while females may experience thinning of their hair.

9. Distal Muscular Dystrophy

The distal muscular dystrophy are a clinically and pathologically heterogeneous group of genetic disorders in which the distal muscles of the upper and the lower limbs are selectively or disproportionately affected. (27,28)

Following are the types of distal muscular dystrophy

Welander's distal muscular dystrophy:

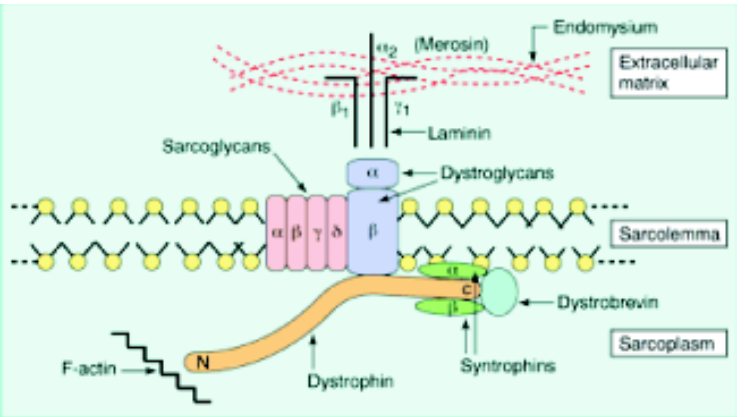
This form of distal muscular dystrophy usually has an onset between 40 and 50 years of age. Upper extremities tend to be affected first and then the lower ones. The degree of muscle weakness involved can range from mild to severe.

Tibial distal muscular dystrophy:

Tibial muscular dystrophy features weakness starting after the age of 40 in the lower extremities (particularly the muscles over the tibia) and progressing slowly to the upper extremities and trunk muscles. This distal myopathy results from mutations in the protein titin, which plays a role in muscle fiber structure and force generation.

Miyoshi distal muscular dystrophy:

This disorder involves weakness that begins in the lower extremities, especially in the calf muscles. It can progress to other muscles as well. Symptoms usually begin between 15 and 30 years of age. The genetic defects that cause Miyoshi myopathy are in the gene for the dysferlin protein. It results in muscle weakness in and around the hips and shoulders.



Muscle membrane proteins. Specific muscular dystrophies have been found to be caused by deficiencies of dystrophin, or a particular sarcoglycan, or merosin ***(Emery AEH. The muscular dystrophies. BMJ 317 : 991)***

Nonaka distal muscular dystrophy:

Usually found in families of Japanese descent, this DD has symptoms that begin between ages 20 and 40. The anterior lower leg muscles are typically affected first, but the disease may progress to affect upper arm and leg muscles and neck muscles. The quadriceps muscles tend to remain strong.

The disease is caused by defects in the GNE gene. The GNE protein that comes from this gene modifies compounds on cell surfaces in a way that is needed for cells to signal each other and adhere to each other.

Gowers-Laing distal muscular dystrophy:

This disorder has its onset from childhood to 25 years of age. Weakness is first seen in the leg and neck muscles, and progresses slowly to include upper leg muscles, hands and more neck muscles.

Gowers-Laing distal myopathy results from mutations in the MYH7 gene, which instructs for myosin heavy chain 7, a protein that participates in muscle contraction.

Hereditary inclusion-body myositis (myopathy) type 1 (HIBM1):

HIBM1 usually begins between the ages of 25 and 40, first affecting the muscles that lift the front of the foot and the thigh muscles. Under the microscope, muscle cells show inclusion bodies, which are abnormal clumps of cellular material; and vacuoles, which are cellular bubbles. The cause is unknown.

Distal muscular dystrophy with vocal cord and pharyngeal weakness:

This disorder has been linked to chromosome 5. MYOT gene is mutated resulting in abnormal production of myotilin protein. Symptoms first appear between about 35 and 60 years of age and include weakness of the hands, legs or voice.

Clinical Presentation:

Distal muscular dystrophy is a form of muscular dystrophy which is characterized by weakness and wasting of the muscles of the hands and forearms and lower legs.

PROGNOSIS

During the first few years of life, muscle fibres that break down in boys with Duchenne muscular dystrophy are continually being replaced. Unfortunately, the body has only a limited capacity to continue replacing muscle fibres . Eventually the rate of regeneration cannot keep up with the rate of degeneration. As a result, there is a reduction in the number of good muscle fibres and the whole muscle becomes weaker. In summary, Duchenne muscular dystrophy is caused when a piece of genetic material is missing. As a result the body fails to make the protein dystrophin. Without dystrophin muscle fibres breakdown. Eventually the body's ability to replace these damaged fibres is exceeded. The child becomes weak because he does not have enough strong muscle.

Duchenne Muscular Dystrophy

- Between age 8 and 10
  - Walking may require use of braces.

  - Joint contractures and limitations of hip flexion, knee, elbow, and wrist extension are worsened by prolonged sitting.
- By age 12
  - Most patients are wheelchair-dependent.
  - Contractures become fixed.
  - Progressive scoliosis often develops.
- May be associated with pain
  - Chest deformity occurs with scoliosis.
- Impairs pulmonary function, already diminished by muscle weakness
- By age 16-18
  - Predisposition to serious pulmonary infections
- Respiratory failure in second or third decade
- Causes of death include:
  - Pulmonary infections
  - Aspiration
  - Acute gastric dilation
  - A cardiac cause of death is uncommon.

Becker Muscular Dystrophy

- Patients have reduced life expectancy.
- Most survive into the fourth or fifth decade.
- Respiratory failure may develop by fourth decade.

Congenital Muscular Dystrophy

- WWS is the most severe, causing death by 1 year of age.

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2

Genetics And Inheritance

Genes linked together on chromosomes, have two functions: They code for the production of proteins, and they are the material of inheritance. Parents pass along genes to their children, providing them with a complete set of instructions for making their own proteins.

Because both parents contribute genetic material to their offspring, each child carries two copies of almost every gene, one from each parent. For some diseases to occur, both copies must be flawed. Such diseases are called autosomal recessive diseases. Some forms of LGMD and DD exhibit this pattern of inheritance, as does CMD. A person with only one flawed copy, called a carrier, will not have the disease, but may pass the flawed gene on to his children. When two carriers have children, the chance of having a child with the disease is one in four for each pregnancy.

Other diseases occur when only one flawed gene copy is present. Such diseases are called autosomal dominant diseases. Other forms of LGMD exhibit this pattern of inheritance, as do MD, FSHD, OPMD, and some forms of DD. When a person affected by the disease has a child with someone not affected, the chance of having an affected child is one in two.

Because of chromosomal differences between the sexes, some genes are not present in two copies. The chromosomes that determine whether a person is male or female are called the X and Y chromosomes. A person with two X chromosomes is female, while a person with one X and one Y is male. While the X chromosome carries many genes, the Y chromosome carries almost none. Therefore, a male has only one copy of each gene on the X chromosome, and if it is flawed, he will have the disease that defect causes. Such diseases are said to be X-linked. X-linked diseases include DMD, BMD, and EDMD. Women are usually not affected by X-linked diseases. Some female carriers of DMD suffer a mild form of the disease, as muscle weakness and cramping, probably

because their one unaffected gene copy is shut down in some of their cells. Females who carry a DMD gene mutation also have an increased risk of developing heart abnormalities including dilated cardiomyopathy. (1,2) Women carriers of X-linked diseases have a one in two chance of passing the flawed gene on to each child born. Daughters who inherit the disease gene will be carriers. A son born without the disease gene will be free of the disease and cannot pass it on to his children. A son born with the defect will have the disease. He will pass the flawed gene on to each of his daughters, who will then be carriers, but to none of his sons (because they inherit his Y chromosome).

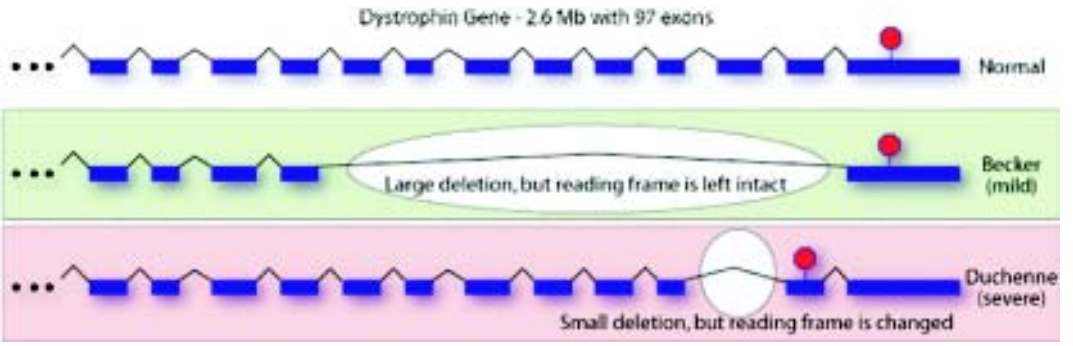
Not all genetic flaws are inherited. As many as one third of the DMD cases are due to new mutations that arise during egg formation in the mother. New mutations are less common in other forms of muscular dystrophy.

1. Duchenne Muscular Dystrophy and Becker Muscular Dystrophy

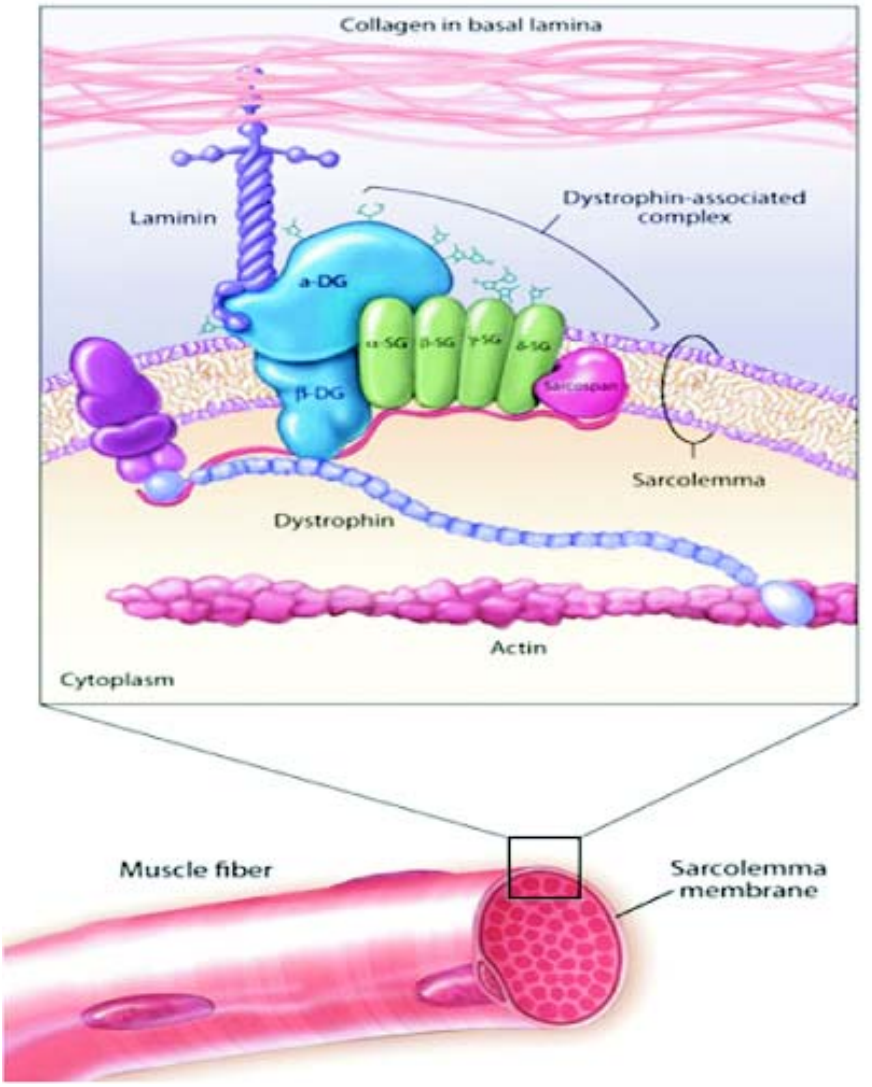
Dystrophin is one of the largest known genes, consisting of almost 0.1% of the human genome (2,500 Kbp). The product of the DMD gene in normal muscle, dystrophin, is a 427 kDa protein. Dystrophin is part of a large protein complex, the dystrophin-associated glycoprotein complex (DAGC) which is a multicomponent complex which includes the dystroglycans, the sarcoglycans, the syntrophins, and sarcospan. (3) Dystrophin interacts with several members of the complex, which forms a mechanical as well as signaling link from the extracellular matrix to the cytoskeleton. (4) Mutations in dystrophin result in membrane damage, allowing massive infiltration of immune cells, chronic inflammation, necrosis, and severe muscle degeneration. (5) Deletions are amenable for analysis by Southern blot hybridization and PCR based methodology. These deletions are spread non-randomly throughout the gene clusterin (around two hot spots, a major region of 44-52 exons and a minor one at the 5 end of the gene (exons 2-19). (6, 7) The frequency of intragenic deletions varies in different populations across the globe. The American studies report mutant alleles with gene deletions in 55-70% of all DMD/BMD cases. (8,9) In European and Asian studies much lower frequency of deletions were observed. (10)

Normally, muscle cells possess the capacity to regenerate in response to injury signals, (4) however, this ability is lost in DMD, presumably due to an exhaustion of satellite cells during ongoing degeneration and regeneration cycles. (11, 12)

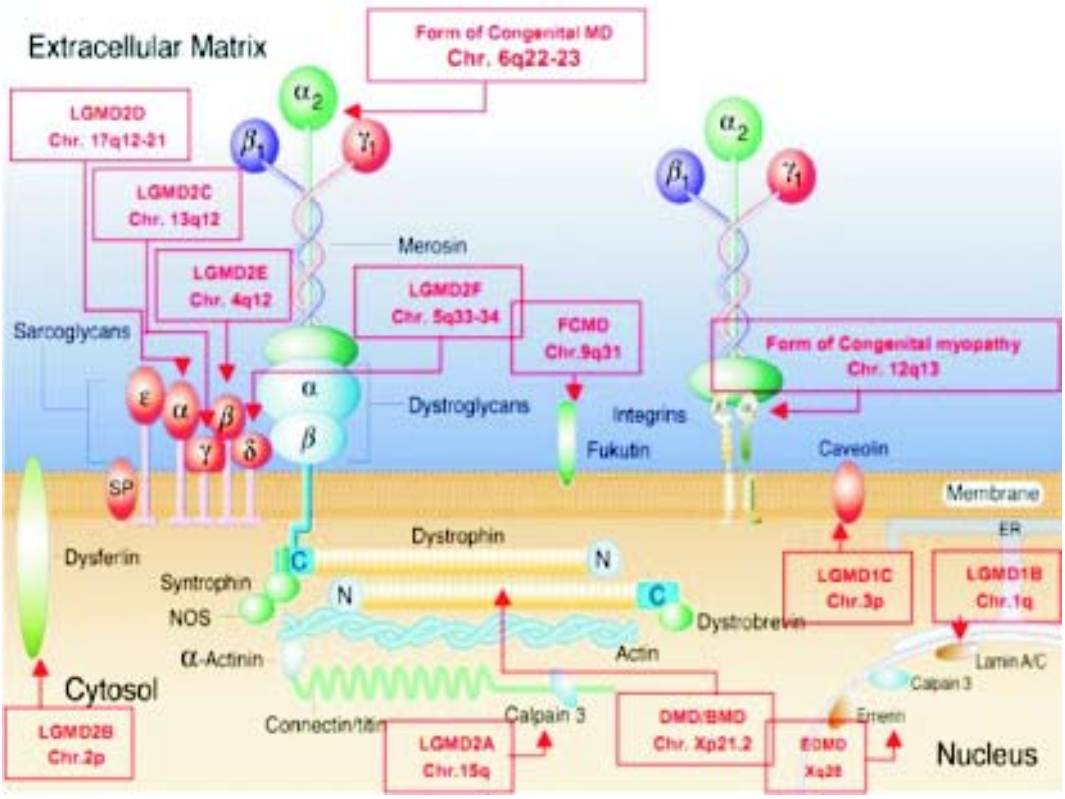
BMD is similar to DMD but less severe. It is estimated to occur at one tenth the frequency of DMD. The disorder is inherited with an X-linked recessive inheritance pattern. It often results from in-frame mutations of the dystrophin gene that allow production of an altered but partially functional protein.(13)



Dystrophin Gene



Dystrophin Protein



Proteins and muscular dystrophies identified by molecular analyses
(Corrado Angelini, Basic Appl Myol 12 (1): 17-25, 2002)

2. Limb Girdle Muscular Dystrophy: (14-18)

Table1: Autosomal Dominant

Subtype	Gene product	Gene localization	Characteristic feature
LGMD 1A	Myotilin	5q31	Dysarthria
LGMD 1B	Lamin A/C	1q21	Cardiac abnormalities
LGMD 1C	Caveolin-3	3p25	Childhood onset
LGMD 1D	-	7q	Very rarely reported

Table 2: Autosomal Recessive

Subtype	Gene product	Gene localization	Characteristic feature
LGMD 2A	Calpain 3	15q15	Scapular winging
LGMD 2B	Dysferlin	2p12	Shoulder and calf involvement
LGMD 2C	γ-sarcoglycan	13q12	Scapular winging, calf hypertrophy
LGMD 2D	α-sarcoglycan	17q21	Scapular winging, calf hypertrophy
LGMD 2E	β-sarcoglycan	4q12	Scapular winging, calf hypertrophy
LGMD 2F	δ-sarcoglycan	5q33	Scapular winging, calf hypertrophy
LGMD 2G	Telethonin	17q11-12	Anterior weakness
LGMD 2H	TRIM32	9q31-33	Slowly progressive
LGMD 2I	FKRP	19q13.3	Calf hypertrophy, dilated cardiomyopathy
LGMD 2J	Titin	2q31	-
LGMD 2K	POMT1	9q34	Childhood onset, weakness and wasting in hip, thigh and shoulder muscles, severe learning disabilities.
LGMD 2L	ANO5	11p14	Cardiac and pulmonary muscles involved.

LGMD 2M	Fukutin	9q31	Age of onset: 10-20 years. Asymmetric wasting of leg muscle. (quadriceps femoralis)
LGMD 2N	POMT2	14q24	Faults in this gene are responsible for a wide spectrum of symptoms, ranging from severe muscle weakness and wasting, learning difficulties and eye problems at birth to a milder form of LGMD
LGMD2O	POMGNT1	8q24	Onset in early childhood and shows very slow progress until the late teens. Muscle biopsy showed dystrophic features with variation in fiber size, internal nuclei, scattered basophilic and few necrotic fibers, and mild endomysial fibrosis

3. Facioscapulohumeral Muscular Dystrophy

In 1992, Wijmenga et al. revealed that FSHD is due to deletions of integral copies of a 3.2 kb tandemly repeated D4Z4 units at the 4q35 locus. These arrays are in subtelomeric regions of 4q and 10q and have 1-100 units. In most patients with FSHD, the D4Z4 repeat is contracted to an array of 1-10 units, and, at least one unit of D4Z4 is required to develop FSHD. Loss of a critical number of D4Z4 repeats compromises the structure of an FSHD gene located within the repeats. Each D4Z4 repeat contains a single open reading frame encoding a putative double homeobox gene, designated DUX4. Unambiguous clinical diagnosis of FSHD depends on determining the array length at 4q35. (19, 20)

4. Oculopharyngeal muscular dystrophy.

OPMD is genetically characterized by a mutation in the polyadenylate binding protein nuclear 1 (PABPN1) gene. This condition was initially genetically mapped to chromosome 14q11.2-q13 in French Canadian families in whom prevalence of the disease is the highest reported anywhere in the world. The first exon of the PABPN1 gene normally contains a (GCG)6 trinucleotide repeat, which is abnormally expanded to 8-13 triplets in patients with OPMD. The mode of inheritance is autosomal dominant in most families, but autosomal recessive cases have also been documented. (21, 22)

5. Emery Dreifuss Muscular Dystrophy

EDMD shows two forms of inheritance patterns, X-linked recessive and autosomal dominant EDMD (AD-EDMD) and autosomal recessive EDMD (AR-EDMD).

The gene responsible for the X-linked form is located on chromosome Xq28. Of the eight genes in this region which were highly expressed in brain and muscle, one in particular, STA was found in the affected individual. The STA gene is 2100 bp in length, consists of six exons and encodes 762 bp mRNA. Its 34 KD protein product of 254 amino acids has been designated as 'emerin'. (23)

The gene responsible for the autosomal dominant and recessive form is LMNA and located on chromosome 1q11-q23. This gene spans approximately 24 kb and is composed of 12 exons. Alternative splicing within exon 10 gives rise to two different mRNAs: a 1992 bp mRNA that codes for pre-lamin A and a 1716 bp mRNA that codes for lamin C. Consequently, two proteins are generated, lamin A (664 aa, 74 kDa) and lamin C (572 aa, 64 kDa). (24)

Emerins and Lamins are members of the intermediate filament protein family and major components of the nuclear envelope. (25, 26)

6. Congenital Muscular Dystrophy

The congenital muscular dystrophies are inherited in an autosomal recessive manner with the exception of collagen VI-deficient CMD which may be inherited in an autosomal recessive or an autosomal dominant manner and LMNA-related CMD (L-CMD) which is inherited in an autosomal dominant manner with all cases to date caused by de novo mutation.

There are currently 12 genetically defined forms of CMD that fall into three groups on the basis of the classes of proteins that are affected. Several forms of CMD are caused by mutations in genes encoding structural proteins of the basement membrane or extracellular matrix of skeletal muscle fibers: collagen VI, laminin 2 and 7-integrin. Mutations in genes encoding putative or proven glycosyltransferase enzymes POMT1, POMT2, POMGnT1, fukutin, FKRP and LARGE involved in the glycosylation of dystroglycan result in a number of forms of CMD, often associated with neuronal migration defects. Mutations in the SEPN1 gene, which encodes an endoplasmic reticulum protein of unknown function, are associated with CMD with rigid-spine syndrome. Accurate description of the clinical phenotype, coupled with comprehensive protein and genetic analysis, are necessary to definitively assign a diagnosis of a specific form of CMD. (27-29)

Type	**Gene**	**Protein**
Laminin-α2-deficient CMD	LAMA2 at 6q22-q23	Laminin α2
Ullrich congenital muscular dystrophy	COL6A1 at 2q37 COL6A2 at 21q22.3 COL6A3 at 21q22.3	Collagen VI
Walker-Warburg syndrome	POMT1 at 9q34.1	Protein-O-mannosyltransferase 1

	POMT2 at 14q24.3	Protein-O-mannosyltransferase 2
Muscle-eye-brain disease	POMGNT1 at 1p34-p33	O-linked mannose β1, 2-N-acetylglucosaminyl-transferase
Fukuyama CMD	FKTN at 9q31	Fukutin
CMD plus secondary laminin deficiency 1	LAMA2 at 1q42	laminin α2 chain of merosin
CMD plus secondary laminin deficiency 2	FKRP at 19q13.3	Fukutin-related protein
CMD with mental retardation and pachygyria	LARGE at 22q12.3-q13.1	Large
Rigid spine with muscular dystrophy Type 1	SEPN1 at 1p36-p35	Selenoprotein N

7. Myotonic Muscular Dystrophy

Two genes associated with myotonic dystrophy are DMPK gene causing myotonic dystrophy type 1, while type 2 results from mutations in the CNBP gene. Both types of myotonic dystrophy are inherited in an autosomal dominant pattern. The protein produced from the DMPK gene may play a role in communication within cells. It appears to be important for the correct functioning of cells in the heart, brain, and skeletal muscles. The protein produced from the CNBP gene is found primarily in the heart and in skeletal muscles, where it probably regulates the function of other genes.

Similar changes in the structure of the DMPK and CNBP genes cause the two forms of myotonic dystrophy. It is caused due to an unstable trinucleotide repeat expansion containing cytosine-thymidineguanosine (CTG) n, located in the 3' untranslated region of chromosome 19q13.3. The CTG trinucleotide is repeated in the normal population from 5 to 36 times but has been found to be expanded up to 2000 times in myotonic dystrophy patients. (30, 31) This amplification is correlated to the severity of the disease. The mutated gene produces an expanded version of messenger RNA. The abnormally long messenger RNA forms clumps inside the cell that interfere with the production of other proteins. These changes prevent muscle cells and cells in other tissues from functioning normally, which leads to the signs and symptoms of myotonic muscular dystrophy.

8. Distal Muscular Dystrophy

Distal muscular dystrophy is a heterogeneous type of muscular dystrophy. The inheritance pattern and genes involved for different types are enumerated below. (32-34)

Type of Distal Dystrophy	Gene Locus	Inheritance Pattern
Welander's distal myopathy	Chromosome 2p13	Dominant
Tibial distal myopathy	TTN gene at 2q31	Dominant
Miyoshi distal myopathy	DYSF at 2p13	Recessive
Nonaka distal myopathy;	GNE at 9p1-q1	Recessive
Gowers-Laing distal myopathy	MYH7 at 14q12	Dominant
Hereditary inclusion-body myositis type 1 (HIBM1)	Unknown	Dominant
Distal myopathy with vocal cord and pharyngeal weakness	MYOT at chromosome 5	Dominant

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3

Diagnosis

Muscular dystrophy is diagnosed through a physical examination, a family history, blood tests, genetic tests, Electromyography,MRI Imaging and muscle biopsy. A preliminary diagnosis can be performed on the basis of past symptoms and characteristic traits.

Muscular dystrophy is characterized by progressive muscle wasting and muscle weakness. All of the muscles may be affected or only specific group of muscles may be affected, such as those around the pelvis, shoulder, or face depending on the type of the muscular dystrophy. Different muscular dystrophies have different age of onset depending on which the patient is diagnosed.

Some of the common presenting symptoms include abnormal gait also referred to as waddling gait with frequent falls, difficulty in rising from the floor and climbing stairs, pseudohypertrophy of calves, positive Gowers' sign and scoliosis or kyphosis. (1)

As discussed in the previous chapter, muscular dystrophy is a genetic disorder in which a family history can be used as a diagnostic tool, but in many cases, as it can also be caused by spontaneous mutations, an absence of family history cannot rule out the possibilities of occurrence of the disorder. The diagnosis cannot be confirmed only on the basis of clinical presentation and family history. Blood tests, Electromyography, MRI imaging, muscle biopsy and genetic tests are essential to confirm the diagnosis.

1. Blood test

Serum creatine kinase (CK) is the initial investigation in patients suspected to have muscular dystrophy on history and clinical examination:

- In DMD the CK level is very high (10-100 x normal from birth).
- A normal CK at presentation excludes DMD. However, later on CK levels fall due to muscle wasting; therefore, it is not reliable as a screening test in those who are already wheelchair users.

When blood tests are performed for muscular dystrophy, the levels of enzyme, creatine phosphokinase (CPK) is estimated. It is found mainly in the brain, heart, skeletal muscles, and other tissues which help cells produce a biochemical reaction that results in high-energy molecules that cells use to perform normal functions. When creatine kinase combines with adenosine triphosphate (ATP) it produces phosphocreatine and adenosine triphosphate (ATP). The muscles use these energy molecules to contract muscle fibers. This enzyme rises in the blood due to muscle damage and may reveal some forms of muscular dystrophy before any physical symptoms appear.

2. Electromyography

Electromyography (EMG) measures muscle response or electrical activity in response to a nerve's stimulation of the muscle. The test is used to help detect neuromuscular abnormalities. A needle is inserted into the muscle at rest and during contraction. By measuring the muscle's response, the muscle damage which has occurred can be measured. (2)

Increased insertional activity or abnormal spontaneous activity may be present if there has been a substantial amount of muscle fiber necrosis.

When the muscle fiber membrane excitability is increased further, these electrical activities may become spontaneous. Although, abnormally increased insertional activity is a well-known abnormality in a denervation process or with muscle fiber necrosis, reduced insertional activity is also abnormal. This may occur in a number of settings, including muscle fibrosis and fatty infiltrates. An important clue to muscle fiber replacement by fibrosis or fatty tissue is that the consistency of the muscle and resistance to the advancing needle are changed. In the case of fatty infiltrate, resistance to the needle is reduced. (3) (Further Details of Electromyography are discussed in Chapter 5)

3. Muscle biopsy

A muscle biopsy is a procedure used to diagnose, diseases involving muscle tissue. It is one of the most reliable tests to confirm the diagnosis of muscular dystrophy. The tissue sample is obtained by inserting a biopsy needle into the muscle and a small piece

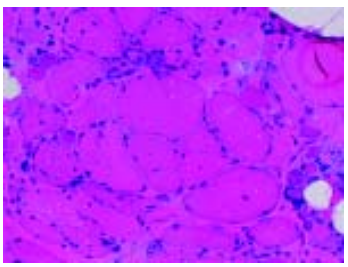

FIG. 1. Marked fiber size variability and endomysial fibrosis are prominent features in this muscle biopsy from an adult with an uncharacterized dystrophy

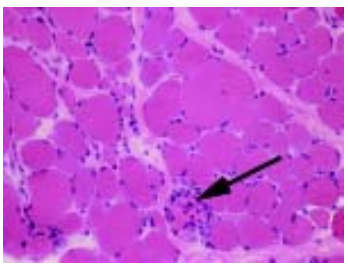

FIG. 2. A degenerating muscle fiber undergoing myophagocytosis is seen in the fiber at the bottom of this image (arrow)

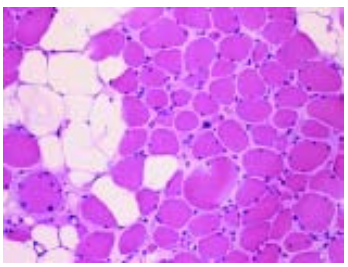

Fig 3. Fatty infiltration of muscle is also a myopathic feature. Here again, the endomysium between muscle fibers is way too thick

of muscle tissue is removed and then examined microscopically. If muscular dystrophy is present, changes in the structure of muscle cells and other characteristics of the different forms of muscular dystrophy can be detected. With the advent of accurate molecular techniques, muscle biopsy is no longer essential for diagnosis of most muscular dystrophies. However, muscle biopsy is necessary to make the diagnosis in most of the acquired muscle diseases. The muscle biopsy shows-Endomysial fibrosis, Variable fiber size (Small fibers rounded), Muscle fiber necrosis & regeneration, Myopathic grouping, Hypercontracted (opaque) muscle fibers, Muscle fiber internal architecture: Normal or immature, Dystrophin: Absent staining, Other membrane proteins Sarcoglycans: Reduced and Aquaporin 4: Reduced; Varied levels.The sample can also be stained using immunohistochemistry, to detect the presence or absence of particular proteins.

The muscle selected for the biopsy depends on the location of symptoms which may include pain or weakness. The muscles often selected for sampling are the biceps (upper arm muscle), deltoid (shoulder muscle), or quadriceps (thigh muscle). (4-6)

4. DNA test

Genetic testing is often the best way to confirm a diagnosis in a patient with signs or symptoms suggestive of a muscular disease. Availability of genetic tests make it possible to diagnose these disorders early and also avoid invasive procedures like muscle biopsy. A muscle biopsy is needed only if the DNA-based test is negative. Genetic tests are available for DMD/ BMD, Myotonic dystrophy, FSHD and few forms of LGMD.

Testing for dystrophin gene deletions or structural inversions in coding regions with the use of DNA-based technology is now the preferred diagnostic test for DMD

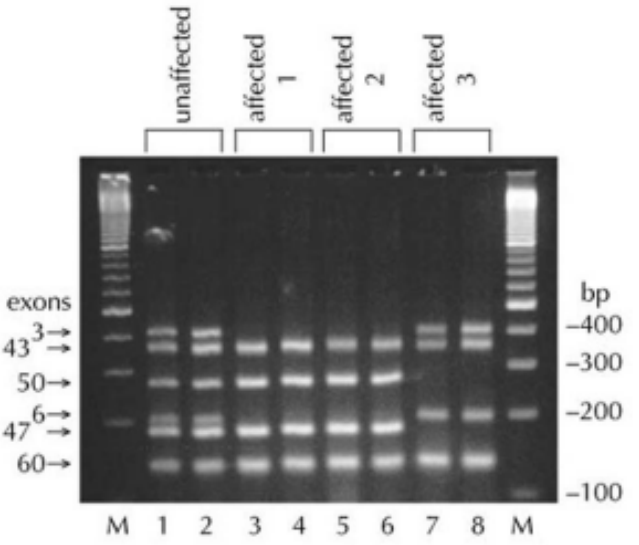

Fig 4: M: 100bp ladder, Lanes 1 & 2: unaffected individual. Lanes 3 & 4 and lanes 5 & 6: affected individual 1 and 2 respectively, wherein the DNA contains deletions of exons 3 and 6. Lane 7 & 8: affected individual 3 wherein DNA contains a deletion of exons 47 and 50

when clinical signs and symptoms suggest the diagnosis. Deletions account for 60-65% cases in DMD; duplications for 5-6% and point mutations for the remaining cases. Using primers targeting 18 hotspot exons in the dystrophin gene, 98% of deletions can be detected. The proximal hotspot encompasses exons 3-7 and the distal hotspot exons 45-51. A negative test occurs in about 30 percent of patients with DMD because some mutations in the dystrophin gene are not detected by current DNA tests available like the multiplex PCR and will require whole gene sequencing. (7-11). In a study of 51 DMD cases done at NeuroGen Brain and Spine Institute, Mumbai, 82% showed deletions in the distal 43-53 exons, 6% showed deletions in proximal 3-7 exons, 6% cases showed deletions in 8-10 exons where as remaining 6% showed deletions in 12-23 exons.

The genetic test for FSHD locates and measures the size of DNA deletion on chromosome 4. The size of the DNA in the normal individual is greater than 51 kilo base pairs while that of the affected one is less than 35 kilo base pairs. Approximately 5% of individuals that have the clinical symptoms of FSHD do not have the DNA deletion on chromosome 4. (12-13)

In Myotonic dystrophy type 1, the mutation is a DNA expansion or an increase in the amount of DNA that is normally located on a chromosome. A section of DNA on the dystrophia myotonica protein kinase (DMPK) gene contains a repeated sequence of three DNA nucleotide bases, CTG. The additional DNA is located on chromosome 19. This test has nearly a 100% rate of accuracy in detecting the genetic mutation. An affected individual has approximately 50 to 2000 CTG repeats depending on the severity of the condition wherein a normal individual has 38 repeats.

In Myotonic Dystrophy type 2, the additional DNA is located on chromosome 3. The Zinc Finger Protein 9 (ZnF9) gene contains a section of DNA that contains a repeated sequence of four DNA nucleotide bases, CCTG. The number of CCTG base pairs in affected individuals averages approximately 20,000.

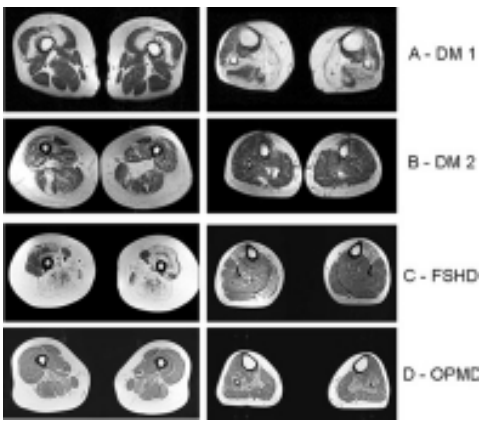

Fig 5: Muscle MRI of lower extremities muscular dystrophies.
(a) Myotonic dystrophy type I showing distal more than proximal muscle involvement. with predominant affliction of the soleus, medial gastrocnemius and proximally the anterior thigh compartment with relative sparing of the rectus femoris. (b) Myotonic dystrophy type II show more involvement of the proximal muscles with affliction of the quadriceps and sparing of the rectus femoris and gracilis muscles. (c) FSHD shows marked asymmetry with the adductor magnus, hamstrings, rectus femoris and tibial anterior being the most frequently affected muscles. (d) OPMD show predominantly posterior thigh and posterior lower leg muscle involvement.

Genetic tests are also available for all the subtypes of LGMD except type 2G, 2H, 2J, 1D, 1E and 1F.

5. Magnetic Resonance Imaging (MRI)

MRI is a readily available, noninvasive method of monitoring tissue structure in muscular dystrophy patients. Several investigators have used MRI as an additional option to physical examination and to investigate the increase in fat tissue in dystrophic muscles. MRI does not use ionizing radiation, produces high-resolution images and can be used for quantitative tissue characterization by measuring the T2 relaxation time of the muscles. In muscular dystrophy patients, the T2 relaxation time in peripheral muscles is significantly different from that measured in healthy control subjects, essentially reflecting differences in fat and water composition between diseased and healthy muscles. Because the T2 relaxation time changes as the disease progresses, it could be used to monitor disease progression and possibly response to therapy in these patients.

Developments in MRI techniques have prompted investigators to explore the advantages of better spatial and contrast resolution. MRI has been used to show the pattern of age-related changes in muscle bulk and fatty infiltration in the lower extremities of untreated patients. Other small studies in which MRI was used showed abnormalities in muscle size and structure in patients with DMD. (14-18) (Further Details of MRI Imaging are discussed in Chapter 4)

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4.

Role of Radiodiagnosis in Muscular Dystrophy

Introduction:

Muscle Imaging is an important diagnostic tool for detection and quantification of dystrophic changes during clinical work-up and follow-up of patients, differential diagnosis of genetically distinct form of neuromuscular disorders is based on characteristic imaging pattern and newer imaging techniques.

Imaging Techniques:

Ultrasound, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) provides diagnostic value in the detection of muscular abnormalities.

Ultrasound:

Ultrasound is a well-established imaging technique in evaluation of patients with muscular dystrophy, allowing visualisation of striated muscles with high temporal resolution (> 0.1mm). Advantages of this imaging technique includes dynamic evaluation of muscles, cost-effectiveness and most importantly lack of radiation exposure making it the perfect imaging technique for evaluating children. However it is highly operator-dependent and its application is limited to superficial group of muscles.

Computed Tomography:

Computed Tomography, an operator independent technique can be used to evaluate the presence and extend of changes (in particular fatty infiltration) in the striated muscles. It allows evaluation of the deeper muscle groups, provides better spatial resolution and multiplanar reconstruction. Relative high radiation dose with limited soft -tissue contrast are the main drawbacks.

Magnetic Resonance Imaging:

Magnetic Resonance Imaging with its high soft tissue contrast is the modality of choice in the evaluation of striated muscles with suspected or proven inherited neuromuscular disorder. Imaging protocol includes obtaining T1-weighted (T1W), T2-weighted (T2W) turbo spin echo and STIR (Short Tau Inversion Recovery) or Fat suppressed T2-weighted sequences (T2WFS) in the Axial and Coronal plane with a slice thickness of 5-7cm and spacing of 5cm. Dystrophic changes such as fatty degeneration appear hyperintense on both T1W and T2W images while Inflammatory changes such as muscle oedema can be best appreciated on T2WFS sequence. The degree of muscular dystrophy in inherited muscle diseases is rated according to amount of fatty degeneration ranging from normal appearance to complete fatty infiltration .

Grade	Mercuri etal.2002	Kornblum et al 2006	Fischer et al 2008
0		Normal appearance	Normal appearance
1	Normal appearance	Discrete moth-eaten appearance with sporadic T1 hyperintense areas	Mild: traces of increased signal intensity on the T1-weighted MR sequences
2	Mild involvement: Early moth-eaten appearance with scattered small areas of increased signal or with numerous discrete areas of increased signal with beginning confluence, comprising less than30% of the volume of the individual muscle.	a. Moderate moth-eaten appearance with numerous scattered T1 hyper intense areas b. Late moth-eaten appearance with numerous confluent T1 hyper-intense areas	Moderate: increased T1-weighted signal intensity with beginning confluence in less than 50% of the muscle
3	Moderate involvement: Late moth-eaten appearance with numerous discrete areas of increased signal with beginning confluence, comprising 30-60% of the volume of the individual muscle	Complete fatty degeneration, replacement of muscle by connective tissue and fat	Severe: increased T1-weighted signal intensity with beginning confluence in more than 50% of the muscle
4	Severe involvement: Washed-out appearance, fuzzy appearance due to confluent areas of increased signal or an end-stage appearance, with muscle replaced by increased density connective tissue and fat, and only a rim of fascia and neurovascular structures distinguishable		End-stage appearance, entire muscle replaced by increased density of connective tissue and fat

Well established visual rating scales of dystrophic changes in striated muscles.

Clinical and Imaging Approach to Muscular Dystrophies

Permanent and progressive muscle weakness is the hallmark of Muscular Dystrophies with a lot of Clinical, pathological and genetic classifications which are overlapping.

I) Approach based on age of onset and pattern of involvement:

Dystrophinopathies(DMD/BMD) - proximal weakness starts in 1st decade of life

Limb-Girdle Muscular Dystrophy (LGMD) - proximal (limb-girdle) weakness starts in second decade of life

Myofibrillar myopathies (MFM) - Adult onset ,usually third or fourth decade affecting the distal muscles

II) Approach based on patterns of muscle involvement:

A) Early onset (proximal) Dystrophinopathies and LGMD

LGMD: are characterised by proximal muscle weakness, elevated creatinine kinase and dystrophic changes on muscle biopsy. LMGD are divided into autosomal dominant (LGMD1, A-E) and autosomal recessive (LGMD2, A-J), the autosomal -recessive forms being more common. The most frequent forms are LGMD2A (due to mutations in the calpain gene and LGMD2I (due to mutations in the FKRP gene)

Duchenne Muscular Dystrophy (DMD): Progressive weakness of skeletal muscles leading to loss of ambulation by 13th year and to death, usually in early adulthood. Abnormal signal in the gluteus maximus and adductor magnus, followed by involvement of the quadriceps, rectus and biceps femoris with selective sparing of the sartorius, gracilis,semimembranosus and semitendinosus. In the lower leg the gastrocnemii are affected earlier and more severely.

LGMD	**Dystrophinopathy (DMD/BMD) & Sarcoglycanopathy (LGMD 2C, D, E & F)**
Greater affliction of posterior	Significant affliction of quadriceps muscle rather than anterior thigh
LGMD 2A (Calpain 3) and LGMD2I (FKRP) Involvement of the posterior thigh and posterior lower led	Dystrophinopathy -Early and marked changes in the gastrocnemii muscles Sarcoglycanopathy-No affliction of gastrocnemii muscle
Calpain 3: Marked involvement of the soleus and medial gastrocnemius muscle with calf atrophy and winging of the scapula. Relative sparing of the vastus lateralis compared to FKRP	
FKRP: Diffuse involvement of the posterior lower leg muscles, with sparing/ hypertrophy of the tibialis anterior muscle	

LGMD 2B (Dysferlinopathies)	
Involvement of the anterior and posterior compartments of the thigh with sparing of the Sartorius and Gracilis.	
Affects posterior compartment of lower legs with relative sparing of medial head of the gastrocnemius muscle	

B) Late-onset (distal) Myofibrillar Myopathies (MFM)

Distinct MFM subtypes include

1) Desminopathy
2) Filaminopathy
3) ZASPopathy

Desminopathy:

Thighs:

Semitendinosus most affected, Early and severe involvement of the Gracilis and sartorius

Lower Legs:

Peroneal more involved than tibialis anterior

Other Subtypes of MFM:

Thighs: Posterior affection with involvement of the biceps femoris, semimembranosus and adductor magnus

Lower legs: Soleus and medial head of gastrocnemius most affected, while the tibialis anterior in the anterior compartment.

Filaminopathy: Gracilis and sartorius equally spared

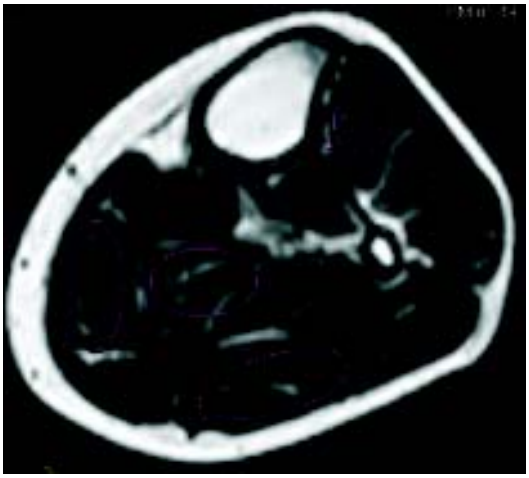
Myotilinopathy: Sartorius more affected than gracilis

FUTURE TRENDS

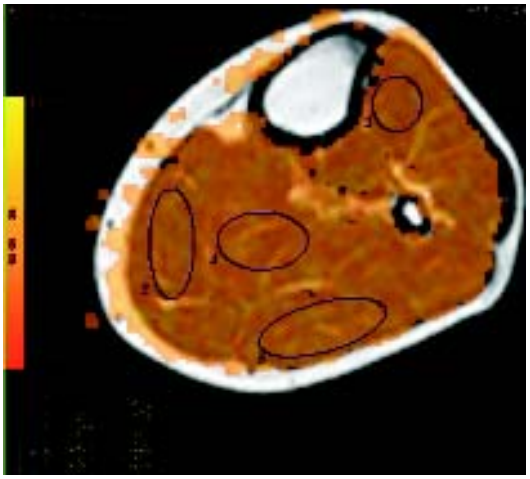
Pattern recognition and visual rating scales have contributed in better understanding of the evolution and progress of the disease; however this is just the beginning and a long road lies ahead .Newer imaging techniques would be very useful in monitoring response to treatment. As per our experience MR Spectroscopy and Diffusion Tensor imaging would add a new dimension and initial results appear to be encouraging. Hydrogen MR Spectroscopy helped in quantification of the fatty infiltration to a certain extent, though Phosphorus MR Spectroscopy would be ideal. Diffusion Tensor Imaging (***Fig)*** with parameters such as FA maps and ADC values would help immensely in understanding the severity of the disease process and to monitor response to treatment

DIFFUSION TENSOR IMAGING IN MUSCLES

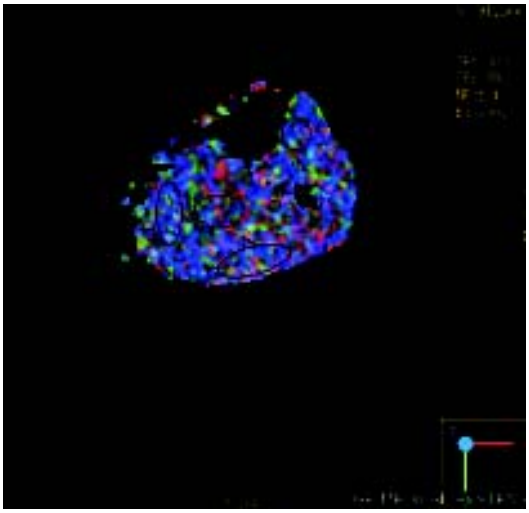
ON GE 1.5HDXT SYSTEM



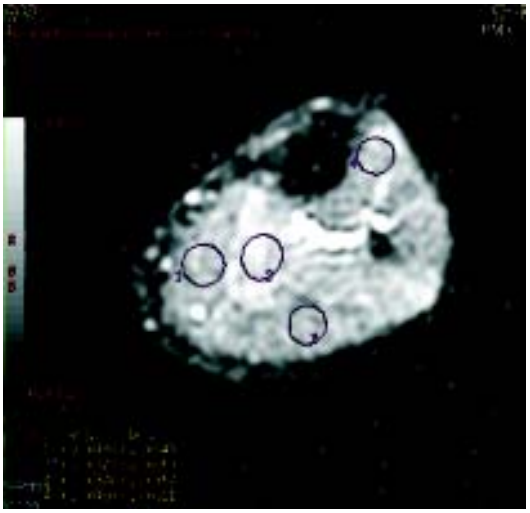
T2 WEIGHTED IMAGES



FUNCTIONAL ANISOTROPHY (FA) VALUES



STRUCTURAL MAPS



APPARENT DIFFUSION COEFFICIENT (ADC) VALUES

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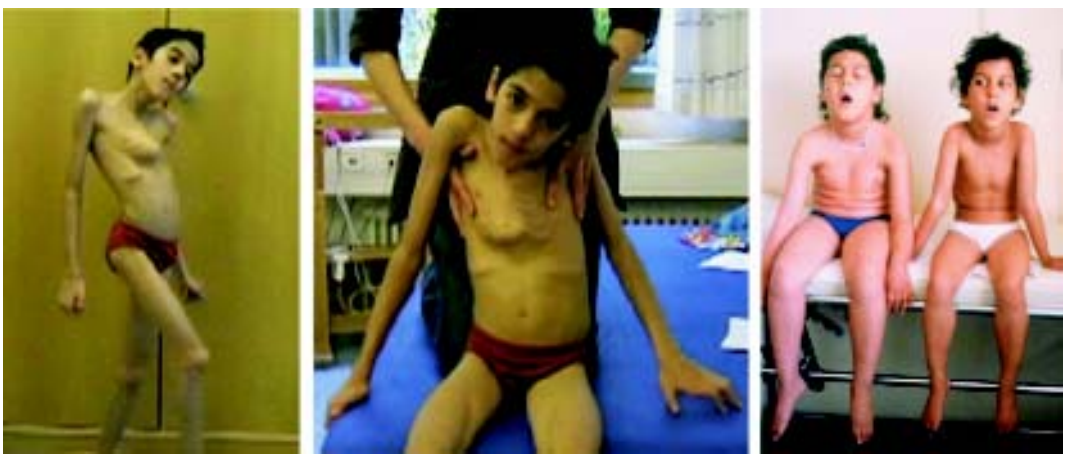
5

Role of Electrodiagnosis in Muscular Dytsrophy

Myopathies are disorders in which a primary functional or structural impairment of skeletal muscle exists. Myopathies can be distinguished from other disorders of the motor unit including Motor Neurone disorder, Peripheral neuropathies and neuromuscular junction disorders by the characteristic clinical and laboratory features.



Electroneuromyographic findings in case of Myopathy

- Sensory nerve conduction studies are essentially normal in Myopathies, except in certain diseases like Mitochondrial Myopathies, where there is an associated Sensory neuropathy.

- Similarly, Motor nerve conduction studies are normal in early stages of myopathies. However, they man reveal low amplitude compound motor action potentials (CMAP's) when recording from severely affected muscles.
- 'F' waves and 'H' reflexes are usually normal except in associated polyneuropathy.

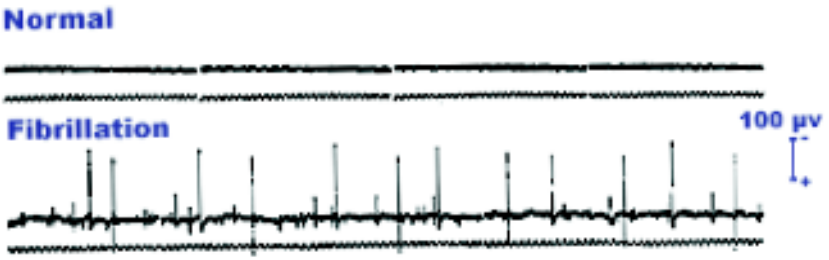
Needle EMG study:

The changes on needle EMG include one or more of the following

1) Abnormal Spontaneous activities:

a. Fibrillation Potentials:

Frequently seen in inflammatorymyopathies and progressive muscular dystrophy.



b. Myotonic Potentials:

These potentials are induced on needle insertion and usually are waxing and waning in character because of variability of frequency and amplitude. The characteristic of these potentials are their association with an unique auditory signal called the "Dive-Bomber". These myotonic potentials are specific for Myotonic dystrophies, Myotoniacongenita and acid maltase deficiency.

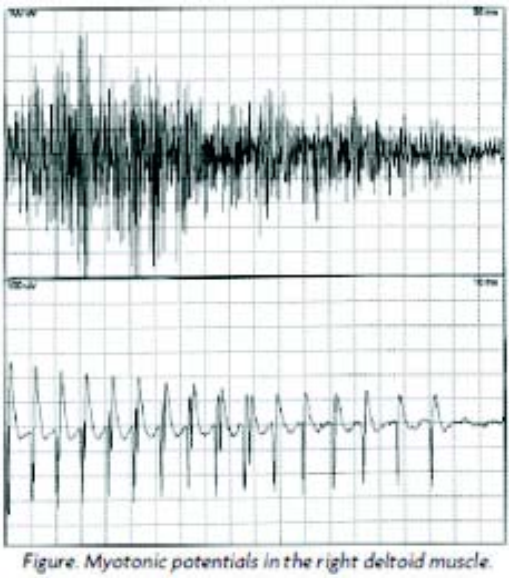
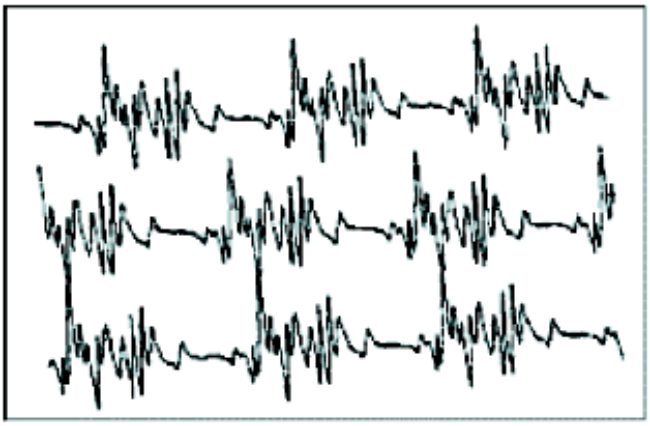


Figure. Myotonic potentials in the right deltoid muscle.

c. Complex repetitive discharges:

Spontaneous discharges of muscle fibres with a characteristic machine like sound are seen in chronic disorders. This phenomenon occurs when a single muscle fibre spontaneously depolarises followed by its ephatic spread to adjacent denervated fibres, hence recurrence of discharges.



2) Change in Motor Unit Potential (MUAP) Morphology:

a. The MUAP's in myopathies are short in duration, low in amplitude and have polyphasic potentials. Short duration of MUAP's is explained by the loss of muscle fibres within the motor unit. Low amplitude MUAP's are seen due to replacement of lost muscle fibres by collagen tissue and hence increasing the distance between muscle fibres and the recording electrode. Variability in fibre conduction velocity and desynchronization of MUAP's within the territory of a motor unit cause the occurrence of polyphasic potentials.

3) Changes in MUAP recruitment:

a. Normal recruitment is seen in mild myopathies.

b. Early recruitment is seen in moderately severe cases, due to muscle fibre loss resulting from inability of muscle fibres to generate enough force.

c. Reduced recruitment with a rapid firing rate occurs in advanced myopathies when loss of muscle fibres is severe, resulting in functional loss of many motor units.

Needle EMG examination of muscles on one side of the body, keeping the other side for muscle biopsy studies.Sample distal, semi-distal, proximal muscles of lower and upper limbs and Para spinal muscles.

Face muscles when relevant and small muscles of hand if myotonic discharges are suspected are also sampled. Look for anatomic distributional pattern of abnormality e.g. hip girdle or face with proximal upper limb muscles.

Advantages of Electrodiagnostic study (EDX):

a. EDX excludes other neuromuscular disorders like neuo-muscular junction disease, peripheral nerve disorder and anterior horn cell disease which sometime mimic a myopathy.

b. EDX study permits widespread muscle sampling and may detect abnormalities that are regional (FSH) or patchy (Polymyositis); in contrast to muscle biopsy which is limited to analysis of one or two specimens.

c. EDX may identify specific features of myopathy e.g. myotonia seen in myotonic dystrophy or fibrillations seen in inflammatory myopathies.

d. Can identify muscles that are significantly affected hence, helping in choosing muscle for biopsy.

e. EDX is used to follow progress in certain myopathies e.g. inflammatory myopathy during treatment or in case of relapse.

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6

Complications And Their Management

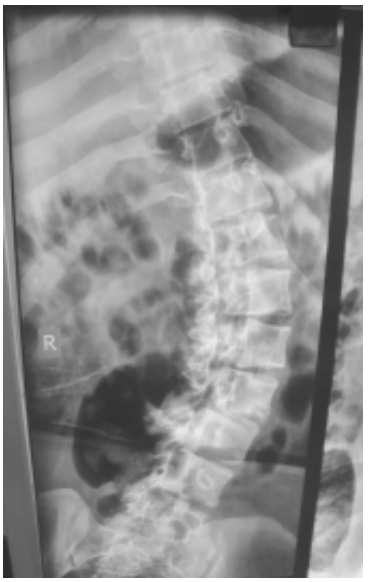
The origin and clinical symptoms vary significantly in muscular dystrophy, but the most frequently encountered complications are of musculoskeletal and neuromuscular origin which most commonly include muscle tightness, contractures, bony rotational deformities, scoliosis, reduced pulmonary and cardiac compliance.

A few of these complications are secondary to immobility such as joint tightness and reduced range of motion. All of which can be easily prevented with the aid of adequate rehabilitation. Complications secondary to steroids are constipation, osteoporosis, obesity and hypertension which require medical management. In few cases weight loss and muscle fatigue can also occur in the late stages of muscular dystrophy.

The most commonly encountered complications and their management are described in detail below.

1. Scoliosis and Contractures

Scoliosis is a complex deformation that involves abnormal lateral and rotational curvature of the spine. It is a long C- shaped curve which involves the thoracic and lumbar spine. This condition is often seen in Duchenne muscular dystrophy cases due to loss of ambulation. Around 75-90% of patients with Duchenne muscular dystrophy (DMD) seem to develop scoliosis. Either an increased kyphosis or thoracic lordosis can be part of the deformity. The consequences of the deformity are loss of sitting balance, shortening of the trunk, and compression of the heart and lungs. The mobility of the ribs is reduced by rotation and deformation of the trunk, causing obstruction in breathing. An increase in deformity can also cause impairment of cardiac and/or pulmonary function. The pelvic obliquity together with weakness of the spinal



X-Ray showing Scoliotic Spine in DMD patient

musculature also impairs the sitting ability in wheelchair.

Surgical correction is recommended to correct the spinal deformity, pelvic obliquity and to prevent further progression and improve quality of life by achieving a better sitting balance. It is mainly performed to restore the balance of the spinal column in both coronal and sagittal planes and to improve table top activities. (1) Surgical techniques used for scoliosis correction in DMD patients range from halo casts with traction wires and buttons, Harrington rods, Luque's segmental spinal fixation to more recent techniques using pedicle screws and hooks. (2-4)

The contractures often develop as a result of various factors, including inability to move a joint through its full range of motion, static positioning in a position of flexion, muscle imbalance about a joint, and fibrotic changes in muscle tissue. (5, 6)

Cases with gradual progression develop more fibrosis and fatty infiltration, have severe contractures while, those with rapidly progressive conditions and neurogenic cause of muscle weakness tend to develop less severe contractures. (7)

Management involves early referral and education regarding the importance of passive range of motion, and splinting while contractures are still mild. As weakness progresses and mobility declines measures such as standing and walking activities, positioning lower extremities in extension and orthoses to facilitate function are prescribed. Once contractures become fixed, they respond poorly to stretching programs and orthopedic surgical management may help to regain lost function or minimize the degree of limitation.

2. Pulmonary Complications

Pulmonary complications including chest infections, atelectasis, pulmonary hypoplasia and respiratory failure are the leading cause of death in the muscular dystrophies. Although people with most forms of muscular dystrophy experience some

deterioration of the respiratory and other skeletal muscles, respiratory involvement in DMD and CMD is inevitable. In CMD, diaphragmatic weakness is a feature even when patients are still ambulant, necessitating early respiratory monitoring. A correlation between motor and respiratory function has been observed in other sub types of CMD. The typical respiratory progression of patients with DMD is seen, as an increase in vital capacity as predicted until about 10 years of age, after which it plateaus. With the development of respiratory muscle weakness along with skeletal deformities, vital capacity starts to fall. The rate at which vital capacity declines is around 8% per year. (8, 9) A prospective study showed that almost three quarters of patients die from hypercapnia caused due to alveolar hypoventilation. (10)

In Myotonic dystrophy, alveolar hypoventilation is an important complication which results from a combination of respiratory muscle weakness and dysfunction of the respiratory centres in the brain. Patients are at risk of aspiration pneumonia due to failure of pharyngo-oesophageal muscle function. (11)

Sarcoglycanopathies (LGMD 2C-2F), sub types of autosomal recessive Limb Girdle Muscular Dystrophy present respiratory involvement in more than 70% of cases with reduced forced vital capacity. In calpainopathy or LGMD 2A, there is late respiratory muscle involvement with sparing of the cardiac muscles.

Respiratory involvement is not typically observed in BMD, autosomal LGMD and distal myopathy. But, development of scoliosis, contractures and spinal rigidity, results in a restrictive pattern of respiratory impairment.

Careful monitoring and anticipation of complications are important so that ventilatory assistance can be started at an appropriate time. Most patients respond well to ventilator support with reduced pulmonary morbidity and extended survival.

A small number of trials on respiratory muscle training have been reported. These have been concentrated on respiratory muscle strength or endurance and shown some benefit. (12) The benefits are likely to be seen in patients with early respiratory muscle involvement rather than in those on the verge of decompensation. The life expectancy in DMD is short, but recent studies have shown that non-invasive ventilation (NIV) can increase the survival of patients. NIV in the form of intermittent positive pressure ventilation via a mask has now largely replaced other non-invasive methods of ventilatory support. It has fewer complications than endotracheal intubation, particularly pneumonia. (13) Continuous ventilation can also be provided using a tracheostomy, when other device interfaces are poorly tolerated or the patient lacks sufficient oromotor and/or neck control to use a mouthpiece interface during the daytime. Other measures such as use of assistive coughing techniques, BiPAP and airway clearance can prevent hospitalization and reduce the incidence of pneumonia

3. Cardiac Complications

Cardiac involvement in muscular dystrophy is very common and significantly affects the quality of life of the patients. It is disease specific and involves conduction disorders, ventricular dilatation and dilated cardiomyopathy. Loss in the integrity of the sarcolemmna, fibre necrosis and replacement of myocardium with connective tissue or fat, results in cardiac complications. Symptoms of congestive heart failure, such as

dyspnea, fatigue, orthopnea, and edema, are seen with varying frequency. Cardiomyopathy in muscular dystrophies most typically takes on a dilated form with enlarged dimensions. Over time, reduced ventricular systolic function can develop. Global or regional impairment of ventricular function can occur in the presence or absence of symptoms of congestive heart failure. Cardiac rhythm disturbances can contribute significantly to the morbidity and mortality associated with muscular dystrophy. (14)

Cardiac involvement in DMD and BMD includes cardiomyopathy and arrhythmias. The incidence of cardiomyopathy increases with age in DMD patients. Cardiomyopathy can be evident at 10 years of age and is nearly universal in DMD patients over the age of 20. Approximately 70% of boys with BMD have cardiac involvement by age 20. Myotonic dystrophy type 1 has a multisystem affliction with prominent cardiac problems leading to an increased incidence of sudden cardiac death. There are reports of young patients with ventricular tachycardia (VT) who have no history of cardiac complaints, with phenotypic characteristics, neuromuscular testing and genetic analysis pointing towards the diagnosis of myotonic dystrophy type 1. Due to the malignant nature of VT, these patients may require an implantable cardioverter/defibrillator. (15)

Combination therapy with angiotensin-converting enzyme (ACE) inhibitor and/or angiotensin receptor blocking drugs, loop-diuretics, spironolactone and the addition of non-selective beta-adrenergic blocking drugs at a later stage is established to control symptoms in patients with cardiac failure of diverse etiologies. The same regimes are also followed to prevent progressive deterioration of heart function and to improve prognosis in patients with asymptomatic left ventricular dysfunction. Some studies also suggest that corticosteroids have a beneficial effect in DMD while cardiac pacemaker implantation is fruitful in the case of Emery-Dreifuss muscular dystrophy. (16)

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7

Experimental Animal Models Of Duchenne Muscular Dystrophy

Spontaneous forms of X-linked muscular dystrophy due to dystrophin deficiency have been identified in mice, multiple dog breeds, and cats . The importance of animal models in new treatment (drug) development is emphasized by the Guidelines for Human Somatic Cell Therapy and Gene Therapy issued by the Center for Biologics Evaluation and Research (CBER), Food and Drug Administration (FDA): "Due to the unique and diverse nature of the products employed in cellular and gene therapies, conventional pharmacology and toxicity testing may not always be appropriate to determine the safety and biologic activity of these agents. Issues such as species specificity of the transduced gene, permissiveness for infection by viral vectors, and comparative physiology in available animal models mimicking the disease indication should be considered in the design of these studies." Further, it is strongly recommended that "Preclinical pharmacologic and safety testing of these agents should employ the most appropriate, pharmacologically relevant animal model available. A relevant animal species would be one in which the biological response to the therapy would be expected to mimic the human response.

(I) MOUSE MODEL:

1. **mdx mouse:** The most widely used DMD mouse model is the mdx mouse, which is a naturally occurring mutant that has a premature stop codon in exon 23 of its dystrophin gene due to a point mutation, resulting in the complete absence of full-length dystrophin expression.
2. **dKO mouse (Double knockout mouse):** Due to the relatively mild phenotype of the mdx mouse, many attempts have been made to exacerbate this phenotype by generating double knockouts. The double knockout that has been used most extensively in preclinical studies for DMD is the utrophin/ dystrophin double knockout (dKO, mdx; utrn-/-) which was generated by

crossing mdx mice with a knock-out of the functional dystrophin homologue, utrophin. The dKO mouse displays a disease phenotype far more similar in its severity to that of DMD patients.

(II) CANINE MODEL

1. **Golden retriever (GRMD) dog model:** The best characterized and most widely used canine model of DMD is the Golden retriever (GRMD) dog model. GRMD lacks dystrophin due to incorrect splicing resulting in a truncated transcript. The major problem with the use of these dogs is of greater individual variation in phenotype, shorter lifespan compared to unaffected siblings, and higher cost, which together limit large-scale breeding and widespread application of this animal model in research.
2. **German shorthaired pointers (GSHPMD) dog model:** The GSHPMD "dystrophin knockout" model can be advantageous for two main reasons. First, scattered dystrophin-positive (revertant) fibers that occur due to aberrant splicing in DMD patients, mdx mice, and dystrophic dogs and otherwise confound results of gene therapy studies should be absent. Second, and more importantly, the lack of these revertant fibers provides a "cleaner" background on which to conduct studies of the immunologic aspects of gene therapy.

(III) FELINE MODEL

The hypertrophic feline (Cat) model for muscular dystrophy also exhibits similar clinical symptoms to human DMD, but so far has not been extensively studied.

(IV) OTHERS

Although lower species such as C. elegans, drosophila, zebra fish, sea urchins, and mammals diverged early in evolution, their muscles share many structural and molecular features, rendering them a relevant model to study muscle function. The animal models of lower species are emerging as useful tools for revealing the complex functions of dystrophin as well as for screening of new drugs or genetic therapies for DMD.

	Human	Dog	Cat	Mouse
X-linked disorder	+	+	+	+
Gene(s)	*DMD*	*GRMD, GSHP*	*FHMD*	*mdx, mdx2–5 cv*
Mutations	Deletions, point, duplications and splicing	Splicing and deletions	Promoter	Point and deletions
Dystrophinopathy	+	+	+	+
Muscle weakness	++	++	–	–
Absolute force	–	–	?	+
Specific force	–	–	?	–
Myofibre hypertrophy	+	+	+	+
Muscle wasting (old)	+++	+++	–	–
Serum creatine kinase	+++	+++	+++	+++

Table 1. Dystrophinopathy Across Different Species.

8

Treatment

Muscular dystrophy is one of the most difficult disorders to treat. Although, its pathogenesis is well understood there is no known cure available for any of the 9 types of muscular dystrophy. Conventional methods of coping with the disease include exercise and drugs that slow down or eliminate muscle wasting like anabolic steroids and supplementation. Skeletal muscle is the most abundant tissue of the body and is composed of large multinucleated fibers, whose nuclei cannot divide. Consequently, any cell or gene replacement method must restore proper gene expression in hundreds of post-mitotic nuclei, which are embedded in a highly structured cytoplasm and surrounded by a thick basal lamina. Similarly, most pharmacological approaches must invade the complex and partly unknown biochemical mechanism of fiber degeneration.

Historical aspect of treatment

Guillaume-Benjamin Duchenne, a French neurologist, who first described Duchenne's muscular dystrophy, used faradic shock for Muscular dystrophy treatment. This was a non-invasive technique of muscle stimulation that used faradic shock on the surface of the skin, which he called "electrisation localisee".

Demonstration of the mechanics of facial expression. Duchenne and an assistant faradize (Faradic shock) the mimetic muscles of "The Old Man.

Current treatment:

The treatment of muscular dystrophy has evolved from electrical simulation to Gene Therapy and Cell Therapy.

Goals of treatment:

1. To correct the genetic defect,
2. To restore functional expression of dystrophin,
3. To slow disease progression, and
4. To improve the quality of life of MD patients

Major therapeutic strategies for Muscular Dystrophy:

1. Gene Therapy:

A. Gene replacement therapy -by

a. Delivery of dystrophin mini-gene contained in vectors like-

- Adenoviral vectors
- AAV (Adeno-Associated Viral Vectors)
- Lentivirus
- Retroviral Vectors
- Naked plasmid DNA
- Human artificial chromosomes (HACs) (episomal vectors)

  (Tedesco et al. described Stem cell-mediated transfer of a human artificial chromosome which ameliorated muscular dystrophy.)

b. Stem cells

- Satellite cells
- Muscle- or bone marrow-derived SP cells
- Bone marrow-derived stromal cells

B. Gene modification therapy (DNA/RNA Manipulation): changing or repairing gene mutations.

a. Antisense oligonucleotides ((AONs)) resulting in exon skipping and short forms of dystrophin

- peptide nucleic acids (PNA),
- 2'-O-methyl-phosphorothiate- AONs (2'OMeAO)

  (i) GSK2402968- based on the 2'OMeAO chemistry and targeting exon 51
- phosphorodiamidate morpholino oligomer (PMO) and

  (i) AVI-4658- based on the PMO backbone also targets exon 51
- cell penetrating peptide-conjugated PMO (PPMO).
- locked nucleic acid (LNA)
- ethylene-bridged nucleic acid (ENA)

b. DNA Chimeraplasts to correct point mutations or small deletions
c. Viral-directed exon skipping (U7-snRNA- a non spliceosome small nuclear RNA (snRNA))

2. Cell Therapy: Delivery of cells that make new muscle to diseased areas.
   A. Muscle precursor cells (Myoblasts)
   B. Stem cells that have the ability to differentiate into muscle cells.
   a. embryonic stem cells (ESCs),
   b. induced pluripotent stem cells (iPSCs) and
   c. adult stem cells (ASCs) which include bone marrow derived stem cells, blood- and muscle-derived CD133+ cells, muscle-derived stem cells (MDSC), side population (SP) cells and mesoangioblasts.
3. Pharmacological Therapy
   A. Drugs to turn on the utrophin gene expression
      a. Heregulin
      b. SMT C1100
      c. okadaic acid
      d. L-arginine
      e. Biglycan
      f. TAT-utrophin
      d. New compounds to be screened
   B. Drugs to cause read-through of a premature stop codon
      a. Aminoglycosides (Gentamicin, Negamicin)
      b. Ataluren (PTC124)- a 1, 2, 4-oxadiazole compound, which is a small molecule that can override nonsense stop translation signals to produce full-length proteins (dystrophin).
      c. More new compounds to be screened
   C. Growth factors/Drugs
      a. IGF-I - to promote muscle repair
      b. Myostatin inhibition (GDF8- TGF-ß superfamily member) - to decrease muscle damage
      c. ACE-031- recombinant fusion protein which promotes muscle growth by inhibiting ActRIIB signaling.
   D. Protease inhibitors to slow muscle breakdown
      a. Leupeptin (calpain inhibition)
      b. BBIC (serine protease inhibition)
      c. MG-132 (proteosome inhibitor)
   E. Anti-inflammatory agents

a. Cyclosporine A
b. Enbrel
c. REMICADE
d. NFκB
e. nNOS (neuronal nitric oxide synthase) upregulation
f. Pentoxifillin

F. Corticosteroids
a. Prednisone
b. Deflazacort (DFZ)- methyloxazoline derivative of prednisolone

G. Drugs to increase muscle strength
a. Creatine supplements
b. Calcium
c. Magnesium

H. Drugs maintaining calcium Homeostasis

I. Antioxidants:
a. Selenium
b. omega -3 Fatty acids

All these methods are aimed at slowing down the progression of the disease, or reducing the symptoms and they are also effective in prolonging the lifespan of affected individuals

1. DRUG TREATMENT

Steroids have been demonstrated to be efficacious in slowing the progression of muscular dystrophy especially DMD and in delaying the loss of independent ambulation, stabilize muscle strength and preserve pulmonary functions. (1, 2)

Corticosteroids may enhance myoblast proliferation and promote muscle regeneration. Alternatively, steroids may inhibit muscle degradation by stabilizing lysosomal-bound proteases or muscle cell membranes. Finally, prednisone could reduce muscle damage and necrosis through its immunosuppressive and anti-inflammatory effects. (3, 4) Multiple randomized trials have found improved function and strength in children treated with prednisone. (5, 6)

Unfortunately, in these studies prednisone had a great deal of side effects including weight gain, cushingoid features, hypertension, hyperactivity, growth retardation, and cataracts. A methyloxazoline derivative of prednisolone, deflazacort (DFZ), has shown some promise in providing similar effects to prednisone with a less concerning side effect profile. (7) If both drugs are similarly effective in improving strength and if weight gain is less evident with DFZ then improvements in functional strength may exceed those seen with prednisone.

Reduction in the total amount of steroids with different treatment schedules, such as alternate-day, pulsed, high-dose intermittent or daily low-dose administration, may decrease side effects.

Therapeutic molecules such as ACE-031 are also being developed for the treatment of DMD patients with the goal of improving strength and preserving physical functions. It is a recombinant fusion protein which promotes muscle growth by inhibiting ActRIIB signaling. (8) In 2010, a phase II study in DMD patients was initiated in Canada but was terminated due to serious safety concerns.

Due to the side effects of the above steroids and therapeutic molecules, many studies have been carried out to study the use of creatine as an effective treatment for muscular dystrophy especially DMD. A study by Tarnopolsky reported the benefits of creatine supplements in patients with DMD. Creatine is a guanidino compound that may confer therapeutic benefit in muscular dystrophy by increasing strength and fat-free mass (FFM), by its antioxidant properties, by reducing protein breakdown and by enhancing sarcoplasmic reticulum calcium reuptake. (9)

Drugs that have been used to treat myotonia include sodium channel blockers such as procainamide, phenytoin and mexiletine, tricyclic antidepressant drugs such as clomipramine or imipramine, benzodiazepines, calcium antagonists and taurine. Till 2009 about 10 clinical trials were carried out to test the safety and efficacy of these drugs. Two small studies suggested that clomipramine and imipramine might have a short-term beneficial effect on the myotonia in myotonic dystrophy and one small study suggested that taurine might have a long-term beneficial effect in myotonic dystrophy. Minor side effects such as dry mouth and dizziness were reported with clomipramine and imipramine, but not with taurine. It was not possible to determine whether drug treatment was safe and effective based on this evidence. Hence, larger, well-designed randomized controlled trials are required. (10)

Few drugs such as Heregulin, L-arginine, TAT-utrophin, okadaic acid and SMT C1100 have shown to turn on the utrophin gene expression.

Heregulin, acts via the N-box motif of the utrophin A promoter (11) and L-arginine, results in an increase in utrophin expression as a result of increased production of nNOS. (12) TAT-utrophin is a recombinant utrophin protein modified with the HIV-derived TAT protein transduction domain, improves delivery across the cell membrane. (13) Okadaic acid have also been identified to upregulate utrophin expression in mdx mice but so far this has not reached therapeutic levels. (14) SMT C1100 targets the primary cause of the disease by reducing the level of muscle membrane damage, as demonstrated by a reduction in force drop following eccentric contractions (15). Serum creatine kinase, muscle fibrosis and necrosis are also reduced indicating that SMT C1100 diminishes the catastrophic secondary pathology associated with the disease. SMT C1100 was taken into Phase I trials, although there were no safety issues, the plasma levels of the drug were not high enough for the trials to continue into patients. New formulations of the drug are currently being explored by Summit plc with a view to taking this

compound back into the clinic. The therapeutic use of these drugs is promising but more screens are required for the same.

Nutritional support is often overlooked but is important especially in order to improve quality of life. Antioxidants and anti-inflammatories have known to offer some benefit. Animal studies have shown that diet rich in omega-3-fatty acids prevent skeletal muscle lesions and improves muscle appearance on histological examination. (16) (Further Details on Nutrition are discussed in Chapter 10)

2. REHABILITATION

Management of muscle extensibility and joint contractures is a key part of rehabilitation management. One goal of physical therapy is to provide regular range-of-motion exercises to keep the joints as flexible as possible, delaying the progression of contractures, and reducing or delaying curvatures of the spine. Braces are used especially on the ankles and feet to prevent equinus gait. Full-leg braces may be used in DMD to prolong the period of independent walking. Strengthening other muscle groups to compensate for weakness may be possible if the affected muscles are few and isolated, as in the earlier stages of the milder muscular dystrophies. Regular, nonstrenuous exercise helps maintain general good health. Strenuous exercise is usually not recommended, since it may damage muscles further. Wheelchairs, canes and walkers are also used to help patients keep their independence and walking capabilities. Treatment programs, especially focusing the shoulder, should be started for the upper extremities. The maintenance of active range of motion and strength results in independence in performance of activities of daily living, such as dressing, oral/facial hygiene, homemaking, and preparation for work.

Effects of rehabilitation will be further discussed in detail in Chapter 16.

3. GENETIC COUNSELING

Genetic counseling is advised for people with a family history of the inherited disorder. It helps to identify families at risk, investigate the problem present, interpret information about the disorder, analyze inheritance patterns and risks of recurrence and review available options with the family. For families living with Duchenne or Becker muscular dystrophy, it can offer several benefits. Genetic counseling plays a major role in DMD; its aim should be to avoid the birth of the affected males. During counseling one can explain the cause of muscular dystrophy, the typical symptoms and course of the disorder, and can discuss and facilitate diagnostic and genetic testing options. Parents often are uncertain about the purpose of genetic counseling and what it entails. In the case of Duchenne muscular dystrophy, the basic purpose of counseling is to help a couple understand the hereditary nature of the disorder and the probable risk for them and other family members of having a dystrophic child. Couples are then able to make informed decisions about future childbearing.

Each time a DMD carrier mother has a child; there are four possible outcomes, each with an equal probability of happening. Thus, the chance of producing an affected

son is one in four, or 25 %. Further breakdown of the risk according to the sex of the child, follows that there is a 50% chance that each son will be affected. All daughters will be unaffected, but each has a 50% chance of being a carrier like her mother.

It is important to know that unaffected son of carrier mothers do not have the DMD gene, and therefore, cannot transmit DMD to their offspring. The same is true for those daughters of carriers who have not inherited the DMD gene. If circumstances should allow a male affected with DMD to reproduce, and if his wife was not a carrier of DMD, then all of his sons would be unaffected and free of the gene but all of his daughters would be carriers.

Carrier Testing

Genetic testing can help tell whether a woman is definitely a carrier or whether she is very unlikely to be a carrier. Carriers have an increased chance of having boys with Duchenne or Becker muscular dystrophy. All women who could be carriers, based on their family history with sons or brothers with DMD/BMD, uncles or cousins on their mother's side of the family who have DMD/BMD, mothers or sisters who are carriers for DMD/BMD, and aunts or cousins in their mother's side of the family who are carriers for DMD/BMD. If a woman knows she is a carrier, she can make more informed childbearing plans. Identifying carriers in the family can provide information to other family members about their chance of also being carriers and having affected sons.

The method for carrier testing should be determined by the woman's family history, including whether the mutation in the family is known .If the mutation is known; only that mutation needs to be tested. If the mutation in the family is not known because the affected person was not tested, it is best to test him first. If genetic testing was done in the past and no mutation was found, it might be appropriate to test the affected individual again using new and improved tests, which can identify more mutations.

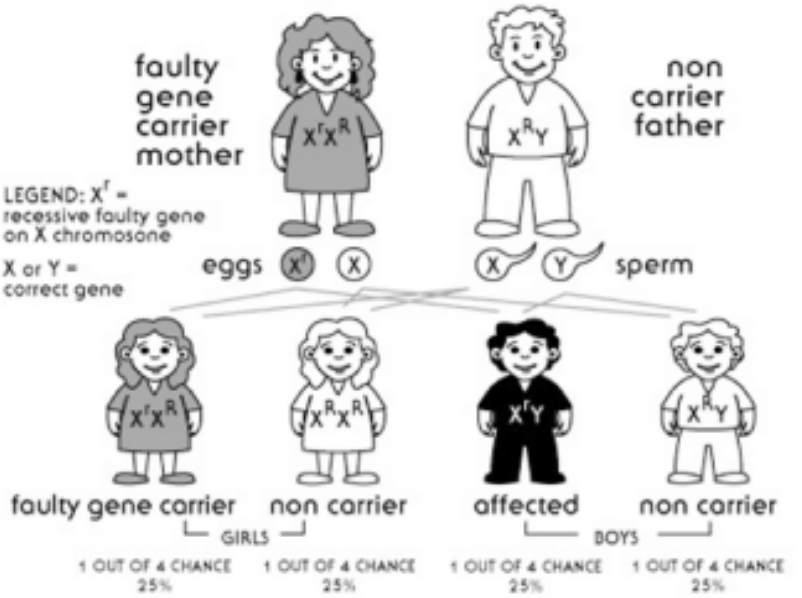
The types of tests that have been used for carrier testing include creatine phosphokinase (CPK) testing, muscle biopsy, and genetic carrier testing. In most cases, CPK testing and muscle biopsy are not good choices for carrier testing. CPK levels are higher in child and adolescent carriers than in adult female carriers, who are the ones more likely to have carrier testing. CPK levels also may be increased for reasons other than muscular dystrophy, such as strenuous activity or sickness. A muscle biopsy is an invasive test, which is less accurate as compared to genetic testing.

If a woman has a child with DMD or BMD and also has other affected male family members, for example an affected brother or nephew, it is extremely likely that she is a carrier. If there are no other affected family members, there is a 66% (or 2 in 3) chance of being a carrier. Approximately 33% (or 1 in 3) of cases of Duchenne muscular dystrophy are caused by what are called new mutations. These are random changes to the genetic code in the dystrophin gene that happen in only one egg or sperm, that one egg or sperm could create an affected male; rarely, a carrier female child who could later have affected children. The possibility for new mutations is one of the reasons

why 1/3 or more of individuals with Duchenne muscular dystrophy will have no family history. Another possibility is that some families have several generations with mostly or all females (that is, they have no boys to express the disease). These families may not know that there are several generations of carriers. Affected people in the same family almost always have the same mutations in the dystrophin gene and will have the same type of muscular dystrophy.

Reproductive Options:

There are many different reproductive options for carrier families with a higher chance of having a child with Duchenne or Becker muscular dystrophy. There is a 25% chance of having an affected child (25% affected son; 25% unaffected son; 25% carrier daughter; 25% non-carrier daughter). If the child is known to be male, the chance of having an affected son is thus 50%; if it is female, the chance of a carrier daughter is 50%.



X - linked recessive inheritance of Muscular dystrophy

1. Mutation in the family is known: Have a natural pregnancy and pursue testing for sex, followed by testing for the gene mutation in the family.

Chorionic villus sampling (CVS) is generally offered between the 10th and 13th weeks of pregnancy. A small piece of the placenta is tested to determine the sex of the baby. If male, those same cells can be tested for the known mutation in the dystrophin gene in the family. Amniocentesis is generally performed starting at 15 weeks, and can be performed through the end of the pregnancy. Cells from amniotic fluid are tested to determine the sex of the baby. If male, those same cells can be tested for the known

mutation in the dystrophin gene in the family. Prenatal testing is often used to prepare for an affected child, or to make pregnancy termination decisions.

2. Mutation in the family is not known: Have a natural pregnancy and pursue testing for sex, followed by linkage testing or fetal muscle biopsy.

For families with a confirmed diagnosis of Duchenne or Becker muscular dystrophy, but where genetic testing has not identified a disease-causing factor, linkage analysis using the genetic material taken from the CVS or amniocentesis may be available. Linkage analysis uses markers along the gene to determine whether the baby has inherited the "at risk" X chromosome. Linkage analysis is usually only available for families that have at least two affected males. This option involves blood draws from multiple generations, including the affected individuals, so discussing this option prior to a pregnancy is strongly encouraged.

When linkage analysis is not possible, some hospitals offer fetal muscle biopsy (taking a small sample of muscle from the developing baby). This procedure is not offered in very many hospitals and has a higher risk for complications, including death of the fetus, than amniocentesis or CVS. Counseling about the risk and benefits of fetal muscle biopsy is absolutely necessary.

3. Preimplantation Genetic Diagnosis (PGD)

PGD combines in-vitro fertilization (IVF) with genetic testing, with the goal of implanting only unaffected embryos into the uterus. Different women will have different numbers of embryos without the dystrophin gene mutation. IVF and PGD are expensive and invasive technologies that are not available in all medical centers.

4. Egg and sperm donation

Carrier females may consider pregnancy with a donor egg. Egg donation from a non-carrier reduces the chance of having a child with muscular dystrophy to the chance in the general population. Males with DMD or BMD may consider using a donor sperm. Sperm donation from an un-affected male reduces the chance of having carrier daughters to the chance in the general population.

5. Adoption

Adoption is another option that may be explored.

In today's world where diagnoses are made earlier, care and management is better, with new therapies on the horizon.

4. GENE THERAPY

Development of gene therapy for muscular dystrophy represents a challenge which requires significant advances in the knowledge of defective genes, muscle promoters, viral vectors, immune system surveillance and methods for systemic delivery of vectors. However, tremendous progress has been made in developing improved viral vectors

and avoiding immune reactions against gene transfer. There is a gene therapy method known as targeting repairing or chimeraplast, using a synthetic blend of DNA and the related RNA, which tricks the patient's own cells to repair the mutation. The chimeraplasts match the patients' own DNA except for where the mutation occurs, attach to the DNA, and then activate DNA repair mechanisms. Although this approach initially appeared promising, the repair rate is generally found to be too low to cure. U7, a non spliceosome small nuclear RNA (snRNA), normally involved in the processing of the histone mRNA 3' end, to enhance the delivery of antisense sequences (17). By slightly modifying the binding site for Sm/Lsm proteins, U7 can be converted into a versatile tool for splicing modulation. Delivery of the appropriately modified U7 snRNA using an adeno-associated virus has demonstrated widespread dystrophin restoration in both the mdx mouse and the GRMD (18) models of DMD following only a single dose.

Gene therapy is further discussed in details in Chapter 11

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9

Ongoing Clinical Trials of Various New Therapies for Muscular Dystrophy

Ongoing clinical trials of new drugs, new methods of gene delivery, cellular therapy, electrostmulation and infrared radiation as various modalities of treatment for muscular dystrophy are as follows:

1. GSK2402968

Phase II Doubleblind Exploratory Study of GSK2402968 in Ambulant Subjects With Duchenne Muscular Dystrophy (DMD117)

GSK 2402968 consists of short pieces of DNA called "antisense oligonucleotides" or "AONs" that are being tested for their ability to convert deletions near Exon 51 in the dystrophin gene from non-functional "out-of-frame" deletions to more functional "in-frame" deletions, such as those typically seen in boys and men with Becker muscular dystrophy. The strategy is commonly called "exon-skipping".

Although variations on this strategy might ultimately be used to try to correct deletions in many parts of the dystrophin gene, GSK 2402968 targets the following deletions: 45-50, 47-50, 48-50, 49-50, 50, 52.

2. PRO044

Phase I/II Study of PRO044 in Duchenne Muscular Dystrophy

PRO044 is similar to GSK2402968 in chemistry &mechanism and also highly sequence-specific, specifically induces exon 44 skipping in the DMD gene.

3. Idebenone

Phase III Study of Idebenone in Duchenne Muscular Dystrophy

Idebenone is a synthetic analogue of coenzyme Q10 and is a powerful antioxidant and essential constituent of the process of energy production on the cellular level. It can protect mitochondria from oxidative damage and boost their impaired function. It is thought that this mechanism will slow decline in heart function that is part of the disease process of Duchenne Muscular Dystrophy (DMD). It is possible that patients may benefit in terms of muscle strength and respiratory function.

4. IGF-1

Safety and Efficacy Study of IGF-1 in Duchenne Muscular Dystrophy

The purpose of this study is to determine whether IGF-1 therapy improves or preserves muscle function in Duchenne Muscular Dystrophy (DMD).

5. Glutamine and creatine monohydrate

Phase III Study to Assess Efficacy and Safety of Glutamine and Creatine Monohydrate on muscle strength in Duchenne Muscular Dystrophy (DMD)

6. Flavocoxid

Safety Study of Flavocoxid in Duchenne Muscular Dystrophy

To evaluate safety and tolerability of flavocoxid administered at the daily oral dose of 500 or 1000 mg/die for one year in DMD patients, alone or in association with steroids

7. CoQ10

To determine if CoQ10 and prednisone, alone and as a combination decrease the decline in cardiopulmonary and skeletal muscle function that occurs in the wheelchair confined phase of DMD.

8. Pentoxifylline

Study of Daily Pentoxifylline as a Rescue Treatment in Duchenne Muscular Dystrophy to see whether the addition of pentoxifylline to a steroid regimen is effective in treating deteriorating muscle strength by comparing the muscle strength of PTX treated subjects and placebo treated subjects.

9. Tadalafil

Tadalafil in Becker Muscular Dystrophy

This study is intended to build on recent findings published in the journal Nature showing beneficial effects of tadalafil (also known as Cialis) in mice with an animal

version of Duchenne and Becker muscular dystrophies. Only two doses of tadalafil improved muscle blood flow, allowing the dystrophic mice to perform more exercise with less muscle injury. This new short-term clinical trial will move the testing from animals to human patients with Becker muscular dystrophy and examine the effects of acute tadalafil dosing on muscle blood flow during a bout of exercise.

10. Sunphenon Epigallocatechin-Gallate (EGCg) in Duchenne Muscular Dystrophy (SUNIMUD)

To investigate safety and tolerance of Epigallocatechin-Gallate (EGCG, the major polyphenol in green tea) in patients with muscular dystrophy of the Duchenne type.

11. Sildenafil

Effect of Modulating the nNOS System on Cardiac, Muscular and Cognitive Function in Becker Muscular Dystrophy Patients

In muscular dystrophy, the cellular protein, dystrophin is affected. During normal conditions, the enzyme neuronal nitric oxide synthase (nNOS), which produce nitric oxide (NO), is attached to dystrophin. NO is important in normal vascular function in each of muscle, heart and brain by stimulating production of cyclic GMP. However, in muscular dystrophy with dystrophin deficiency, nNOS do not have the normal cellular anchor, resulting in decreased NO levels and subsequent reduced cyclic GMP production. Sildenafil inhibits degradation of cGMP thus prolonging and increasing a cGMP response. Such effects are the basis for use of sildenafil in pulmonary hypertension and erectile dysfunction. Current hypothesis: Sildenafil restores the cyclic GMP function affected in muscular dystrophy wit nNOS deficiency resulting in improved muscle, cardiac, cerebrovascular and cognitive function.

12. Oxatomide (tinset)

KUL0401: An Open-label Pilot Study of Oxatomide in Steroid-Naive Duchenne Muscular Dystrophy

To determine the safety and efficacy of the mast cell stabilizer Oxatomide as a treatment for Duchenne muscular dystrophy (DMD).

13. Gene Transfer of rAAV1.tMCK.Human-Alpha-Sarcoglycan

Phase I Gene Transfer of rAAV1.tMCK.Human-Alpha-Sarcoglycan for Limb Girdle Muscular Dystrophy Type 2D (LGMD2D)

Insufficient levels of the protein alpha-sarcoglycan result in muscle weakness that worsens over time. The purpose of this study is to evaluate the safety and effectiveness of gene therapy in treating children and adults with LGMD2D.

14. AAV1-gamma-sarcoglycan vector injection

Phase I Clinical Study of AAV1-gamma-sarcoglycan Gene Therapy for Limb Girdle Muscular Dystrophy Type 2C

To study the evaluation of clinical safety and feasibility of gene therapy in patients with limb girdle muscular dystrophy type 2C (gamma-sarcoglycanopathy).

15. Electrostimulation

Electrostimulation of Shoulder Girdle and Quadriceps Muscles inFacioscapulohumeral Muscular Dystrophy Patients

To evaluate clinical tolerance, biological tolerance, feasibility and efficacy of daily electrostimulation training of shoulder girdle and quadriceps muscles in patients with facioscapulohumeral muscular dystrophy.

16. Stamulumab (MYO-029)

Phase I/II, multicenter, safety trial is to study MYO-029 in adult patients with muscular dystrophy.

Myostatin is a protein that inhibits the growth of muscle tissue, stamulumab is a recombinant human antibody designed to bind to and inhibit the activity of myostatin.

Stamulumab (MYO-029) is an experimental myostatin inhibiting drug

17. Albuterol and Oxandrolone

Study of Albuterol and Oxandrolone in Patients With Facioscapulohumeral Dystrophy (FSHD)

To determine whether albuterol or oxandrolone, alone or in combination, are able to increase strength and muscle mass in patients with FSHD.

18. Mexiletine

Clinical Efficacy Trial of Mexiletine for Myotonic Dystrophy Type 1

To investigate the effects of mexiletine treatment for 6 months on ambulation, myotonia, muscle function and strength, pain, gastrointestinal functioning, cardiac conduction, and quality of life in myotonic dystrophy type 1 (DM1).

19. Dehydroepiandrosterone (DHEA)

Phase 3 Study of Oral Dehydroepiandrosterone (DHEA) in Adults With Myotonic Dystrophy

To test the efficacy and safety of two doses of dehydroepiandrosterone (DHEA) in adults with myotonic dystrophy

20. Transvenous Limb Perfusion With Normal Saline

Safety and Feasibility of Transvenous Limb Perfusion With Normal Saline in Human Muscular Dystrophy

To determine the safety and feasibility of a particular delivery method for gene therapy that could be used in the future to treat people with muscular dystrophies.

21. Infrared Radiation

Phase 1 Study to Determine the Efficacy of Using Far Infrared Radiation to Manage or Treat Muscular Dystrophies.

To investigate the use of far infrared radiation for managing muscular dystrophies.

10

Nutritional Support in Muscular Dystrophy

Nutritional requirement in patients with Muscular Dystrophy is often ignored due to lack of research. However it is gaining importance due to the nutritional deficiencies often seen among such patients.

Patients with muscular dystrophy may be prone to nutrient deficiency due to mobility limitations or oropharyngeal weakness. Patients with myotonic muscular dystrophy may be particularly prone to such deficiencies from associated dysmotility of the entire gastrointestinal tract. Research demonstrated inadequate nutrient intake of protein, energy, vitamins (water and fat soluble), and minerals (calcium and magnesium). Significant correlations were found between measures of strength and certain individual nutrients (e.g. copper and water-soluble vitamins). Research indicates that a substantial number of adults with muscular dystrophy do not meet current dietary intake recommendations. (1)

Requirement of Energy and Proteins vary from patient to patient depending on the level of physical activity. The recommended dietary allowances for other nutrients also vary. However, foods rich in nutrients like calcium, magnesium, copper, selenium are administered to such patients.

A) Energy:

The energy requirement in muscular dystrophy cases is 30 % more due to severe muscle wasting. (2)

Okada et al. (3) found that the basal metabolic rate (BMR) of patients with DMD was higher than that of controls for all ages, with the difference increasing with age, and being about 20% to 30% higher in older boys with DMD. Boys under the age of 14 need to watch the total caloric intake as obesity may set in due to restricted physical

activity. However, in older boys undernutrition is observed and researchers have tried to link the BMR and BEE (basal energy expenditure) to the rate at which muscle wasting occurs.

Therefore, an approximate calculation for energy is, (4)

Energy = Weight * 25 (+500) kilocalories

B) Protein:

Proteins are molecules of amino acids which are required by the body for proper functioning of cells, tissues and muscles. Since a large part of the muscles contain protein, the daily requirement of patients with muscular dystrophy is set to be approximately 1.2 gms /kg body weight. The excess protein requirement is to replenish the muscle proteins. Good quality protein with higher biological value is recommended. Egg whites, whole beans and pulses, sprouts, milk and milk products, soy proteins (if no allergy) must be included in the daily diet.

C) Calcium and Magnesium:

Calcium and magnesium is critical for the muscular and nervous system and for the production of ATP molecules which provides cellular energy. Whether dystrophin and its associated proteins have a direct role in the regulation of calcium ions, calcium channels or intracellular calcium stores, or indirectly alters calcium regulation through enhancement of membrane tearing, remains unclear. (5)

Calcium is available in many foods. Most people think of dairy when they think of calcium. Though cheese is a good source of calcium it is high in saturated fat. A varied diet should be taken to get the best calcium absorption. It is estimated that only 30% of dietary calcium is absorbed.

Factors which inhibit calcium absorption and may contribute to calcium loss are:

Aluminum (foods cooked in aluminum cookware including the use of acidic foods with the cookware), aluminum foil, antacids containing aluminum and high levels of magnesium. Zinc, oxylates (a chemical that is found in sweet potatoes, dried beans, concentrated forms of phytic acid (such as found in wheat bran and dried beans)and dietary fiber inhibit calcium absorption.

Alcohol, phosphates (in soft drinks and meats), sugar, and protein increase calcium excretion. High levels of sodium may also be linked to calcium excretion. Including foods such as whole grain cereals like ragi, jowar, leafy vegetables, till seeds, flaxseeds, methi (fenugreek seeds), almonds, and walnuts can increase the calcium intake in the daily diet.

The scientists also found that patients had lower-than-normal levels of a form of bioactive vitamin D and adequate dietary calcium intake seems to be an effective first-line approach that controls bone turnover, corrects vitamin D deficiency. (6)

D) Selenium:

It is an antioxidant that works closely with vitamin E in actions like production of antibodies. Selenium protects the cell "machinery" that generates energy. It is also

necessary for the production of prostaglandins, substances which affect blood pressure and platelet aggregation. Deficiency of selenium has been associated with premature aging, heart attack, muscular dystrophy. (7)

Studies by Ornadhl et al have shown drastic improvements in patients with Myotonic dystrophy with additional dosage of Selenium and Vitamin E. However, further studies and trials have to be done to confirm the improvement in such patients.

E) Green tea:

Over a last few decades green tea is under tremendous research for the amazing health benefits imparted on it.

A research study conducted in Switzerland concluded that the antioxidant mechanism in green tea improved muscle health by delaying muscle necrosis in mice. (8)

Before the identification of the deficient proteins that underlie muscular dystrophies, such as

Duchenne muscular dystrophy (DMD), oxidative stress was proposed as a major cause of the disease. (9).

The antioxidants in green tea neutralize these free radicals thereby preventing cell damage. Dorchies et al have conducted studies on mice with green tea extracts preventing muscle necrosis. (10)

F) Omega 3 fatty acids:

The inclusion of omega 3 fatty acids in the diet is not only said to be effective for patients with cardiomayopathy, but also improves the muscle tissue appearance. Fiaccavento et al carried out a study wherein dystrophic animals were fed flaxseed-derived ω3-α-linolenic fatty acid. They found that histological appearance of the muscular tissue was improved, the proliferation of interstitial cells was decreased, and the myogenic differentiation originated new myocytes to repair the injured muscle. In addition, muscle myofibers were larger and cell membrane integrity was also preserved, as witnessed by the correct localization of α-, β-, and γ-sarcoglycans and α-dystroglycan. (11)

OTHER NUTRIRIONAL ISSUES IN PATIENTS WITH MUSCULAR DYSTROPHY

- Although the causes of gastrointestinal symptoms in patients with MD are multifactorial, small intestinal bacterial overgrowth is an important diagnostic consideration that is easily diagnosed using glucose breath hydrogen testing and often shows a good response to treatment with common antibiotics. (12)
- Constipation is often an issue with such patients. Dealing with abdominal distention and feeling of fullness is of primary concern. Bringing about dietary changes like including high fiber foods in the diet such as fruits and vegetables along with plenty of fluids. This increases the fecal bulk by absorbing the water in the colon relieving constipation.

- Childhood obesity is another major concern in such children. Overfeeding along with lack of physical activity further aggravates the weight gain process. (13)

DIETARY GUIDELINES FOR MUSCULAR DYSTROPHY PATIENTS:

- Small frequent meals throughout the day.
- A good heavy breakfast comprising of cereals and pulses or protein foods, as it provides energy for the entire day.
- The afternoon meal must be a balanced one with complex carbohydrates (whole cereals) and a serving of protein food with high biological value.
- Mid morning and evening snacks which must be low in calorie and fiber rich foods.
- A very light dinner with soft and easy to digest vegetables to avoid gastrointestinal discomfort.
- Plenty of fluids (soups, lime juice, buttermilk, coconut water) throughout the day to relieve constipation.
- Non-vegetarian foods like chicken and fish can be included provided they are cooked in lesser amount of fat.
- Including soy protein can be beneficial if no food allergy is seen, however more research is in progress.
- Indian condiments and spices are very rich in calcium, iron, and antioxidants, hence must be a part of the daily diet. Eg; cinnamon, jeera / cumin, till / sesame seeds, flaxseeds / alsi, ova/ ajwain, ginger, garlic etc. The digestion processes is also enhanced by including such foods.

In short, a complete well balanced diet with plenty of vegetables, fruits, whole cereals and pulses with omega 3 fatty acids and packed with antioxidants can contribute to better and healthy living.

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11

Gene Therapy And Other New Strategies

Gene therapy is a technique used for correcting the defective genes responsible for the development of the disease. The development of methods for delivering the genes into the defected cells over the past decades, has stimulated interest in treating the genetic disorders by gene based therapies. Muscular Dystrophy is a heterogeneous group of inherited disorders characterized by progressive muscle degeneration. Many of these myopathies are caused by mutations in genes that encode for structural proteins that link the cytoskeleton of muscle fibers to the extracellular matrix. Since the discovery of the dystrophin gene and protein over 18 years ago, more than 30 different forms of muscular dystrophy have been molecularly identified. Although, research has helped understanding the molecular basis of this disorder, there is still no effective treatment available. Several novel strategies for replacing or repairing the defective gene are in development, with early encouraging results from animal models. In most of the gene therapies a normal gene is inserted into the genome to replace the abnormal gene causing the diseases. A vector which is a carrier molecule to deliver the therapeutic gene to the patient's target cells is used. Currently the virus vectors are most commonly used to carry normal human DNA, after it is genetically altered.

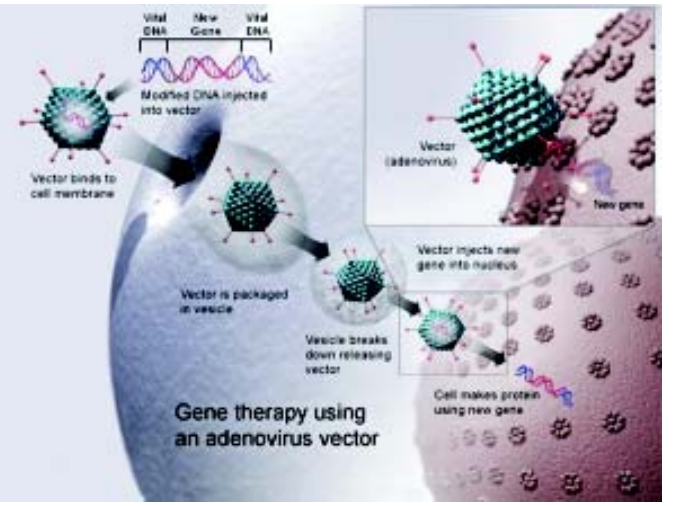
The size of the dystrophin gene has been an important challenge for gene-therapy researchers. To replace a defective dystrophin gene, vectors with a large capacity were needed, which are too large to easily cross the extracellular matrix that surrounds mature myofibres and there are not many adenoviral attachment receptors on the surface of myofibres. Whereas, non-viral DNA plasmid vectors can be engineered to contain these large inserts. These vectors are synthetic and non-infectious, so they are highly suitable for use. However, this delivery strategy is not efficient in muscle tissue, hence, electroporation, cationic lipid formulations, pressurized isolated-limb perfusion or

microbubbles and ultrasound are required to enhance transfection efficiencies. Less invasive, and preferably systemic, methods are needed before plasmid vectors can be routinely used. (1-5)

1. Viral Vectors

The single gene mutation underlying DMD makes viral vector-mediated gene replacement an attractive strategy. Studies have been carried out on adenoviral (Ad), retroviral, and adeno-associated viral (AAV) vectors, the delivery via these vectors of full-length or shortened but functional dystrophin improves the disease phenotype, as displayed in animal models. (6-8)

a) Adenoviral vectors:



Adenoviral vectors are among the most commonly used vectors for gene therapy because of their large cloning capacity, non-oncogenic nature and ability to transduce both dividing and non-dividing cells with high efficiency. A major problem associated with early generations of adenoviral vectors has been severe immune response against both viral and transgene products. (9) To overcome immunological problems, the third generation or 'helper dependent' (hd) or gutted adenoviral vectors were developed which contain only the inverted terminal repeats (ITRs) and a packaging sequence around the transgene while lack all the viral genes. It has a cloning capacity of about 35 kb, which is ideal for carrying large genes such as the full-length dystrophin gene. (10) However, gutted versions of Ad vectors are difficult to grow and scale up to pharmaceutical levels, humoral and cellular reactions in the hosts may result from the use of high vector doses and intravenous administration of adenoviral vectors results in preferential localization to the liver. Moreover, Ad vectors do not integrate into the host genome for transgene expression and the relatively short-term expression of the transgene product requires repeated administration.

b) Retroviral Vectors

Retroviral vectors are attractive for treatment of genetic diseases when stable long-term integration in the genome is required. Different classes of retroviruses have cloning capacities between 7 and 11 kb, so these vectors are limited to delivering only the mini- and micro-dystrophins and they show a very low toxicity profile. (11) Retroviruses are difficult to grow in large quantities, preventing robust transduction of muscle by direct

injection of vector. Nonetheless, all types of retroviruses efficiently integrate into the host genome, potentially allowing persistent gene transfer. Oncoretroviral vectors require dividing cells for efficient cell entry and transgene expression is dependent on the site of integration and cell division. Moreover, retroviral vectors integrate in somewhat random locations and thus can cause insertional mutagenesis and activation of nearby genes, including oncogenes. (12)

On studying the transduction efficiency of retroviral vectors carrying truncated dystrophin, in animal models, it was found to be poor and resulted in only minimal dystrophin expression. (11)

c) Lentiviral Vectors:

Another viral vector being tested for gene transfer to muscle is the lentiviral vector based on the human immunodeficiency virus which can carry 7.5 to 9 kb of cargo DNA, which is largely sufficient for cloning sizeable transgenes such as minidystrophin, selectable markers, and the promoters needed for expression. This feature is important, especially when using large tissue-specific promoters. They transduce dividing and non-dividing cells, and have shown to permanently transduce and stably express transgenes in muscle cells and their precursors, making them the delivery system of choice for muscle progenitor cell based gene transfer. (13-16)

d) Recombinant Adeno-Associated Viral Vectors (rAAV):

Above all, the recombinant adeno-associated virus (rAAV) has emerged as the most promising gene delivery vector owing to its high tropism for skeletal muscle and low immunogenicity. AAV is a single-stranded DNA virus with an average size of 20 nm and requires a helper virus such as adenovirus or herpes virus for its replication. Wild-type AAV has a 4.8 kilo base (kb) genome, and in a recombinant AAV vector a therapeutic gene expression cassette of up to 5 kb can be efficiently packaged. Its small packaging capacity is the major drawback.

The rAAVs in use today are deleted of all viral genes, specifically the rep and cap genes that encode the nonstructural and structural proteins respectively. rAAV for gene transfer has been developed using a pseudotyping approach that consists of a recombinant genome framed by the ITR of AAV serotype 2 and a capsid based on any one of the cloned AAV serotypes.

Since, its genome is too small for the insertion of a large dystrophin gene, microgenes were produced by removal of most of the middle rod domain and portions of the amino- and carboxyl terminals of the dystrophin gene. It was reported that minidystrophin and microdystrophin could improve the phenotype of muscular atrophy in an mdx mouse model. (17, 18)

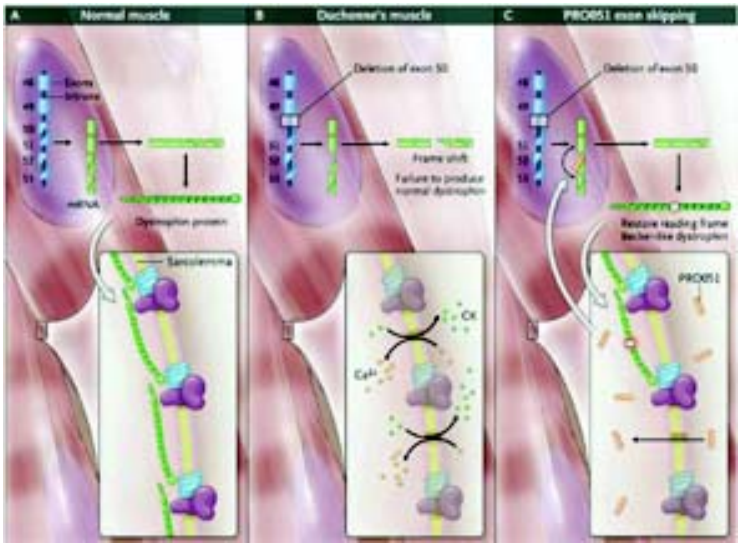
In LGMD, gene transfer with AAV vectors was also investigated in LGMD2D (α-sarco-glycanopathy). (19) In that research, (α-SG) was delivered with an AAV vector via local intramuscular injection in α-SG-knockout mice. Strong and persistent expression of the α-SG gene and restoration of the dystrophin-glycoprotein complex were observed without definite cytotoxicity.

A successful clinical trial of gene transfer of human α-sarcoglycan (α-SG) genes

with an AAV vector was recently performed in patients with LGMD2D. (α-sarcoglycanopathy). It was a double-blind, randomized controlled trial, wherein an AAV vector containing α-SG genes was injected locally in the extensor digitorum brevis muscle. Sustained expression of the α-SG gene and restoration of the dystrophin-glycoprotein complex were seen without any evidence of adverse events. A phase I/II clinical trial for DMD using an AAV vector for intramuscular delivery of microdystrophin into the biceps has been underway in the USA since 2006. AAV vectors are expected to be applied more to muscular dystrophies involving genes smaller than dystrophin. (20,21) Further improvements in vector design with the goal of strictly limiting gene expression to muscle will undoubtedly add to the safety of AAV vectors on several levels. Optimization of methods to produce enough rAAV vector for routine use in patients, and the ability to develop techniques that allow transduction of enough of the musculature to provide a therapeutic benefit while minimizing toxicity will favorably influence the realization of therapeutic success in the clinic.

2. Antisense- Induced Exon Skipping

Exon skipping of dystrophin gene exons containing a mutation is a promising potential therapy for DMD and other recessive forms of muscular dystrophy.(22) Specific removal of an exon from a defective gene has the potential to allow synthesis of a semi-functional dystrophin, hence helping in reducing the presumable progression of the muscle wasting. (23) The studies involving exon skipping utilize antisense oligonucleotides (AONs) or adeno-associated vectors expressing small nuclear ribonucleoproteins (snRNPs) to direct the lack of inclusion of targeted exons containing nonsense or frame-shift mutations into the translated mRNA. AONs which are used for exon skipping are usually 20-25 bases long and chemically synthesized. Various chemistries for AOs have been proposed to overcome the unstable nature of single-strand DNA or RNA molecules. Several modifications of AONs include bicyclic locked nucleic acid (LNA), peptide nucleic acid (PNA), ethylene-bridged nucleic acid (ENA),



2'- O-methyl phosphorothioate AO (2'-O-MePS AO) and phosphorodiamidate morpholino oligomer (PMO). Among them, 2'-O-MePS AON and PMO are the most frequently utilized because of their suitable properties.

In case of nonsense mutations in which a single base change alters a codon into a premature stop codon, selective removal of the flanking exons can result in an in-frame mRNA transcript. Such an in-frame mRNA transcript can be translated into a quasi-dystrophin protein. AONs, which hybridize the sequences near the splice acceptor or donor sites as well as within exons, can alter gene expression via steric block interference with the splicing machinery, and thereby direct the exclusion of one or more exons in the final transcript, resulting in restoration of the reading frame of dystrophin mRNA and the expression of a shorter, truncated but functional dystrophin. (24)

Some deletions and duplications of the dystrophin gene are more common than others hence, it has been estimated that skipping 12 exons would treat 73.3% of deletions. Among these possibilities, skipping exon 51 is the first choice because it could theoretically be therapeutic for 20% of dystrophin deletions.

The first evidence of antisense based exon skipping for human therapeutics came from a study (2001) which used this strategy of skipping exon 46 in muscle cells from DMD patients(with exon 45 deletion) leading to improved expression of dystrophin gene in them. (25)

3. Read through Stop Codon Strategies

10% of mutations in the dystrophin gene are point mutations leading to premature termination of translation, therefore "read-through therapy" would be of potential therapeutic interest. Aminoglycoside antibiotics have been known to suppress stop-codon recognition by interfering with the ribosome's codon recognition site.

The most commonly used aminoglycoside is gentamicin. High-dose gentamicin therapy was studied in mice models which reported to cause readthrough of premature stop codons and allow the restoration of dystrophin expression. (26-27) The read through efficiency was reported to vary markedly with different stop codons. The efficiency of translational readthrough is higher for UGA sequences than for UAG or UAA sequences. In addition, the nucleotide immediately downstream of the stop codon significantly influences the readthrough efficiency, in the order C>U>A>G. (28)

However, two human trials of intravenous gentamicin have failed to show a definite benefit in patients with DMD and BMD. Whilst, ototoxicity and nephrotoxicity are well-known adverse effects associated with gentamicin in long-term use. As a result, investigations for new drugs that do not exhibit these adverse effects but have better readthrough efficiency are in process.

One of those drugs, PTC124, a 1, 2, 4-oxadiazole compound, is a small molecule that can override nonsense stop translation signals to produce full-length proteins. (29) Welch et al. reported that PTC124 restores dystrophin production in primary muscle cells from DMD patients and mice models. It also improves the function of striated muscle in mdx mice within 2-8 weeks of drug administration and decreases serum creatine kinase levels. The readthrough efficiency of PTC124 does not vary with different

stop-codons as reported in gentamicin. A phase I trial found good tolerability of PTC124 in 62 healthy adult volunteers, with only some mild adverse effects, including dizziness, headache, and gastrointestinal disturbances, being noted. (30)

Data analysis of the Phase II clinical trials of PTC124 in patients with DMD and BMD in October, 2010 confirmed that the low dose did seem to provide some slowing in the loss of walking abililty, while the high dose did not. (31)

Sebahattin Cirak et al carried out an open-label; phase 2 clinical trial to study the clinical safety and biochemical efficacy of intravenously administered AVI-4658 phosphorodiamidate morpholino oligomer (PMO) and also the pharmacokinetic properties and the ability of AVI-4658 to induce exon 51 skipping and dystrophin restoration by RT-PCR, immunohistochemistry, and immunoblotting in 19 patients with Duchenne muscular dystrophy. It was found that AVI-4658 was well tolerated with no drug-related serious adverse events and it induced exon 51 skipping in all cohorts and new dystrophin protein expression in a significant dose-dependent (p=0·0203), but variable, manner in boys from cohort 3 (dose 2 mg/kg) onwards. Seven patients responded to treatment, in whom mean dystrophin fluorescence intensity increased from 8·9% (95% CI 7·1-10·6) to 16·4% (10·8-22·0) of normal control after treatment (p=0·0287). The three patients with the greatest responses to treatment had 21%, 15%, and 55% dystrophin-positive fibres after treatment and these findings were confirmed with western blot, which showed an increase after treatment of protein levels from 2% to 18%, from 0·9% to 17%, and from 0% to 7·7% of normal muscle, respectively. The dystrophin-associated proteins α-sarcoglycan and neuronal nitric oxide synthase were also restored at the sarcolemma. Analysis of the inflammatory infiltrate indicated a reduction of cytotoxic T cells in the post-treatment muscle biopsies in the two high-dose cohorts. (32)

4. Utrophin Upregulation

Upregulation therapy is based on increasing the expression of alternative genes to replace a defective gene and is particularly beneficial when an immune response is mounted against a previously absent protein. Upregulation of utrophin, an autosomal paralogue of dystrophin, has been proposed as a potential therapy for Duchenne muscular dystrophy. (33)

Enhancement of utrophin expression could therefore be a therapeutic option devoid of an immune response against novel antigens. It was observed in mice models that, when utrophin is overexpressed it localizes to the sarcolemma of muscle cells and restores the components of the dystrophin-associated protein complex (DAPC), which prevents dystrophic development and in turn leads to functional improvement of skeletal muscle. (34, 35)

Upregulation of endogenous utrophin to sufficient levels to decrease pathology might be achievable by the delivery of small, diffusible compounds. Studies of increased utrophin expression in mouse models have shown to be effective, and no toxicity was observed when utrophin was ubiquitously expressed, which is promising for the translation of this therapy to humans. (36)

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Section B

12

An Overview on Stem cells and Stem Cell therapy

Regenerative medicine is a newly evolving branch of modern medicine that deals with cell based therapies which use healthy cells cultured in the laboratory to replace damaged cells in adult organisms to treat disease. This could therefore potentially hold the key for addressing ailments which currently have no proven treatments or cures, such as, neurological disorders (spinal cord injury, cerebral palsy, brain stroke, muscular dystrophy, Alzheimer's disease, multiple sclerosis, etc.), diabetes, cardiovascular disorders, bone disorders, hematopoietic disorders, cancers, hepatic, renal and dermatological disorders.

One of the building blocks of this therapy is stem cells. Regenerative medicine aims to repair or re-grow parts or tissues which are lost as a consequence of disease or injury. Stem cells have the capability to multiply manifolds and convert or differentiate into any specialized cell types of the body. Hence, the potential of these invaluable assets could even be projected as far as, sometime in the near future, to replace organ transplantation.

Depending on the source, the potency or plasticity of stem cells varies. Stem cells procured from the 5-6 day embryo (usually from wasted or excess fertilized embryos from IVF clinic), referred to as embryonic stem cells, have theoretically the capacity to give rise to the whole embryo and cells of all the germ layers (pluripotent).However, they are surrounded by hordes of ethical issues regarding the source of these cells. Also, formation of "teratomas" is a serious possibility in the long-term with these cells.

In order to bypass the ethical and medical issues associated with embryonic and fetal stem cells, researchers and clinicians have researched and developed other sources of stem cells, such as haematopoietic and mesenchymal stem cells from the bone marrow

and umbilical cord, stem cells from the adipose tissue, olfactory ensheathing, endometrium, neural stem cells, etc., which have varying potencies for differentiating into different cell types. A body of work has been ongoing on the use of these cells, in various specialties and disorders.

This book endeavors to assimilate all the current information on understanding stem cells, its potential and more specifically its role in treating incurable and intractable disorders of the brain, spinal cord and the muscular system.

The nervous system is like the central processing unit of the animal body. In humans, it is more evolved and specialized. Since, disorders and injuries affecting the nervous system lead to irreparable damage and disability, this area has become a major focus point in the arena of regenerative medicine. The hope is that by using the plasticity of the nervous system and combining it with the regenerative potential of the stem cells it would be possible to evolve definitive treatments for degenerative and traumatic disorders of the nervous system.

BASICS OF STEM CELLS

Every cell in the human body can be traced back to a fertilized egg that came into existence from the union of the egg and the sperm. The body is made up of over 200 different types of cells. All of these come from a pool of stem cells in the early embryo. During early development as well as later in life, the stem cells give rise to the specialized or differentiated cells that make up our body. Over the past 2 decades scientists have been gradually deciphering the processes by which unspecialized stem cells become the different types of specialized stem cells. Stem cells can regenerate themselves or produce specialized cell types. This is the property that makes them appealing as a method for creating medical treatment that can replace lost or damaged cells. In this chapter we will look at some of the fundamental basic properties of Stem cells.

What Are Stem Cells?

A stem cell is defined by two properties. First, it is a cell that can divide indefinitely, producing a population of identical offspring. Second, stem cells can, on cue, undergo an asymmetric division to produce two dissimilar daughter cells. One is identical to the parent and continues to contribute to the original stem cell line. The other varies in some way. This cell contains a different set of genetic instructions (resulting in an alternative pattern of gene expression) and is characterized by a reduced proliferative capacity and more restricted developmental potential than its parent. Eventually a stem cell becomes known as a "progenitor" or "precursor" cell, committed to producing one or a few terminally differentiated cells such as neurons or muscle cells. (1)

Developmental Hierarchy in Stem Cell (SC) Compartment:

There exists a hierarchy in the stem cell compartment, depending on their 'potency' or fate restriction.1) Totipotent stem cells give rise to embryonic as well as the extra embryonic tissue. This means, it has the capacity to form the whole of the embryo, including the placenta. The physiological totipotent stem cell is a fertilized oocyte (zygote) or first blastomere which comprises of the 8 cell stage. The artificial counterpart

is a clonote obtained by somatic cell nuclear transfer (SCNT) to an enucleated oocyte.2) Pluripotent stem cells in turn have the capacity to give rise to cells of all the three germ layers of the embryo, i.e., endoderm, mesoderm and the ectoderm. Pluripotent stem cells are cells from the inner cell mass of the blastocyst (ICM), epiblast (EPSC) and SC obtained as immortalized cell lines - blastocyst derived embryonic stem cells (ES) and Primordial Germ Cell-derived embryonic germ cells (EG). 3) Multipotent stem cells give rise to cells of one of the germ cell layers only, either ecto-, meso- or endoderm. Sources range from 8 day old embryo to adult bone marrow. 4) Monopotent stem cells are tissue-committed stem cells that give rise to cells of one lineage, e.g., hematopoietic stem cells, epidermal stem cells, intestinal epithelium stem cells, neural stem cells, liver stem cells or skeletal muscle stem cells. (2)

Though the above classification has evolved over decades, understanding of the potency of these cells are everchanging. Many of these cells, which were earlier considered to be multipotent, have shown limited pluripotent properties Also, transdifferentation of monopotent/unipotent cells by external stimulation or manipulation have shown that these classifications, based on fate restriction or potency, are fast becoming redundant.

Classification of Stem Cells

Stem cells are classified as embryonic stem cells, umbilical cord stem cells and adult stem cells on the basis of their origin.

Embryonic Stem cells: Embryonic stem cells are pluripotent in nature which are derived from the inner cell mass (ICM) of 5 to 7 day blastocyst, obtained from IVF clinics. (3)

Developmental studies in mouse revealed that the fertilized oocyte, the zygote, has the capacity to form the whole embryo. It further divides progressively to give rise to an 8 cell staged, 16 celled, 32 celled blastomere and then finally the blastocyst.

The blastocyst is demarcated into the outer transparent trophoblast (which forms the extra embryonic tissue/the placenta) and the Inner cell mass (ICM) which is a 30-34 celled clump. (Figure 1)

The ICM ultimately gives rise to the three germ layers and subsequently the whole embryo. Hence, the inner cell mass is the source for the derivation of the embryonic stem cells, which has lost the "totipotency" of the zygote, but is now "pluripotent".

The potential of the embryonic stem cell to form the "germ layers" & its capacity to self renew indefinitely as well as its ability to form any cell type of the body, has led to opening up of this field widely, not only with respects to its use in regeneration, but has thrown up debates regarding ethics and legalities.

However, even before the first embryonic stem cell line was derived in 1981, embryonal carcinoma cells derived from germline tumors called "teratocarcinomas" were widely studied. After transplantation to extra-uterine sites of appropriate mouse strains, these "funny little tumors" produced benign teratomas or malignant teratocarcinomas. (4)

Uses of Embryonic Stem Cells:

1. **Embryonic stem cells as cellular models**
   Experiments designed to understand gene function in the context of an organism require genetic strategies. Enhancer and promoter traps, gene traps, random activation of gene expression (RAGE) and genome-wide cell-based knockout (GECKO) represent genome-wide strategies to identify, isolate, or determine gene function. Because of gene-targeting techniques, transgenic mice have also proven critical to the creation and evaluation of some models of human disease. Embryonic stem cell lines have proven to be useful mediums for genetic manipulation, for understanding developmental processes and correction of genetic defects. (5)

2. **Embryonic stem cells in pharmacology and embryotoxicology**
   Stem cells also represent a dynamic system suitable to the identification of new molecular targets and the development of novel drugs, which can be tested in vitro for safety or to predict or anticipate potential toxicity in humans. (6)

   Human ES cell lines may, therefore, prove clinically relevant to the development of safer and more effective drugs for human diseases. Three aspects are relevant to this issue. 1) At present, insufficient methods exist in some areas of in vitro toxicology to predict target organ toxicity. 2) In embryotoxicology, interspecies variation complicates data analysis, and human cell systems may enhance the identification of hazardous chemicals. 3) Human ES-derived cells cultured in vitro may reduce the need for animal testing in pharmacotoxicology.

   The application of hES cells in pharmacology and embryotoxicology could have a direct impact on medical research, but to date, such an approach has primarily been used with mouse ES cells.

3. **In stem cell based therapies:**
   The in vitro developmental potential and the success of ES cells in animal models demonstrate the principle of using hES-derived cells as a regenerative source for transplantation therapies of human diseases. Before transfer of ES-derived cells to humans can proceed, a number of experimental obstacles must be overcome. These include efficient derivation of human ES cells in the absence of mouse feeder cells, and an understanding of genetic and epigenetic changes that occur with in vitro cultivation. It will be necessary to purify defined cell lineages, perhaps following genetic manipulation, that are suitable for cell-based therapies. If manipulated, then it will be important to guard against karyotypic changes during passaging and preparation of genetically modified ES-derived cells. Once introduced into the tissue, the cells must function in a normal physiological way. Finally, assurances against the formation of ES cell-derived tumors and donor/recipient immunocompatibility are additional requirements of stem cell-based therapies. As pointed out, significant progress has been made in the isolation of defined cell lineages in mouse, and important advances have already been seen with hES cells. Before therapeutically applicable, any ES-based treatment must, however, show limited potentials for toxicity, immunological rejection, or tumor formation, and

at present, human ES cell research has not reached this threshold.

The availability of human ES cells, however, represents an extraordinary opportunity for cell transplantation that may be applicable to a wide range of human ailments. Three properties make ES cells relative to adult stem cells very attractive for replacement therapies.1) Human ES cells can be grown indefinitely in culture.2) ES cells can be genetically manipulated, and loss of function genes (e.g., CTFR) can theoretically be repaired by the introduction of transgenes into ES cells either by random transgenesis or through gene targeting. 3) Numerous differentiation protocols have already been established that permit the generation of almost any cell type, either through the use of established culture conditions or when coupled with genetic manipulations. In theory, hES cells could be applied to a wide range of human ailments, but the proof of principle has largely come from the use of mouse ES cells.(7-8)

Adult Stem Cells

Adult stem cells are pluripotent, clonogenic, self renewing, having ability to differentiate into the mature cell of it resident environment and also, may have transdifferentiating abilities.

Adult stem cell niches have been found in most organs of the human body,

eg. liver, brain, bone marrow, adipose tissue, heart, etc. The primary role of these adult stem cells is initiation of repair process in the organ following an injury. These cells have been, in practicality, difficult to obtain due to the following reasons:

1) Inaccessibility and small numbers (e.g. neural stem cells)
2) Lack to markers for characterization and isolation of the "stem cell population" from various organs.(9)

The field of Regenerative medicine, which got opened up widely following the discovery of the embryonic stem cells, is now in search of the "almighty" pluripotent stem cell, following ethical, legal and medical questions raised against the ES cell research and therapeutic use.

The search has now been directed towards adult stem cell niches, which pose a non controversial and safe option for use in human subjects. However, the debate over its pluripotency is ongoing and the fields as well as the concept of adult stem cell plasticity have been extremely dynamic.

Bone Marrow Derived Cells

Bone marrow is the most accessible and most studied source of adult stem cells. Different types of stem cells have been found to be present in the bone marrow, which differ in their potential to differentiate and form cells from one or more germ layers.

Initially, the bone marrow was thought to contain only haematopoietic stem cells. The excitement regarding HSCs diminished after it was found to have limited potency. However, increasingly, evidence is pouring in regarding the heterogenous population of cells having varying plasticity.

Potential Pluripotent Stem Cells candidates identified in adult tissues (especially, bone marrow)

1) **Mesenchymal Stem Cells (Multipotent Mesenchymal Stromal Cells):**
Human mesenchymal stem cells (MSCs) are thought to be multipotent cells that have the potential to differentiate into multiple lineages including bone, cartilage, muscle, tendon, ligament fat and a variety of other connective tissues. Indeed, marrow-derived cells seem to retain a remarkable plasticity, since they have much wider differentiation potential than previously thought. Marrow cells have been reported to contribute to angiogenesis, somatic muscle development, liver regeneration, and the formation of central nervous system cell types. It is likely that MSC may be contaminated by other populations of primitive non-hematopoietic stem cells. This possibility should be considered whenever a "transdedifferentiation" of MSC into cells from other germ layers is demonstrated. Because various inconsistencies have come to light in the field of MSC research, the International Society for Cellular Therapy recently recommended avoiding the name of MSC stem cells and changing it to multipotent mesenchymal stromal cells instead. (10)

2) **Multipotent Adult Progenitor Cells (MAPC):**
MAPC are isolated from BM as well from various adult organs as a population of CD45 GPA-A- adherent cells and they display a similar fibroblastic morphology to MSC. Interestingly MAPC are the only population of BM derived stem cells that have been reported to contribute to all three germ layers after injection into a developing blastocyst, indicating their pluripotency. (11) The contribution of MAPC to blastocyst development, however, requires confirmation by other, independent laboratories

3) **Marrow-isolated adult multilineage inducible (MIAMI) cells:**
This population of cells was isolated from human adult BM by culturing BM MNC in low oxygen tension conditions on fibronectin . MIAMI cells were isolated from the BM of people ranging from 3- to 72-years old. Colonies derived from MIAMI cells expressed several markers for cells from all three germ layers, suggesting that, at least as determined by in vitro assays, they are endowed with pluripotency. However, these cells have not been tested so far for their ability to complete blastocyst development. The potential relationship of these cells to MSC and MAPC is not clear, although it is possible that these are overlapping populations of cells identified by slightly different isolation/expansion strategies

4) **Multipotent Adult Stem Cells (MACS):**
These cells express pluripotent-state-specific transcription factors (Oct-4, Nanog and Rex1) and were cloned from human liver, heart and BM-isolated mononuclear cells. MACS display a high telomerase activity and exhibit a wide range of differentiation potential. Again the potential relationship of these cells to MSC,MAPC and MIAMI described above is not clear, although it is possible that these are overlapping populations of cells identified by slightly different isolation/ expansion strategies.

5) **Very Small Embryonic Like (VSEL) Stem Cells:**
Recently, a homogenous population of rare (~0.01% of BM MNC) Sca-1+ lin- CD45-

cells was identified in murine BM. They express (as determined by RQ-PCR and immunhistochemistry) markers of pluripotent stem cells such as SSEA-1, Oct-4, Nanog and Rex-1 and Rif-1 telomerase protein (12) Direct electron microscopical analysis revealed that VSEL (2-4 μm in diameter) display several features typical for embryonic stem cells such as i) a large nucleus surrounded by a narrow rim of cytoplasm, and ii) open-type chromatin (euchromatin). Interestingly, these cells despite their small size possess diploid DNA and contain numerous mitochondria. VSEL, however, do not express MHC-1 and HLA-DR antigens and are CD90- CD105- CD29.

Umbilical Cord Stem Cells

Umbilical cord blood stem cells can be obtained from the umbilical cord immediately after birth. Like bone marrow, umbilical cord blood is another rich source of hematopoietic stem cells, since 1988. The blood remaining in the umbilical vein following birth contains a rich source of hematopoietic stem and progenitor cells, has been used successfully as an alternative allogeneic donor source to treat a variety of pediatric genetic, hematologic, immunologic, and oncologic disorders. Fresh cord blood is also a promising source of non-hematopoietic stem cells. Among others, it contains endothelial cells, MSCs and unrestricted somatic stem cells (USSC). These hematopoietic stem cells are less mature than those stem cells found in the bone marrow of adults or children.

Umbilical cord blood contains circulating stem cells and the cellular contents of umbilical cord blood appear to be quite distinct from those of bone marrow and adult peripheral blood. The characteristics of hematopoietic stem cells in umbilical cord blood have recently been clarified. The frequency of umbilical cord blood hematopoietic stem cells equals or exceeds that of bone marrow and they are known to produce large colonies in vitro, have different growth factor requirements, have long telomeres and can be expanded in long term culture. Cord blood shows decreased graft versus host reaction compared with bone marrow, possibly due to high interleukin-10 levels produced by the cells and/or decreased expression of the beta-2-microglobulin. Cord blood stem cells have been shown to be multipotent by being able to differentiate into neurons and liver cells.

The advantages of using cord blood as a source of stem cells are:

1) It is a non-invasive source and can be obtained from the umbilical cord immediately after birth.
2) Available in vast abundance; thousands of babies are born each day and the umbilical cord and placenta are discarded as waste.
3) Despite its high content of immune cells, it does not produce strong graft-versus-host disease
4) Therefore, cord blood grafts do not need to be as rigorously matched to a recipient as bone marrow grafts. A 4 out of 6 match is sufficient for clinical use.

Hence, cord blood has recently emerged as an alternative source of hematopoietic stem cells for treatment of leukemia and other blood disorders.

All over the world, innumerable cord blood banks have cropped up for storage of umbilical cord stem cells. These are generally either pure public banks or private banks. There are certain banks which offer both types of banking (mixed type). Umbilical cord stem cells banks also differ in the type of biological material that they store. Some banks only store the cord blood (from the umbilical vein) which predominantly carries the haematopoietic stem cells. Increasingly, banks have started storing pieces of the placenta and cord, which are a rich source of mesenchymal stem cells.

MECHANISM OF ACTION

Stem cells are instrumental in the formation of new tissues and thereby promoting repair and regeneration. Their role, in the normal wear and tear of the body, appears to be assistance of repair and maintenance of normal tissue structure and function. Recreation of this ability in vitro as well in animal models of various diseases is the basis of devising therapeutic modalities for degenerative disorders through remodeling of the injured tissues. Cell-based therapy could therefore potentially be used to treat a wide array of clinical conditions where cellular damage is the underlying pathology.

More importantly, the use of adult stem cells as opposed to human embryonic stem cells for therapy avoids ethical problems and has two additional advantages:1) Adult stem cells can be isolated from patients, and this overcomes the problem of immunological rejection and 2) The risk of tumor formation is greatly reduced as compared to the use of embryonic stem cells.(13)

Plasticity, Pluripotency and Production

While pluripotency and plasticity are considered properties of early ESC, adult stem cells are traditionally thought to be restricted in their differentiation potential to the progeny of the tissue in which they reside. However, a remarkable plasticity in differentiation potential of stem cells derived from adult tissues has been seen. (14)

The events underlying stem cell plasticity could relate to a variety of mechanisms such as dedifferentiation, trans-differentiation, epigenetic changes, and/or cell fusion. Rerouting of cell fate may result from the multistep process known as dedifferentiation where cells revert to an earlier, more primitive phenotype characterized by alterations in gene expression pattern which confer an extended differentiation potential.

Another mechanism put forward to explain stem cell switch to a novel phenotype is a process known as trans-differentiation. Cells may differentiate from one cell type into another within the same tissue or develop into a completely different tissue without acquiring an intermediate recognizable, undifferentiated progenitor state. (15) or may undergo cell fusion resulting in nuclear reprogramming and changes in cell fate. (16,17) It is now recognized that adult stem cells from bone marrow may fuse with cells of the target organ. So far, bone-marrow-derived cells were shown to form fusion heterokaryons with liver, skeletal muscle, cardiac muscle, and neurons. There is evidence that such fused cells become mono-nucleated again, either by nuclear fusion or by elimination of supernumerary nuclei.(18)

The Paracrine Effect

Exploration of the various cellular processes occurring (both during normal

physiology as well as after tissue injury) in the process of stem cell renewal and differentiation, suggests that stem cell treatment or transplantation of stem cells remodels and regenerates injured tissue, improves function, and protects tissue from further insult. Stem cells transplanted into injured tissue express paracrine signaling factors including cytokines and other growth factors, which are involved in orchestrating the stem cell-driven repair process through increasing angiogenesis, decreasing inflammation, preventing apoptosis, releasing chemotactic factors, assisting in extracellular matrix tissue remodeling and activation of resident/satellite cells which is discussed further in details.

Increased Angiogenesis

Stem cells produce local signaling molecules that may improve perfusion and enhance angiogenesis to chronically ischemic tissue. Although the particular growth factors contributing to this neovascular effect remain to be defined, the list includes vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and basic fibroblast growth factor (FGF2). (19,20)

Decreased Inflammation

Stem cells appear to attenuate infarct size and injury by modulating local inflammation. When transplanted into injured tissue, the stem cell faces a hostile, nutrient-deficient, inflammatory environment and may release substances which limit local inflammation in order to enhance its survival. Modulation of local tissue levels of pro-inflammatory cytokines by anti-inflammatory paracrine factors released by stem cells (such as IL-10 and TGF-?) is important in conferring improved outcome after stem cell therapy. (21)

Anti-Apoptotic and Chemotactic Signaling

Stem cells in a third pathway promote salvage of tenuous or malfunctioning cell types at the infarct border zone. Injection of MSC into a cryo-induced infarct reduces myocardial scar width 10 weeks later. MSCs appear to activate an anti-apoptosis signaling system at the infarct border zone which effectively protects ischemia-threatened cell types from apoptosis.

Beneficial Remodeling of the Extracellular Matrix

Stem cell transplantation alters the extracellular matrix, resulting in more favorable post-infarct remodeling, strengthening of the infarct scar, and prevention of deterioration in organ function. MSCs appear to achieve this improved function by increasing acutely the cellularity and decreasing production of extracellular matrix proteins such as collagen type I, collagen type III, and TIMP-1 which result in positive remodeling and function.

Activation of Neighboring Resident Stem Cells

Finally, exogenous stem cell transplantation may activate neighboring resident tissue stem cells. Recent work demonstrates the existence of endogenous, stem cell-like populations in adult hearts, liver, brain, and kidney. These resident stem cells may

possess growth factor receptors that can be activated to induce their migration and proliferation and promote both the restoration of dead tissue and the improved function in damaged tissue. Mesenchymal stem cells have also released HGF and IGF-1 in response to injury which when transplanted into ischemic myocardial tissue may activate subsequently the resident cardiac stem cells. (22)

To sum up, although the definitive mechanisms for protection via stem cells remains unclear, stem cells mediate enhanced angiogenesis, suppression of inflammation, and improved function via paracrine actions on injured cells, neighboring resident stem cells, the extracellular matrix, and the infarct zone. Improved understanding of these paracrine mechanisms may allow earlier and more effective clinical therapies

Remyelination

Remyelination involves reinvesting demyelinated axons with new myelin sheaths. Previous attempts aimed at regenerating myelin-forming cells have been successful but limited by the multifocal nature of the lesions and the inability to produce large numbers of myelin- producing cells in culture. Stem cell-based therapy can overcome these limitations to some extent and may prove useful in the future treatment of demyelinating diseases.

Contrary to the general expectations that stem cells would primarily contribute to formation of tissue cells for repair, other mechanisms such as paracrine effects and remyelinations appear to be important ways via which stem cells seem to exert their effect. More Basic research to understand these mechanisms is underway throughout the world.

SURGICAL ASPECTS OF STEM CELLS THERAPY

The stem cell therapy process using autologous bone marrow derived stem cells consists broadly of 3 stages. (1) Procurement of the stem cells from the bone marrow via a bone marrow aspiration in the operating theatre (2) separation, harvesting, enriching &/or expansion and differentiation in the laboratory and finally (3) transplantation or delivery of the cells to the desired location. The laboratory aspects have already been dealt with in the previous chapter therefore in this chapter the procurement and transplantation aspects will be discussed.

Procurement of Stem cells - Bone marrow aspiration

The choice of site may be dependent on various factors such as age, weight, marrow distribution, physical status of the patient, physicians experience etc. However the most common site is the pelvis. The aspiration is easily done from either of the iliac crests (posterior or anterior). The posterior superior iliac spine is easily accessible and identifiable, however to access this, the patient has to be turned in the lateral or prone position which can be troublesome and cumbersome. The anterior superior iliac spine can be accessed with the patient lying comfortably in the supine position. In obese patient, the landmarks may be obliterated due to fat distribution. Sampling is not normally discordant between the anterior or posterior iliac spines.

The site of the aspiration is palpated. For the posterior superior iliac spine, in thin individuals, it is usually palpated as the bony prominence superior and three finger breadth laterals to the intergluteal cleft. The anterior superior iliac spine can be palpated as an anterior prominence on the iliac crest. The overlying skin is prepared in a manner similar to preparation of any site for surgery. The area is anaesthetized by intradermally administering a local anesthetic such as lignocaine using a 25G or 26G needle. A 1 cm area is anesthetized.

A standard bone marrow aspiration needle is inserted through the skin till the bone is felt. Before using the needle it is flushed with heparin. Some surgeons make a small incision with a surgical blade and expose the bone before putting in the needle, however in our experience this is rarely required. The needle which is firmly fixed to the obturator is firmly inserted inside, clockwise and anticlockwise, in a screwing motion with exertion of downward pressure, until the periosteum is reached. With similar motion, the needle is inserted till it penetrates the cortex. At this point initially a sudden giving way of the resistance is felt as the needle enters the soft trabecular bone and then the needle feels firmly fixed in the bone. The angle of insertion of the needle is important as it has to be in alignment with the curve of the bone. If this is not done properly the needle will make a through and through penetration across both the cortical surfaces with the tip now being outside the marrow. A study of the anatomy of the pelvis with a model and personal experience over time make this a very simple procedure.

The stylet is now removed and a 10 ml or 20 ml syringe, with some heparin in it, is attached and the aspiration is done. A total of 100-120 ml is aspirated in adults and 80-100 ml in children. This is collected in heparinized tubes which need to be appropriately labeled. The bone marrow collected is transported to the laboratory in a special transporter under sterile conditions.(23)

Transplantation of Stem Cells

The other surgical aspect in the process of stem cell therapy is the delivery of the cells which may either be done systemically (through intravenous or intraarterial routes) or locally (intrathecal or direct implantation into the spinal cord or brain). Different centers are following different routes to transplant the cells and as of now there are no comparative studies that could tell us which is the preferred method. However keeping in mind the existence of the blood brain barrier, local delivery would seem to be a more logical option.

Intrathecal delivery

The patient is positioned in the lateral decubitus position, in the curled up "foetal ball" position. Occasionally, the patient is made to sit, leaning over a table- top. Both these maneuvers help open up the spinous processes. The back is painted and draped and local anaesthetic is injected into the L4-5 or L3-4 space. An 18G Touhy needle is inserted into the sub-arachnoid space. After ascertaining free flow of CSF, an epidural catheter is inserted into the space, far enough to keep 8-10 of the catheter in the space. The stem cells are then injected slowly through the catheter, keeping a close watch on

the hemodynamics of the patient. The cells are flushed in with CSF. The catheter is removed and a benzoin seal followed by a tight compressive dressing is given. This procedure is usually done under local anesthesia. General anesthesia is given to children.

A spinal needle instead of a catheter is preferred in patients with cardiac problems, where excessive intravenous infusion is to be avoided, in patients on anti-coagulant or anti-platelet drugs so as to avoid bleeding into the sub-arachnoid space, in case where the spine is scoliotic which happens often in patients with muscular dystrophy and in some previously operated cases of lumbar spine surgery.

Sometimes in patients with severe spinal deformities such as scoliosis it is very difficult to get the needle intrathecally and at times assistance has to be taken of the C arm to exactly locate the point and direction of needle placement.

Callera et al (2007) demonstrated for the first time that autologous bone marrow CD 34+ cells labelled with magnetic nanoparticles delivered into the spinal cord via lumbar puncture (LP) technique migrates into the injured site in patients with spinal cord injury. They conducted the trial on 16 patients with chronic SCI. 10 of them were injected intrathecally with labelled autologous CD 34+ cells and the others received an injection containing magnetic beads without stem cells. Magnetic resonance images were obtained before and 20 and 35 days after the transplantation. Magnetically labelled CD 34+ cells were visible at the lesion site as hypointense signals in five patients, which were not visible in the control group.(24)

Intraspinal transplantation

Direct implantation into the spinal cord may be done in one of many ways:-

a) Through a complete laminectomy from one level above to one level below the injury site so that there is sufficient access to the transplantation site. The dura is incised, sparing the arachnoid, which is subsequently opened separately with microscissors. The dorsal surface of the contusion site is located under high-power microscopic magnification. After exposure of sufficient surface in the contusion site, 300µL aliquots of cell paste (total volume, 1.8 mL) are injected into six separate points surrounding the margin of the contusion site. To avoid direct cord injury, 2 × 108 cells are delivered at a rate of 30 µL/min, using a 27-gauge needle attached to a 1-mL syringe. The depth of the injection site is 5 mm from the dorsal surface. To prevent cell leakage through the injection track, the injection needle is left in position for 5 min after completing the injection, after which the dura and arachnoid are closed. The muscle and skin are closed in layers. (25)

b) Though a minilaminectomy and exposure of the spinal cord. The dura is opened and a 27 gauge scalp vein is used by cutting one of the wings. The other wing is held by a hemostat and inserted at a 45 degree angle into the dorsal root entry zone. It is inserted 3mm deep into the spinal cord. Two injections are made on either side above the injury site and two injections are made below the injury site. In China, surgeons are injecting 35 µL of stem cells. In his planned trials, Wise Young is intending to inject an escalating dose of 4 µL, 8 µL and 16 µL.

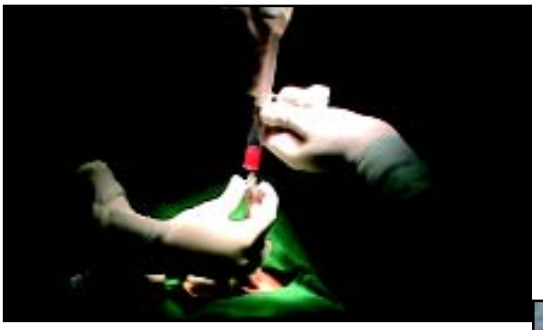

Fig 1: Bone marrow aspiration

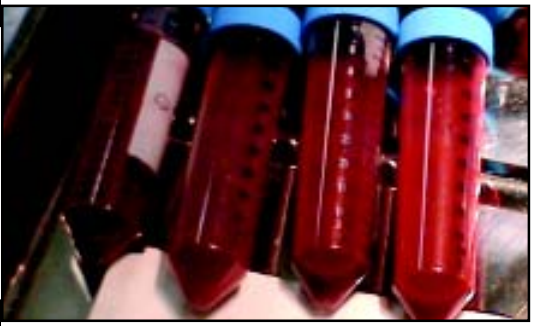

Fig 2: Bone marrow samples

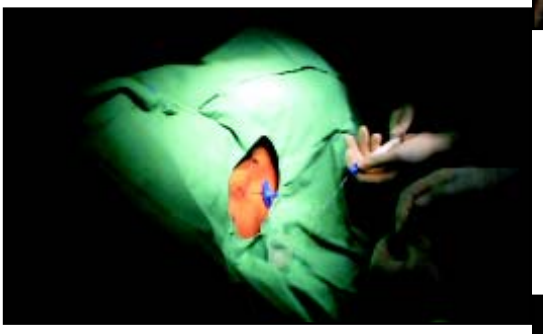

Fig 3: Lumbar Puncture

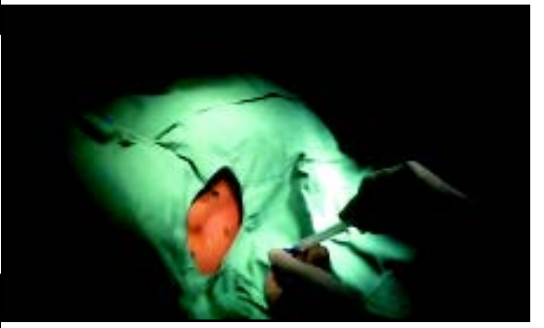

Fig 4: Intrathecal injection of stem cells

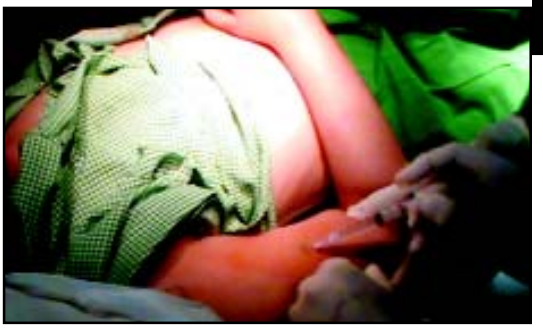

Fig 5: Intramuscular injection of bone marrow derived stem cells

c) In their ongoing trials, Geron and Neuralstem are using stereotactic systems specifically designed for intraspinal injections. They have the advantage of precision as well as being less invasive. Geron is using a stereotactic frame with a straight needle and injecting 25 µL.

Intra-arterial injection

Following revascularization surgery such as Carotid endartrectomy or Superficial Temporal artery to Middle Cerebral artery bypass, stem cells could be injected directly intra-arterially immediately after the completion of the revascularization procedure. The advantage of this approach is that the stem cells would go directly to the ischemic brain and also that since the artery is already exposed no separate procedure needs to be done for the stem cell injection. The other method of direct intra-arterial injection would be via the endovascular interventional route. This is done by making a puncture in the femoral artery and negotiating a catheter to the arteries supplying the brain. The advantage of this is that it is a relatively non invasive procedure and the limitations of intravenous injection are avoided.

Stereotactic implantation into the brain

Cell transplantation for neurological conditions started with stereotactic implantation of fetal cells for Parkinson's disease. (26) However, after a randomized trial done by Freed et al showed that the clinical outcomes were not significantly different from non transplanted patients this has now been given up. (27) There are many stereo tactic systems available all over the world however the two most popular ones are the Leksell Stereotactic system and the CRW Stereotactic system. The Leksell system involves fixing the frame on the patients head and then getting a MRI done with the frame on. The area where the tissue is to be transplanted is identified on the MRI scan and then using the MRI software the X, Y and Z coordinates are obtained. The patient is now shifted to the operating room where a small burr hole is drilled into the skull and then through this the cells to be transplanted and inserted at the desired location using the X, Y and Z coordinates. The entire procedure is done under local anesthesia.

Intramuscular injection

In certain disorders, especially Muscular dystrophy, cells are also transplanted into the muscle. The points at which these have to be injected are termed as the "motor points. At these motor points, the area is cleaned with povidone iodine. The cells diluted in CSF are injected with the 26G needle going into the muscle at an angle (approx. 45 degrees).The piston/plunger of the syringe is slightly withdrawn to verify the needle is not inside a blood vessel. The cells are then injected, the needle removed and the site immediately sealed with a benzoin seal.

Stem cell transplantation , in its various forms, has been practically attempted for various degenerative disorders, including diabetes, cardiac disorders and neurodegenerative disorders.World wide reports reveal the use of bone marrow derived mononuclear cells and mesenchymal cells, umbilical cord blood stem cells, Mesangioblasts,myoblasts, neural stem cells for various incurable and intractable neurological disorders.

CLINICAL IMPROVEMENTS IN NEUROLOGICAL DISORDERS AFTER STEM CELL THERAPY

At NeuroGen Brain and Spine Institute, stem cell therapy was carried out on neurological disorders like muscular dystrophy, cerebral palsy, multiple sclerosis, stroke, spinal cord injury and motor neuron disease. (Total 300 patients in the year 2009-10).

72 muscular dystrophy patients underwent intrathecal autologous bone marrow derived mononuclear cell transplantation, 41 were suffering from Duchene Muscular Dystrophy type, 17 had Limb Girdle Muscular Dystrophy, 11 had Congenital Muscular Dystrophy, 2 had Becker's Muscular Dystrophy and 1 had Fascio Scapulohumeral Dystrophy. The mean follow up of 6 months showed that out of 72, 32 showed improved trunk strength, 30 improved in their lower extremity strength with 11 of them showing gait improvement and 20 improved in upper extremity strength.

16 cerebral palsy patients underwent bone marrow derived autologous stem cell transplantation, 6 showed improvement in oromotor functions like speech, swallowing and neck holding, 8 of them showed reduction in seizure frequency and 10 showed normalization of tone.

22 multiple sclerosis patients underwent intrathecal autologous bone marrow derived mononuclear cell transplantation. The mean follow up of 6 months showed that 11 patients shifted on EDSS Scale showing objective Neurological Improvement. On assessing them symptom-wise 17 patients showed reduction in spasticity,9 showed improved upper extremity and trunk coordination,, 6 improved in speech clarity and 8 showed increased in muscle strength.

74 spinal cord injury patients underwent intrathecal autologous bone marrow derived mononuclear cell transplantation, 12 patients shifted on ASIA scale by 2 grades showing improvements in muscle power and gait with assisted devices. On assessing them symptom-wise 48 patients showed improvement in sitting balance (static and dynamic),13 showed improvement in muscle strength, 4 showed complete recovery in bladder and bowel functions, 9 showed sensory recovery and 8 of them showed complete recovery from postural hypotension.

47 motor neuron disease patients underwent intrathecal autologous bone marrow derived mononuclear cell transplantation, 14 showed some minor improvements whereas 33 patients kept on deteriorating with symptoms of early fatigue, weakness, muscle wasting and bulbar symptoms, which progressed with the natural course of the disease. Out of the 14 patients who improved, symptoms which showed results were improved neck holding, speech, swallowing, reduction in fasciculations and a halt in the progression of muscle weakness.

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Stem Cell Therapy for Muscular Dystrophy

Stem cells give rise to every tissue and organ in the body. They are defined by their capability of self-renewal and multipotent long-term proliferation, differentiating into multiple cell lineages. Stem-cell based therapies for the repair and regeneration of various tissues and organs offers an alternative therapeutic solution for a number of diseases, including musculoskeletal, hematopoietic, neurological and cardiovascular diseases. Cells used for such strategies include embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) and adult stem cells (ASCs) which include bone marrow-derived stem cells, blood- and muscle-derived CD133+ cells, muscle-derived stem cells (MDSC), side population (SP) cells and mesoangioblasts. (1, 2)

ESCs are derived from mammalian embryos in the blastocyst stage and are capable of differentiating into any of the tissues of the body while, iPSCs are cells which are reprogrammed from differentiated, adult somatic cells to an ESC-like status, by pluripotency transcription factor expression. Although the therapeutic potential of ESCs and iPSCs is enormous because of their auto-reproducibility and pluripotency, various limitations to their use are imposed by cell regulations, ethical considerations, and genetic manipulation. In contrast, ASCs are easily available, immunocompatible and no ethical issues are involved related to their use as long as they are of autologous tissue origin. They are intrinsic to various tissues of the body and are capable of maintaining, generating and replacing terminally differentiated cells within their own specific tissue following cell turnover or tissue injury. In addition, a growing number of studies have demonstrated that ASCs, under certain micro environmental conditions, give rise to cell types other than the cell type in the tissue of origin. Based on these advantages, ASCs are gradually becoming a candidate for regenerative medicine. (3)

Cell therapy has evolved as one of the promising treatments for muscular dystrophy. The main goal of cell therapy is to directly regenerate wasted, adult muscle fibres through systemic or targeted injection of stem cells, which function to block muscle loss and restore, at least partially, the normal muscular activity. (4) The mechanisms by which stem cells function and reverse the effects of cell death include differentiation, cell fusion, and secretion of cytokines or paracrine effects. (5-7)

Stem cells show high plasticity, i.e. the complex ability to cross lineage barriers and adopt the expression profile and functional phenotypes of the cells unique to other tissues. The plasticity can be explained by transdifferentiation (direct or indirect) and fusion. Transdifferentiation is the acquisition of the identity of a different phenotype through the expression of the gene pattern of other tissue (direct) or through the achievement of a more primitive state and the successive differentiation to another cell type (indirect or de-differentiation). By fusion with a cell of another tissue, a cell can express a gene and acquire a phenotypic element of another parenchyma. (8) During cell fusion, the cells connect and exchange vital cell components. (9)

So far, bone marrow-derived stem cells and their paracrine factors have shown all the necessary attributes for tissue regeneration, namely angiogenesis, inhibition of apoptosis, anti-inflammation, immunosuppression, homing stimulation of endogenous cells, and possible regulation of specific metabolic pathways. Thus, research into paracrine factors and mechanisms has shown that stem cell therapy is much more complicated and greatly enhances the potential and variety of therapeutic applications. (10-12)

Angiogenesis consists of several distinct processes which include sprouting and proliferation of pre-existing capillaries to form new networks. This process is tightly regulated by hypoxia through a number of proangiogenic factors, including VEGF, FGFs, P1GF, and hepatocyte growth factor (HGF). (13-15) Furthermore, these cytokines act not only in a coordinated time and concentration-dependent manner, but one cytokine may inhibit or stimulate the effect of another.

Homing signals are extremely important for the efficacy of cell therapy because it is via these paracrine effects that the precise localization of transplanted cells is possible and can be improved. Cell homing, transmigration, adhesion, and tissue invasion are the result of many complex steps. Naturally, the migration, differentiation and growth are mediated by the tissue, degree of injury and Stem cells (SCs) involved. Damaged tissue releases factors that induce homing. The tissue, intended as stromal cells, extracellular matrix, circulating growth and differentiating factors, determines gene activation and a functional reaction on stem cells, such as homing, differentiating in a particular cell type or resting in specific niches. These factors can alter the gene expression pattern in SCs when they reside in a new tissue. (16)

Encouraging and pioneering experiments are being carried out in animal models for various muscular dystrophies. Diseased tissue may be regenerated in vivo by transplantation of healthy cells that can extensively replicate. Progenitor and stem cells have this intrinsic ability, and are used in certain clinical settings to enhance or restore damaged tissue. In attempts to regenerate muscle cells replete with dystrophin in the muscles of patients with dystrophin deficiency, several types of muscle-derived cell

transplantation strategies have been tested in animals and in a few DMD patients. A muscle precursor cell, known as the myoblast, was one of the first cell types explored in DMD studies. In 1990, the first muscle stem cell transplantation was carried out in a 9 year old DMD patient, showing dystrophin production. (17) Soon after, many clinical trials in DMD patients were conducted. (18-25) Although, it was found to be a safe procedure, clinical benefits were recorded in none.

Since, myoblast transplantation has not shown effective results mainly due to rapid death of most injected myoblasts and the failure of injected myoblasts to migrate more than 0.5 mm away from the injection site, (26) satellite stem cells have been explored as an alternative. These cells which are specialized muscle stem cells, have the ability to both replicate and differentiate into various types of muscle cells. They are positioned between the plasma membrane and the surrounding basal membrane of adult skeletal muscle fibers, and expresses CD34, Pax 3 and Pax 7. (27) These cells upon activation may also express MyoD, Myf-5 and M-Cadherin. CD34 and M-Cadherin are not so consistent markers of human satellite cells. Among the more reliable markers of satellite cells in human muscle is neural cell adhesion molecule (CD56), which, however, also marks lymphocytes that may enter degenerating muscle in large numbers. (28) Dr. Rudnicki's team found that the Wnt7a protein, when introduced into mouse muscle tissue, significantly increased the population of these satellite stem cells and fueled the regeneration process, creating bigger and stronger muscles. Muscle tissue mass was increased by nearly 20 per cent in the study. (29)

A study was carried out to track the pathway of bone marrow derived stem cells (BMSC) to satellite cell to myofiber, unfractionated green fluorescent protein-positive (GFP+), BMSCs were transplanted into irradiated recipients. Irradiation served to both ablate the bone marrow compartment and decrease satellite stem cell numbers in muscle tissue. GFP+, BMSC-derived satellite cells were identified in muscle tissue of bone marrow transplanted (BMT) recipients by morphology and also by their ability to self-renew and differentiate into myotubes in vitro. The cells were karyotyped, and the "re-programmed" cells were diploid. The level of BMSC derived multinucleate muscle fibers in BMT-recipient mice was greatly increased when the animals underwent physical activity for 6 months. (30) This study is important because it provides evidence that BMSC to muscle differentiation occurs via repopulation of the muscle stem cell compartment. In 2008, Wallace et al carried out a study wherein they transplanted adult muscle mononuclear cells (AMMCs) in -sarcoglycan-null dystrophic mice. They found that AMMCs were 35 times more efficient at restoring sarcoglycan compared to cultured myoblasts. The single injections of AMMCs provided long term benefit for muscular dystrophy and found persistent regeneration after 6 months. (31)

A few other myogenic precursor cell types distinct from satellite cells have also been explored. One of them is the muscle-resident side population (SP) cells. A study has shown that these cells could serve as a vehicle for delivering the dystrophin gene contained in a viral vector into mdx mice. (32) Muscle derived stem cells (MDSCs) or multipotent adult progenitor cells (MAPCs) have also reported to have a high capacity for muscle regeneration. However, compared to conventional satellite cells, many of these SP cells do not display a promising myogenic potential. (33)

Little progress has also been made towards the use of embryonic stem cells (ESC) to study its potential in muscle regeneration. (34-35) It has been observed that injection of wild type ESCs into the mdx blastocysts produce mice with improved pathology and function. (36)

However, due to high rate of rejection and ethical issues related to ESCs, not many studies have been carried out on humans, which are necessary to demonstrate the therapeutic benefits of ESCs in muscular dystrophy patients.

Blood and muscle derived CD 133+ cells have shown to give rise to dystrophin-positive fibers when transplanted into mdx mice. (37) These cells have been demonstrated as safe, following their intramuscular transplantation. In accordance to which, Torrente et al in 2004 2007, carried out a phase I double blind trial with autologous muscle derived CD 133+ cells in 8 boys affected with DMD and was found safe with no adverse events reports. (38, 39)

Experimental studies have shown that sub-populations of human umbilical cord blood (HUCB) cells have myogenic potential and can differentiate into muscle cells. (40,41) A single blind study in mice showing dysferlin deletions was conducted, wherein HUCB cells were transplanted and the expression of dysferlin positive muscle cells was recorded providing support for the hypothesis that a subpopulation of HUCB has myogenic potential. (42)

In 2009, Jazedje et al analyzed the potential of CD34+ cells from umbilical cord blood to do the same. It was observed that, these cells differentiated into mature myotubes after 15 days and dystrophin positive regions were also detected through immunofluorescence analysis. (43) A study was carried out on 82 progressive muscular dystrophy (PMD) cases, which were treated by using double transplantations of BMSC and CB-MSC. No adverse reactions were reported. It was found that 37.8% obtained a remarkable efficacy, 45.1% were effective and 17.1% had no change. Hence, it was safe, convenient and effective therapy for PMD. (44)

Mesenchymal stem cells (MSC) are also attractive candidates for the treatment of muscular dystrophy. Bone marrow derived mesenchymal stem cell transplantation in mouse models have shown to result in ultrastructural changes in muscular tissue due to migration of the cells to lesioned muscular tissue via blood circulation and further resulting in repair and regeneration. (45-51)

In immunosupressed mdx mice, 3H-thymidine labeled human bone marrow derived MSCs were transplanted. One month later, the mice showed greater radioactivity in most of the tissues and organs especially in the bone marrow and skeletal muscle compared to the control mice. Dystrophin positive cells were also detected at 1 month. The percentage of dystrophin positive fibres was 6.6% at 1 month and 8.9% at the end of 4 months. (52)

In 2007, a fetal to fetal transplantation strategy was carried out in mice embryo, human fetal MSCs via intramuscular, intravascular and intraperitoneal delivery. Wherein, it was found that intravascular and intraperitoneal delivery led to systemic spread of the cells. (53)

In mdx mice, MSCs derived from adult adipose tissue have homed to, differentiated into skeletal muscles and repaired injured muscle tissue. The repair is correlated to

with reconstitution of dystrophin expression on the damaged fibres. (54-55)

Bone marrow-derived mesenchymal stem cells (MSCs) can differentiate into mesodermal cells, including myoblasts (56). MSCs have the advantages of being able to fuse with and genetically complement dystrophic muscle, possessing anti-inflammatory properties, and producing factors that enhance the activity of endogenous repair cells (57).

At the NeuroGen Brain & Spine Institute, Mumbai, a study was carried out on 72 muscular dystrophy patients who underwent intrathecal autologous bone marrow derived mononuclear cell transplantation, 41 were suffering from Duchene Muscular Dystrophy type, 17 had Limb Girdle Muscular Dystrophy, 11 had Congenital Muscular Dystrophy, 2 had Becker's Muscular Dystrophy and 1 had Fascioscapulohumeral Dystrophy. The mean follow up of 6 months showed that out of 72, 32 showed improved trunk strength, 30 improved in their lower extremity strength with 11 of them showing gait improvement and 20 improved in upper extremity strength. (58) (The results have been enumerated as 100 Case Reports in Section C).

Induced pluripotent stem (iPS) cells are a recent development which has brought a promise of great therapeutic values. Studies conducted on animal models, have demonstrated iPS cells to have myogenic regenerative potential. (59-60)

Further research is ongoing, and is clearly necessary to make this therapy a viable treatment option for patients with muscular dystrophy.

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14

Anesthetic Considerations in Muscular Dystrophy

The anesthetic management of patients with muscular dystrophy can be quite complicated and needs careful peri-operative planning. The management is patient-specific rather than disease-specific, as each patient presents with different manifestations. This chapter is a brief overview of the pre-anesthetic considerations, intra-operative management and post-operative precautions taken during stem cell therapy for patients with muscular dystrophy.

Firstly, a brief overview of the various systems affected by the disease:

CARDIAC

Cardiac changes are mainly caused by degenerative changes in the cardiac muscle.

ECG

It shows evidence of right ventricular strain, with tall R waves and inverted T waves. Resting tachycardia is one of the early signs of cardiac involvement. The ECG may also show conduction defects, with 1st degree AV block and left anterior hemi-block occurring very commonly. Atrial arrhythmias are also seen.

2D Echocardiogram

It shows evidence of dilated cardiomyopathy and cardiac enlargement. Mitral regurgitation due to papillary muscle dysfunction is also a common finding.

Patients with Duchenne, Becker's and Myotonic muscular dystrophy are more likely to have cardiac problems. In fact, cardiac findings may manifest earlier than skeletal in Becker's muscular dystrophy.

RESPIRATORY

Respiratory problems are mainly due to muscle weakness and progressive kyphoscoliosis.

- There is a decreased ability to cough out secretions.
- Frequency of infections increases.
- There is a progressive restrictive pulmonary defect.
- Bulbar weakness, esp. seen in myotonic dystrophy, leads to repeated episodes of aspiration.
- All these factors eventually lead to decreased alveolar ventilation, resulting in chronic hypoxaemia and hypercapnia.

PRE-ANAESTHETIC EVALUATION:

A detailed history and examination of the patient is mandatory. The aim of pre-anaesthetic evaluation is to understand the extent of cardiac and respiratory compromise, which helps us to anticipate and tackle problems in the peri-operative period.

History:

- Cardiac: history of palpitations, dyspnoea, syncope, pedal oedema
- Respiratory: history of recent changes in pulmonary symptoms, frequency and severity of lower respiratory tract infections, changes in cough pattern, difficulty in swallowing etc.
- History of drug allergies and addictions
- History of steroid therapy

Investigations:

- Routine hematological investigations viz CBC, blood sugar, creatinine, electrolytes, liver function tests, and a coagulation profile
- ECG and echocardiogram to evaluate the cardiac status
- Pulmonary function tests to evaluate the respiratory status
- X-ray chest

ANAESTHETIC MANAGEMENT:

The patient has to be anaesthetized twice; once during the aspiration of the bone marrow, and secondly during the injection of the stem cells. Routine premedication includes ondansetron and pantoprazole. Fentanyl (1-2µg/kg) and midazolam (0.03mg/kg) is administered as sedation. The induction agent of choice is propofol. The patient breathes spontaneously, with oxygen supplementation. Measured aliquots of propofol are used for maintenance of anaesthesia. Local anaesthetic (a mixture of lignocaine 1% and bupivacaine0.25%) is injected both at the site of marrow aspiration and the spinal injection. In co-operative patients, propofol may not be required. Adequate antibiotic

coverage is administered. During the injection of the stem cells, fentanyl and midazolam may be repeated in a lower dose, depending upon the sedation level of the patient. The induction agent of choice is again propofol.

Fluid Management:

The incidence of post-spinal headache is high, since a wide bore needle is used to inject the stem cells in the subarachnoid space. Hence the patients are well hydrated, with an average adult receiving 2.5 litres of a crystalloid over 12 hrs. but if the patient has evidence of cardiac compromise, a small bore lumbar puncture needle (25G) is used to inject the cells. Infusion of IV fluid is then restricted to 1.5 litres for an adult.

Difficulties Encountered In Lumbar Puncture:

Lumbar puncture becomes difficult in extremely obese patients, and those with kyphoscoliosis. In case of kyphoscoliosis, X-rays and 3D CT scans serve as a useful guide to locate the inter-spinous space.

MITOCHONDRIAL MYOPATHY:

Patients with mitochondrial myopathy are very difficult to anaesthetize. Most anaesthetic drugs have a depressant effect on mitochondrial function. Anaesthesia risk in these cases stems from the high chances of a complete atrio-ventricular block, which requires pacing. These patients require stringent peri-operative glucose control; both hypo and hyperglycaemia are harmful. Excessive starvation, metabolic stress, pain etc. should be avoided.

POST-PROCEDURE MANAGEMENT:

The main objectives of post-procedure management are:

- Adequate pain relief
- Abdominal binder and adequate fluids to prevent spinal headache
- Monitoring and maintenance of vital parameters till complete recovery from anaesthesia and sedation
- Avoid shivering, as it can precipitate myotonic episodes

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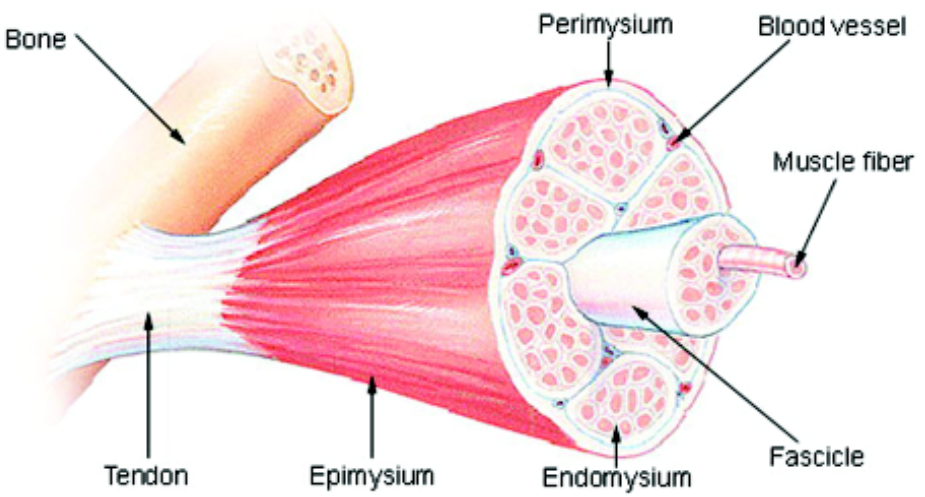
15

Muscle Physiology And Concept Of Motor Points In Stem Cell Transplantation

STRUCTURE OF A MUSCLE

In human body, muscles are composed of many muscle fibres, which are separated from each other by connective tissues called endomysium and are arranged in bundles called fascicules, where individual fibres are arranged parallel to each other. Each fasciculus has an outer connective tissue membrane called perimysium and muscle as a whole consists of all these fascicules together with outer layer called epimysium.



Types of Muscles in human body

There are three major types of muscles skeletal, smooth and cardiac. The characteristics of each type are summarized below.

Type of Muscles in Human Body	Characteristics	Location in the human body
Skeletal Muscle	striped, striated, somatic, or voluntary muscles, most abundant	attached to skeleton
Smooth Muscles	plain, unstriped, non-striated, visceral, or involuntary muscles	often encircle or surround the viscera
Cardiac Muscle	intermediate in structure, being striated and at the same time involuntary.	form myocardium of the heart
Myoepithelial Cells	Function: assist in expulsion of secretion from the acini.	present at the bases of secretary acini of sweat gland

Out of the four kinds of muscles, the skeletal muscles are most abundant in the body and have three major types.

TYPES OF SKELETAL MUSCLE FIBERS

The human body has three major types of skeletal muscle fibers: fast fibers, slow fibers, and intermediate fibers.

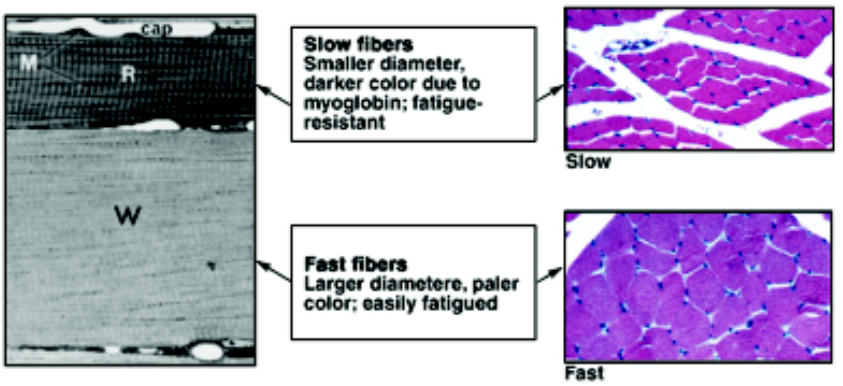
i. Fast Fibers:

Most of the skeletal muscle fibers in the body are called fast fibers, because they can contract in 0.01 sec or less after stimulation. Fast fibers are large in diameter; they contain densely packed mofibrils, large glycogen reserves, and relatively few mitochondria. The tension produced by a muscle fiber is directly proportional to the number of sarcomeres, so muscles dominated by fast fibers produce powerful contractions. However, fast fibers fatigue rapidly because their contractions use ATP in massive amounts, so prolonged activity is supported primarily by anaerobic metabolism. Several other names are used to refer to these muscle fibers, including white muscle fibers, fast-twitch glycolytic fibers, and Type II-A fibers.

ii. Slow Fibers:

Slow Fibres are only about half the diameter of fast fibers and take three times as long to contract after stimulation. Slow fibers are specialized to enable them to continue contracting for extended periods, long after a fast muscle would have become fatigued. The most important specializations in them is improved mitochondrial performance. Slow muscle tissue contains more extensive network of capillaries than in a typical fast muscle tissue and so has a dramatically higher oxygen supply. In addition, slow

fibers contain the red pigment myoglobin . This globular protein is structurally related to hemoglobin, the oxygen-carrying pigment in blood. Both myoglobin and hemoglobin are red pigments that reversibly bind oxygen molecules. Although other muscle fiber types contain small amounts of myoglobin, it is most abundant in slow fibers. As a result, resting slow fibers contain substantial oxygen reserves that can be mobilized during a contraction. Because slow fibers have both an extensive capillary supply and a high concentration of myoglobin, skeletal muscles dominated by slow fibers are dark red. They are also known as red muscle fibers, slow-twitch oxidative fibers, and Type I fibers.



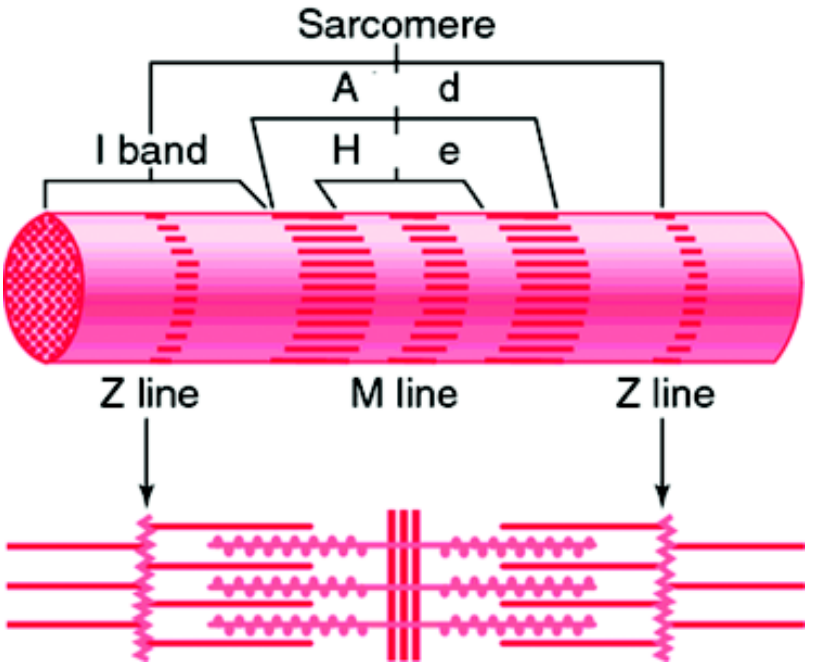
iii. Intermediate Fibers:

The properties of intermediate fibers are intermediate between those of fast fibers and slow fibers. In appearance, intermediate fibers most closely resemble fast fibers, for they contain little myoglobin and are relatively pale. They have a more extensive capillary network around them, however, and are more resistant to fatigue than are fast fibers. Intermediate fibers are also known as fast-twitch oxidative fibers and Type II-B fibers.

MUSCLE PHYSIOLOGY

Sarcomere is the contractile unit of a myofibril, which are repeating units and delimited by the Z bands along the length of the myofibril.

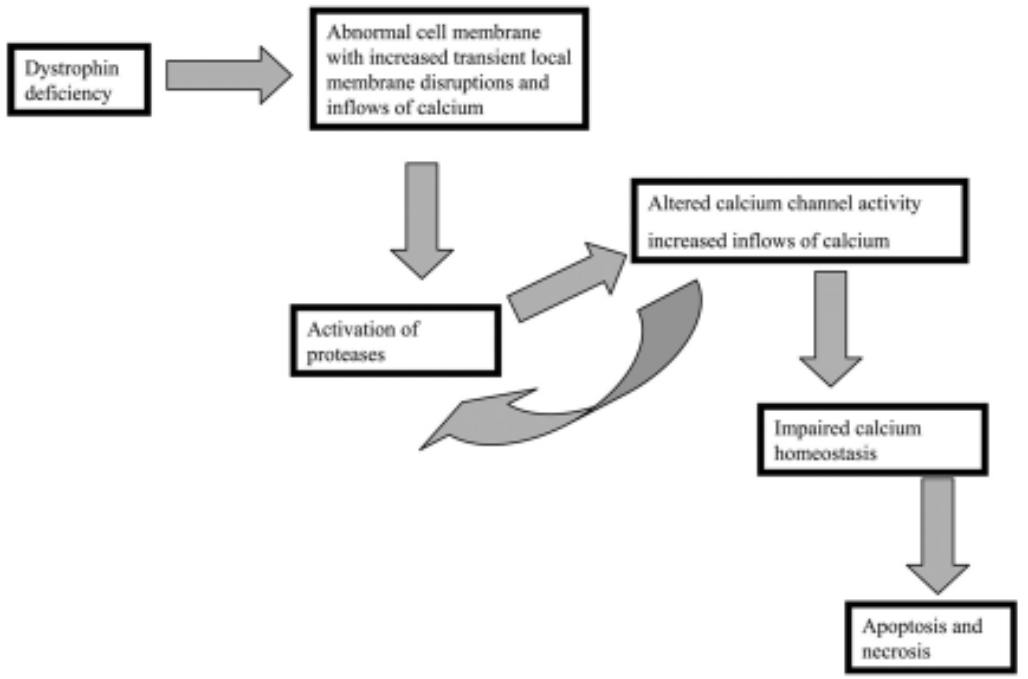
Muscle units are separated from other muscle groups by plasma membranes called the sarcolemma and the cytoplasm within is called the sarcoplasm. Within the sarcoplasm are multiple long protein bundles called myofibrils, and many ATP producing mitochondria, as well as glycogen (a form of stored glucose for energy) and myoglobin (oxygen stored in blood for the breakdown of glycogen). Bundles of parallel myofilaments make up the myofibrils which is where most of the action takes place. In the myofilaments are contractile proteins called myosin (thick filaments), and actin (thin filaments).When signaled, the actin and myosin interlock and slide over each other to stretch or slide into one another to contraction. They are signaled from the nervous system followed by a series of chemical reactions involving ATP, calcium, sodium and potassium ions.



There are many other proteins involved in the process. Aside from the contractile proteins, there are regulatory proteins called tropomyosin and troponin which act like a switch to determine when to contract and when to relax. On the muscle fiber the 'I band' is the space between the myosin (thick) filaments, where lies only the thin filaments. In the middle of each 'I band' is a dark disc called the 'Z disc' made of titan, (elastic filament), which is connected to the sarcolemma by the cytoskeleton. The space between each Z disc, where these filaments interact, is called the sarcomere. As the muscle contracts the 'I band" shrinks and the sarcomere shortens and as the Z disc's come closer together pulling on the sarcolemma shortening the cell. This is how the muscle contracts. One of the most clinically important accessory proteins here is dystrophin which is located just under the sarcolemma in the cytoplasm in the area of the 'I band'. It is produced by specific genes and links the actin filaments to the protein extracellular matrix in the membrane known as the dystrophin-associated protein complex. Elements of the dystrophin gene and the protein structure have been identified, yet the exact functional role is still a bit unclear. However, as research continues it is thought that its primary function is to provide mechanical reinforcement to the structure of the sarcolemma and thereby protecting the membrane from the stress or tearing during contraction.

In Muscular Dystrophy patients, as dystrophin is defective or absent, the membrane breaks down and molecules like proteins and enzymes leak out of the fiber into circulation. These enzymes and chemicals that leak out are responsible for certain chemical reactions and disruption of the process of muscle contraction which thus causes irreparable damage.

Pathophysiology of Protein deficient Muscle:



Blake D J et al. Physiol Rev 2002;82:291-329

To summarize, important abnormalities of dystrophin-deficient muscle cells have been demonstrated in three areas:

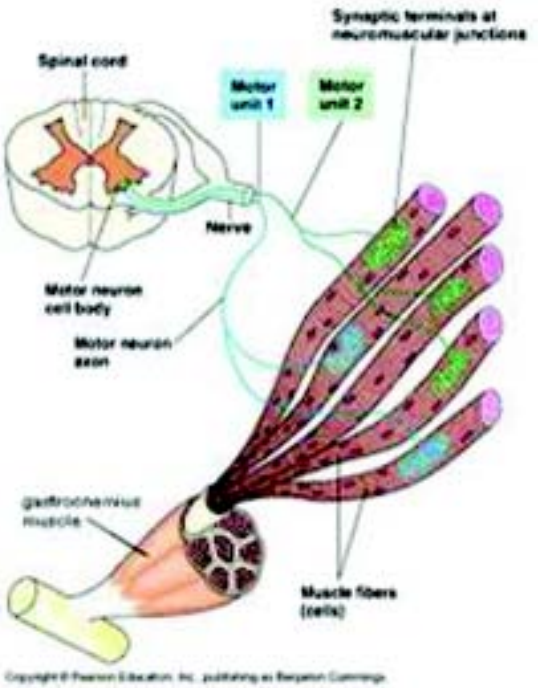
1. Calcium homeostasis,
2. An increased susceptibility to oxidative toxins, and
3. Increased (and stress enhanced) membrane permeability.

MOTOR POINT

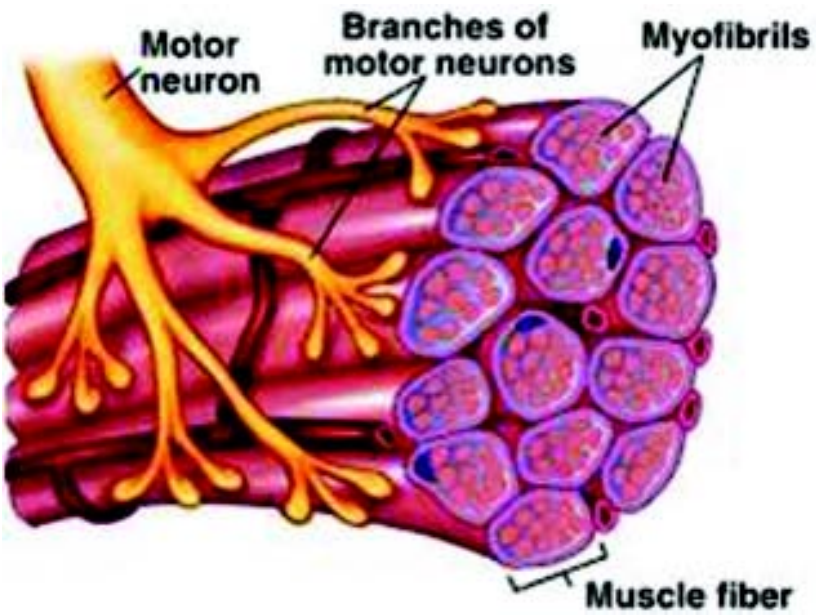
Motor point is the point at which the main nerve enters the muscle or, in case of deeply placed muscle, the point where the muscle emerges from under covers of the more superficial ones.

Facts about Motor points:

Motor points are frequently at the junction of the upper & middle one thirds of the fleshy belly of the muscles, although there are exceptions e.g.: the motor point of vastus medialis, whose nerve enters the lower part of the muscle, is situated a short distance above the knee joint. Deeply placed muscles may be stimulated most satisfactorily where they emerge from beneath the more superficial ones, e.g.: extensor hallucis longus in the lower one third of the lower leg. This is the point on the skin region where an innervated muscle is most accessible to percutaneous electrical excitation at the lowest intensity. This point on the skin generally lies over the neuro



A Neuromuscular Junction



The Motor Unit

vascular hilus of the muscle & the muscles band or zone of innervations. Muscle fibres do not always extend the whole length of a muscle & myoneural junctions are not uniformly spread out all over the muscle but are concentrated in a confined area-the zone or band of innervations where the greatest concentration of motor endplates & the other large diameter nerve fibres may be reached with less concurrent painful stimulation of the smaller diameter cutaneous fibres.

The exact location of motor point varies slightly from patient to patient but the relative position follows a fairly fixed pattern. Some motor points are superficial & are easily found, while others belonging to deep muscles are more difficult to locate.

CONCEPT OF MOTOR POINT STIMULATION

When a nerve is stimulated at a nerve cell or an end organ, there is only one direction in which it can travel along the axon, but if it is initiated at some point on the nerve fibre it is transmitted simultaneously in both directions from the point of stimulation.

When a sensory nerve is stimulated the downward travelling impulse has no effect, but the upward travelling impulse is appreciated when it reaches conscious levels of the brain. If impulses of different durations are applied, using the same current for each, it is found that the sensory stimulation experienced varies with the duration of the impulse. Impulses of long duration produce an uncomfortable stabbing sensation, but this becomes less as the duration of the impulse is reduced until with impulses of 1 ms & less only a mild prickling sensation is experienced.

When a motor nerve is stimulated, the upward -travelling impulse is unable to pass the first synapse, as it is travelling in the wrong direction, but the downward travelling impulse passes to the muscles supplied by the nerve, causing them to contract.

When a stimulus is applied to a motor nerve trunk, impulses pass to all the muscles that the nerve supplies below the point at which it is stimulated, causing them to contract.

When a current is applied directly over an innervated muscle, the nerve fibres in the muscle are stimulated in the same way. The maximum response is thus obtained from stimulation at the motor point.

Preparation of the patient

Clothing is removed from the area to be plotted & the patient is supported comfortably in good light. The skin has high electrical resistance as the superficial layers being dry, contain few ions. The resistance is reduced by washing with soap & water to remove the natural oils & moistening with saline immediately before the electrodes are applied. Breaks in the skin cause a marked reduction in resistance which naturally results in concentration of the current & consequent discomfort to the patient. To avoid this broken skin is protected by a petroleum jelly covered with a small piece of non absorbent cotton wool to protect the pad. The indifferent electrode should be large to reduce the current density under it to a minimum. This prevents excessive skin stimulation & also reduces the likelihood of unwanted muscle contractions, as it may not be possible to avoid covering the motor points of some muscles.

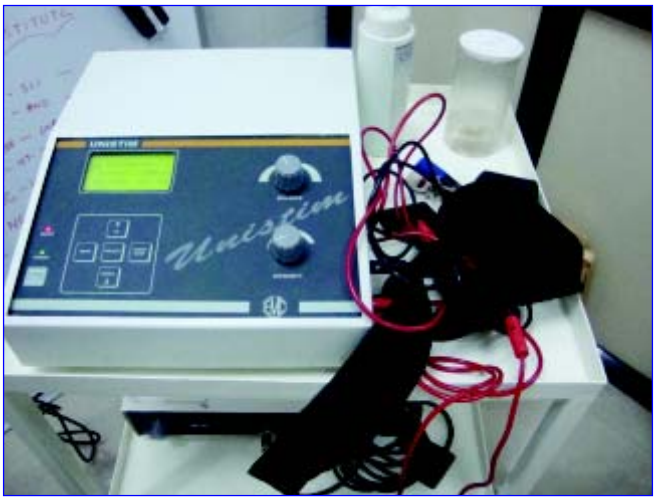
Preparation of apparatus

Faradic type of current

A low frequency electronic stimulator with automatic surger is commonly used. A faradic current is a short -duration interrupted direct current with a pulse duration of 0.1 - 1 ms & a frequency of 50 - 100 Hz. Strength of contraction depends on the number of motor units activated which in turn depends on the intensity of the current applied & the rate of change of current. To delay fatigue of muscle due to repeated contractions, current is commonly surged to allow for muscle relaxation.

Stimulation of Motor points

This method has the advantage that each muscle performs its own individual

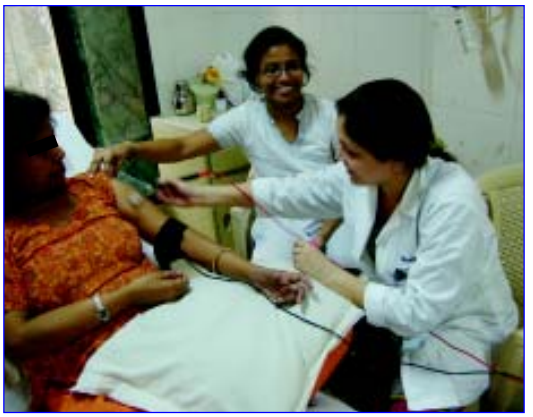


Electrical stimulator used for stimulation and plotting of motor points.

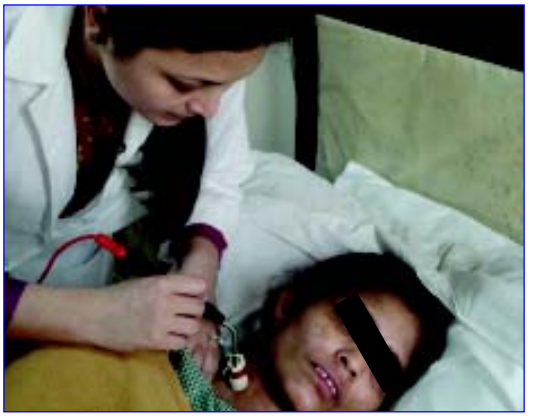
action & that the optimum contraction of each can be obtained, by stimulating the motor point. The indifferent electrode is applied & secured in a suitable area. The indifferent electrode is placed over the motor point of the muscle to be stimulated. Firm contact ensures a minimum of discomfort & where possible the whole of operators hand should be in contact with the patient's tissues so that she /he can feel the contractions produced.

Selection of the Individual muscles for intramuscular injection of stem cells in Muscular Dystrophy Patients:

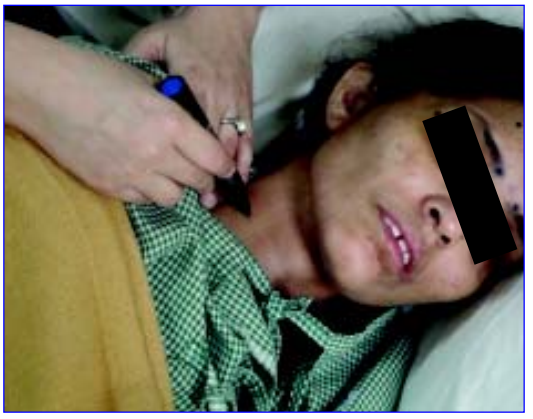
Patients with Muscular Dystrophy have primarily weak antigravity muscles like hip knee extensors , back extensors and ankle Dorsiflexors in lower limbs. In upper limb the proximal shoulder girdle muscles like deltoids, biceps triceps and scapular stabilizers like rhomboids and serratus are the most commonly affected. All of these muscles are needed for mobility and activities of daily living , but as they progressively get weaker , patients begin to get dependent for functional activities.



Preparation of the patient for motor point plotting



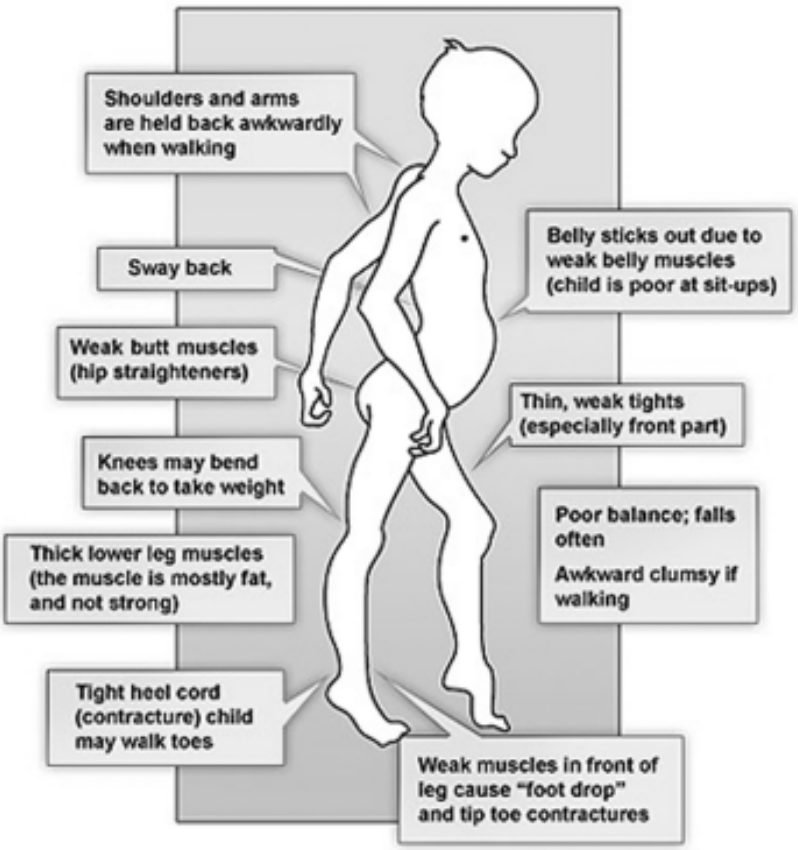
Plotting of motor point
(strenomastoid muscle)



Marking of sternomastoid muscle motor point.

Although MD can affect several body tissues and organs, it most prominently affects the integrity of muscle fibers.It causes muscle degeneration, progressive weakness, fiber death, fiber branching and splitting, phagocytosis (in which muscle fiber material is broken down and destroyed by scavenger cells), and in some cases, chronic or permanent shortening of tendons and muscles. Also, overall muscle strength and tendon reflexes are usually lessened or lost due to replacement of muscle by connective tissue and fat.

So selection of muscles (motor points) for intramuscular injection depends on manual muscle testing & patient's complain of weakness & difficulty in activities of daily living. So rehabilitation team (Physiotherapists and Occupational therapists)



decides motor points of which muscles need to be injected with stem cells. Also the Electromyography and Musculoskeletal MRI , aid in locating muscles with severe affection in the form of fatty infiltration or reduced interference pattern on voluntary contraction.

In few selective types of Muscular Dystrophies like Oculopharyngeal MD , facial muscles are weak and are therefore considered for intramuscular injection .

Commonly considered muscles for injection are as follows

A) Major muscles of upper limbs that are generally considered:

a) Deltoid: Anterior, middle & posterior fibres.
b) Biceps brachialis.
c) Triceps: long, lateral & medial heads.
d) Thenar muscles: Opponens pollicis & abductor pollicis brevis & flexor pollicis brevis.
e) Hypothenar muscles: abductor, flexor & opponens digiti minimi.

B) Major muscles of lower limbs that are generally considered:

a) Quadriceps: vastus medialis, vastus lateralis, rectus femoris.
b) Hamstrings: Biceps femoris, Semimembranosus & semitendinosus.
c) Glutei.
d) Dorsilflexors: Tibialis anterior, Peronei longus & brevis, EHL.

C) In trunk:

Abdomen & back extensors are considered, & in neck muscles sternocleidomastoid.

D) Facial Muscles:

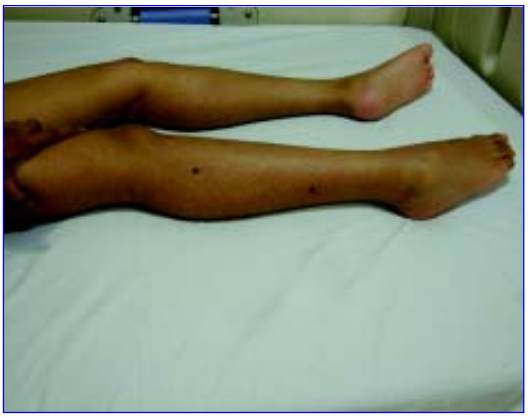
In case of facial muscle weakness : orbicularis oris, orbicularis oculi, Buccinator, rhizorius, frontalis, mentalis, etc.

Intramuscular stem cells injection in motor points within the muscle, ie the area with high concentration of motor end plates is very specific transplantation. Also multiple motor points in choosen muscle group allows for a graded response, thus allowing increment in muscle strength clinically depending on, further specific training & strengthening of individual injected muscles. An injection of stem cell in the motor end plate potential, can be identified in the neuromuscular system within few hours, although the onset of clinical effects is noticed as early as 72 hours post transplant, which varies from patient to patient.

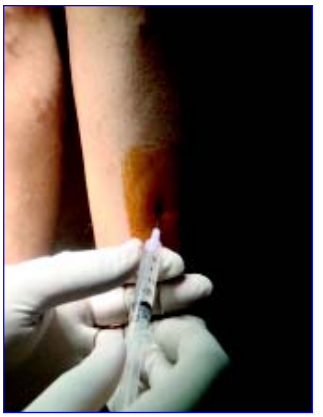
MECHANISM OF ACTION OF INTRAMUSCULAR STEM CELL INJECTION AT MOTOR POINTS

As motor point is the point at which the main nerve enters the muscle. Delivery of stem cells at this point facilitates further specific implantation of the stem cells in isolated individual muscles and aids in enhancing the healing of the degenerated muscle. Also the stem cells promote regeneration by enhancing angiogenesis, suppression of inflammation and improved function via paracrine actions on injured cells ,neighboring resident stem cells , extracellular matrix , and the infarcted zone. (*Refer chapter 12)*

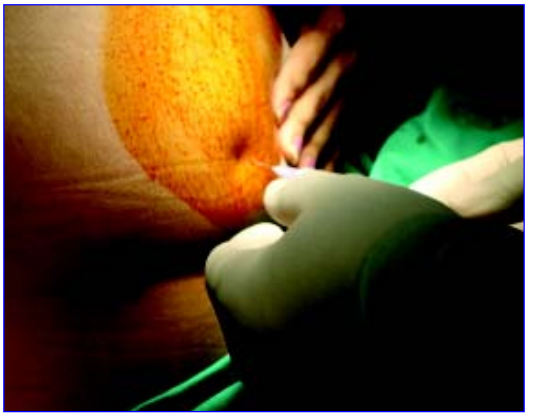
Post stem cell injection these muscles need specific training & individual muscle strengthening program so that results are seen by following mechanisms:



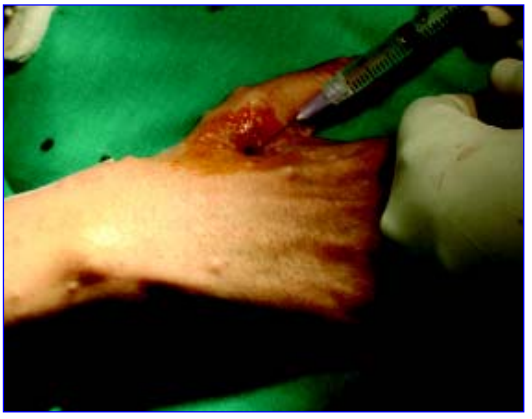
Plotted motor points of tibialis anterior and peronei muscle



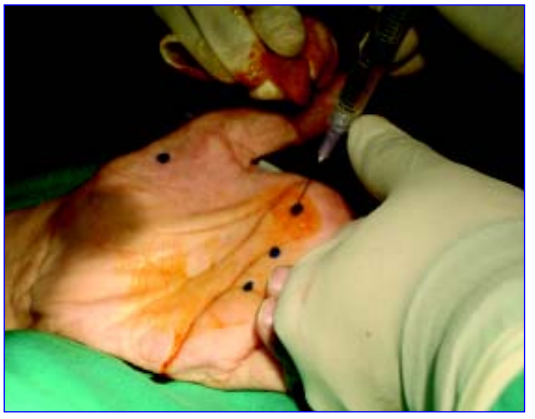
Injection of stem cells in tibialis anterior muscle motor point.



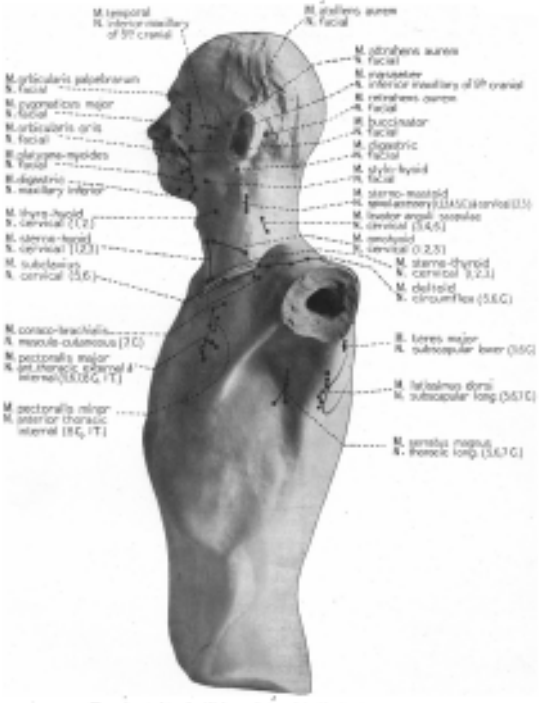
Injection of stem cells in the glutei muscle motor point.



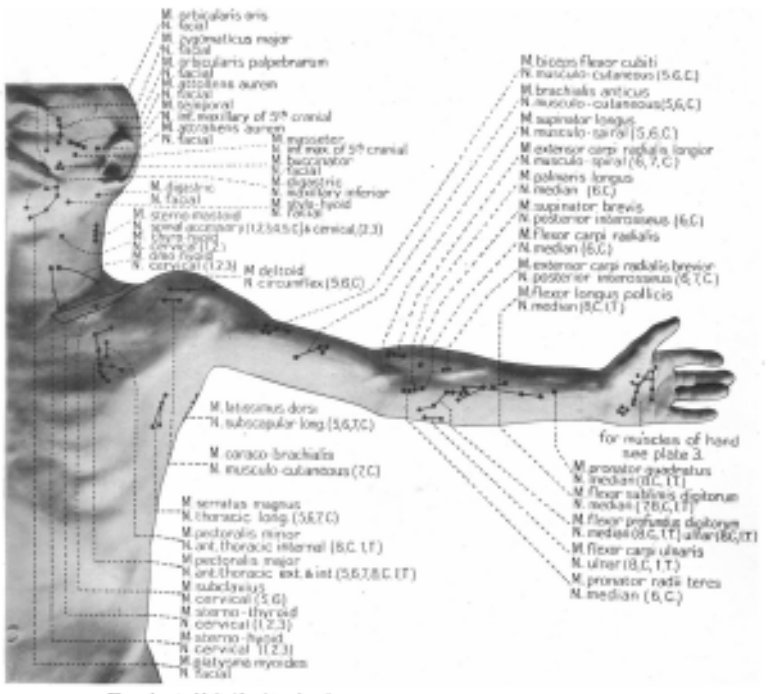
Injection of stem cell injection in the adductor pollicis muscle motor point.



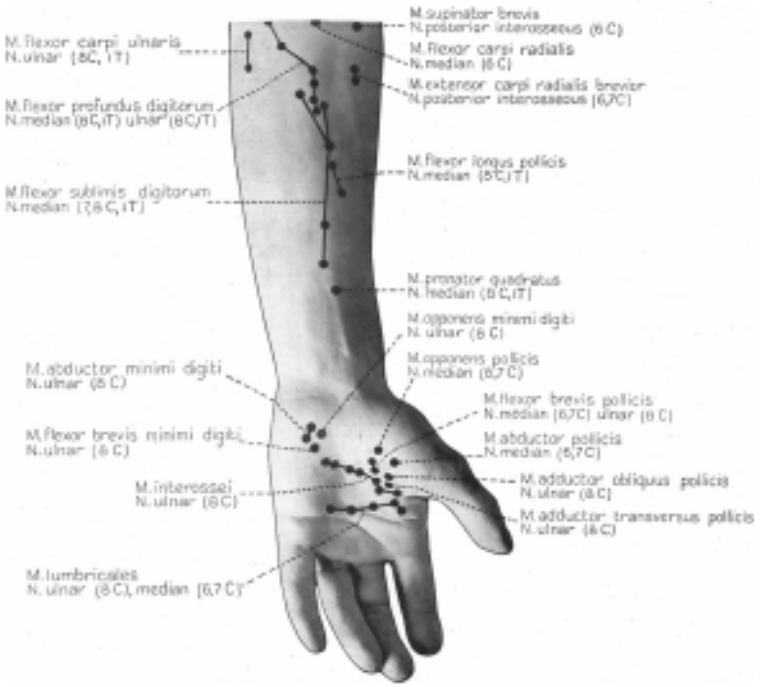
Injection of stem cells in the lumbrical muscle motor points



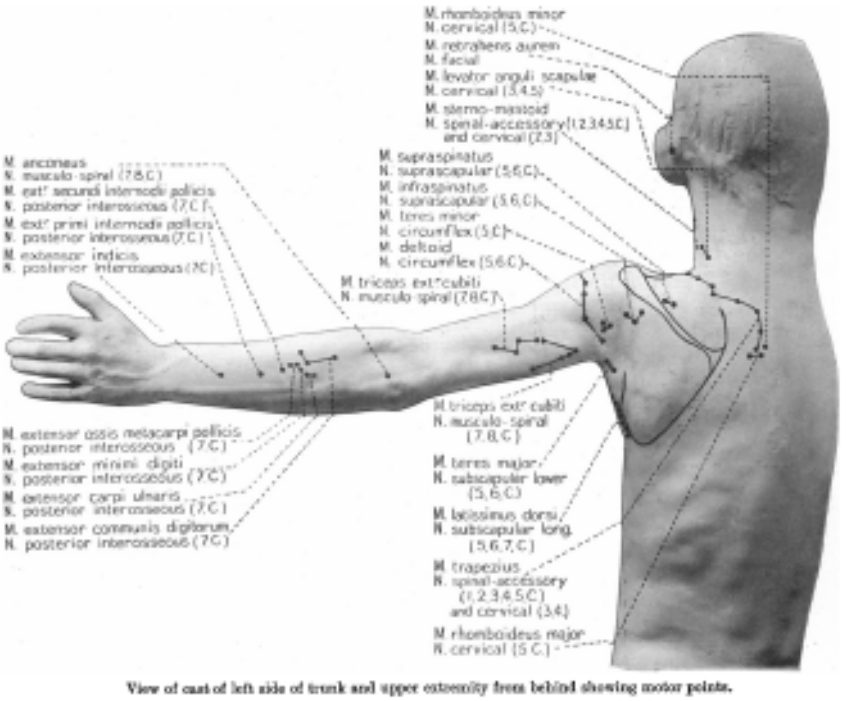
View of cast of trunk of living male from left side showing motor points.
(Prepared in the Anatomy Department of University of Aberdeen.)



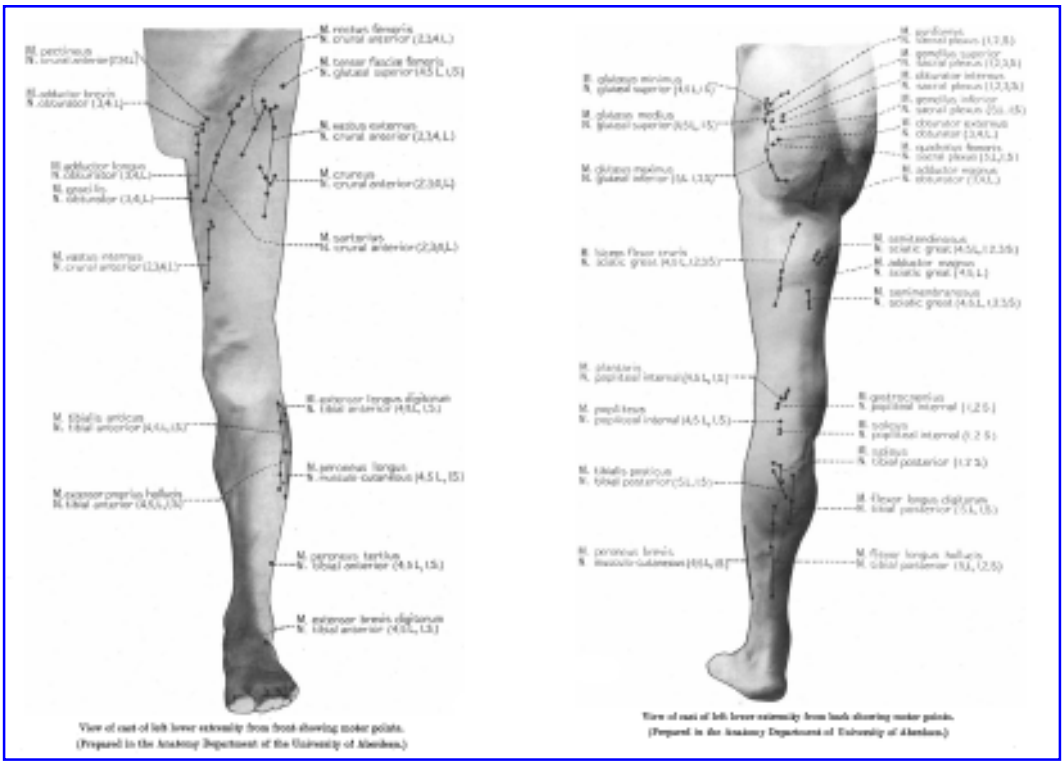
View of cast of left side of trunk and upper extremity from front showing motor points.
(Prepared in the Anatomy Department of University of Aberdeen.)



View of cast of left fore-arm and hand from front showing motor points.
(Prepared in the Anatomy Department of University of Aberdeen.)

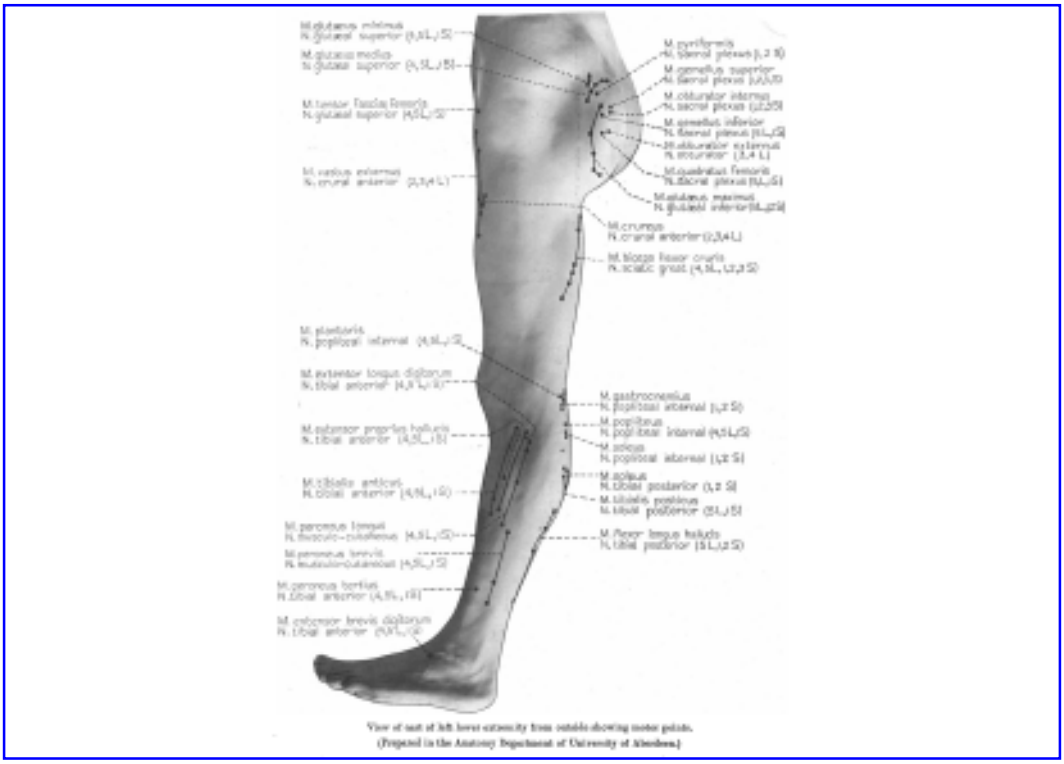


View of cast of left side of trunk and upper extremity from behind showing motor points.
(Prepared in the Anatomy Department of University of Aberdeen.)



View of cast of left lower extremity from front showing motor points.
(Prepared in the Anatomy Department of the University of Aberdeen.)

View of cast of left lower extremity from back showing motor points.
(Prepared in the Anatomy Department of University of Aberdeen.)



View of cast of left lower extremity from outside showing motor points.
(Prepared in the Anatomy Department of University of Aberdeen.)

1. In muscles that contain a mixture of fast and intermediate fibers, the proportion can change with physical conditioning. For example, if a muscle is used repeatedly for endurance events, some of the fast fibers will develop the appearance and functional capabilities of intermediate fibers. The muscle as a whole will thus become more resistant to fatigue.
2. Exercise leads to stimulation of Satellite cells (special stem cells which lie adjacent to skeletal muscle fibre and play a role in muscle regeneration and repair)
3. As dystrophy patients muscles lack enzyme , which produces nitric oxide , which in turn leads to vasodilatation , in order to stimulate satellite cells .Natural stimulation of satellite cells in them is very slow , thus leading to rapid degeneration and braek down to muscles.But direct stem cell intramuscular transplantation and exercise leads to angiogenesis and vasodilatation , leading to stimulation of satellite cells and thus repair and regeneration of muscles.

Gradually as the muscle strength increases patient gains efficiency & independency in activities of daily living (ADL).

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16

Importance of Neurorehabilitation in Muscular Dystrophy

Neurorehabilitation is the clinical subspecialty that is devoted to the restoration and maximization of functions that have been lost due to impairments in patients with Muscular Dystrophy, a genetic disease of neuromusculoskeletal system. The goals of neurorehabilitation team is to help patients with impairments and disabilities and to make them functionally independent, with the aid of team members consisting of physical therapists, occupational therapists, speech therapist and psychologist The philosophic foundation of rehabilitation team is to promote purposeful activity thereby preventing dysfunction and eliciting maximum adaptation.

CONCEPT OF NEURO REGENERATIVE REHABILITATION THERAPY (NRRT)

The concept of Neuro Regenerative Rehabilitation Therapy(NRRT) at NeuroGen promotes a multidisciplinary and holistic approach to bring about recovery of neural function with a close integration of Neuro regenerative (including stem cell therapy), Neuro protective (medications)and neurorehabilitative therapies (physical / occupational / speech). Thus, it combines the best neurobiological repair technologies and neurorestorative techniques. The rehabilitation protocol is then individualized to the specific requirements of each patient emphasizing on functional recovery and independence in ADL.

The rehabilitation team sets up goals and the injected stem cells from within the body help in achieving those goals. Studies have shown that exercise induces mobility in the injected stem cells, thereby enhancing the achievable outcomes. Hence, neurorehabilitation appears to work complimentarily with stem cells therapy.

Pre assessment symptoms and stages, in which the patient presents, helps in deciding the rehabilitation protocol for them.

CLINICAL STAGES OF MUSCULAR DYSTROPHY

As some muscular dystrophies are progressive in their disease course while others are very slow; these disease can be divided into stages according signs and the pattern of involvement.

Stage 1: Early/pre-symptomatic :

During presymptomatic stage, diagnosis remains unnoticed unless there is some positive or strong family history or unless for some reasons any blood investigations are done. Symptoms of delay in early developmental milestones like crawling, walking or child been flaccid, are the markers.

Stage 2 : Early ambulatory (Walking)

Patients in this stage show classic traids like Gower's Manoeuvre in which the child gets up from the floor by using his arms to crawl up his own legs, has waddling type of gait and toe walking with difficulty in activities such as running, hopping and climbing stairs.

Stage 3: Late Ambulatory (going off feet)

In this stage mobility becomes labourous with difficulty in climbing stairs and walking distances. They present with frequent falls and have difficulty or are unable to get up on their feet without assistance. Also early involvement of scapular stabilizers results in decrease in arms and hands movements during reachout activities.

Stage 4 : Early non-ambulatory

Patients in this stage are able to sit up on their own independently but are unable to walk. In this stage, wheelchair becomes a main aid for propulsion where they can self propel for some period of time. Good postural management is required as most of time they remain in sitting posture. Since there is poor trunk control because of muscle imbalance, there is increased risk of developing scoliosis and management of same is mandatory.

Stage 5: Late non-ambulatory

Postural imbalance and malalignment is the main concern seen in this stage with decrease in upper limb function which results in decline in performing ADLS like dressing, feeding and difficulties with oro-motor function can lead to nutritional problems. Apart from physical impairments there is impairment seen in respiratory and cardiac functions and they thus, require interventions for same.

Stage 6 Palliative Care/ End of Life .

Functional Transitions in patient with Muscular Dystrophy. (These stages help in deciding the goals for rehabilitation team)

1. Walks with mild waddling gait with lordosis. Running becomes strenuous but can ascend, descend steps, curbs.
2. Walking with moderate waddling gait with lordosis. Running becomes impossible. Climbing stairs and curbs becomes difficult .Uses Gower's maneuver while getting up from floor but can rises from chair independently .
3. Walks with moderately severe waddling gait and lordosis. Can raise himself from chair independently but ascending descending curbs or stairs or rise from floor becomes totally dependent.
4. Walks with assistance or with bilateral KAFOs. Can have surgical release for contractures. Can propel manual chair slowly and wheelchair propulsion for community mobility. Independent in bed and self -care even though some help is needed in dressing and bathing because of time constraints.
5. Unable to walk independently but can bear and shift weight to walk with orthoses and can transfers from wheelchair independently. Can propel self in manual chair but with limited endurance whereas motorized wheelchair becomes more functional . Independent in self care with transfer, need assistance for bath or shower.
6. Independence in motorized wheelchair but requires trunk support or orthosis

Assistance is needed in bed and with major dressing, is independent for performing self -grooming but dependent for toileting and bathing .

7. Independence in motorized wheelchair but need to recline intermittently while in chair. Needs assistance for hygiene and most self care requiring proximal upper limb control.
8. Uses both hands for single hand activities, can perform simple table- level hand activities, and can perform self-feeding with arm support.
9. Can sit in wheelchair only with trunk support and intermittent reclining or transfer to supine position .May require nighttime ventilatory support or intermittent daytime PPV. Some hand control can be achieved if arms are supported and needs help for turning at night.
10. Totally dependent and cannot tolerate upright position and needs home ventilatory support if needed for prolonged ventilation, then tracheostomy is needed.

BIOMECHANICS IN MUSCULAR DYSTROPHY PATIENTS

Patterns of muscle weakness and compensation according to stages :

Early stage:

Weakness seen in hip extensors, ankle dorsiflexors, hip abductors, hip adductors, abdominals, neck flexors, shoulder depressors, extensors and abductors and elbow extensors (mainly the antigravity muscles).

Compensation :

1. Increased lumbar lordosis to keep force line behind hip joint.
2. Lack of heel strike.
3. Foot may be pronated and everted.
4. Hip waddling gait
5. Decreased Cadence.
6. Gower's Maneuver.

Middle stage:

Weakness seen in quadriceps and ankle evertors in addition to muscles mentioned above in early stage.

Compensation:

1. Line of gravity infront of knee joint and behind hip joint.
2. Base of support widens to maintain balance and due to tightness in iliotibial band
3. Increased ankle plantar flexion and equinus posture to avoid knee flexion.
4. Frequent falls.
5. Strong action of tibilias posterior results in inversion attitude at ankle.

- ***Tightness:*** develops in iliotibial bands & tensor fascia lata, hip flexors, hamstrings, gastrosoleus and posterior tibialis.
- ***Functional Losses:*** All activities against gravity like ability to rise from floor, stair climbling and rising from chair.
- ***Compensated Gait:*** Standing and toe walking with wide base of support and extreme lumbar lordosis, extreme lateral trunk lurch and limb abduction .
- ***Treatment :*** Prescription of long leg braces like KAFO with or without surgery should be done to prolong ambulation.

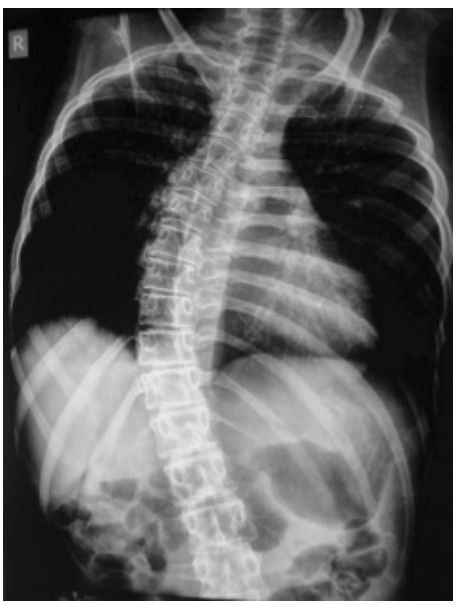
Late or non-ambulatory stage:

Weakness in upper limb interferes with functional activities, mainly muscles affected are elbow extensor, forearm supinator, wrist and finger extensor along with above mentioned muscles in stage two. Distal hand functions are preserved.

- ***Compensation:*** Here in this stage compensation are used to maintain upright posture and facilitate ambulation, achieve support and stability in sitting and upper limb function.
- ***Tightness*** is seen elbow flexors, pronators, wrist and finger flexors and neck extensors results in development of upper limb contracture.
- ***Scoliosis*** results as there is more of sitting posture with loss of ambulation.
- Loss of functional activity is seen in upper limb activities, sitting ability and in doing ADLS.

COMPLICATIONS

1. Scoliosis



Scoliosis can be explained into two phases: one in ambulatory phase and non-ambulatory phase.

- ¢ During ambulatory stage, scoliosis is flexible, functional and is minimized by protective spinal hyperextension and lateral trunk lurching.

  Factors that influence whether or not scoliosis appears prior to final loss of ambulation:

  1. Age at which walking ceases.
  2. Intervention (rehabilitation) used or not used to prolong ambulation.
  3. Final gait pattern.

- ¢ In non-ambulatory phase, scoliosis becomes more prominent as there is constant use of wheelchair and no ambulation. It can lead to decline in pulmonary function, upper extremity function and sitting ability.

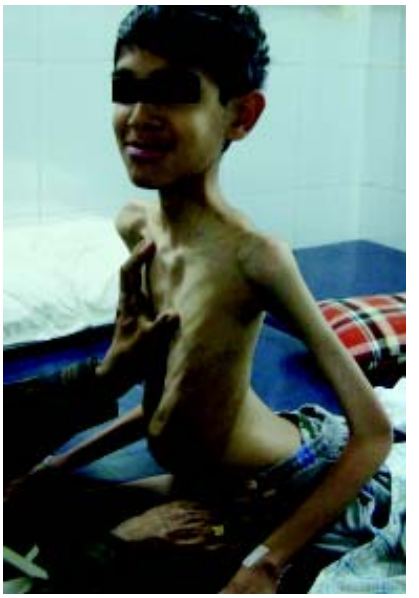
2. Osteoporosis:

It is more common in vertebral column than in long bones, worse in lower extremities than in upper extremities and is aggravated by steroids.

3. Respiratory Affection.

It is compromised by number of factors:

1. Decrease in thoracic and spinal mobility due to progressive muscle weakness leading to replacement into fibrous tissue and restricted pattern of breathing.
2. Asymmetrical breathing pattern due to muscle weakness.
3. Total lung capacity, vital capacity and forced inspiratory and expiratory abilities decreases and residual volume increases.
4. Breathing becomes strenuous from initial shallow breathing to more rapid breathing to less chest or lung volume/expansion leading to decline in breathing volume.

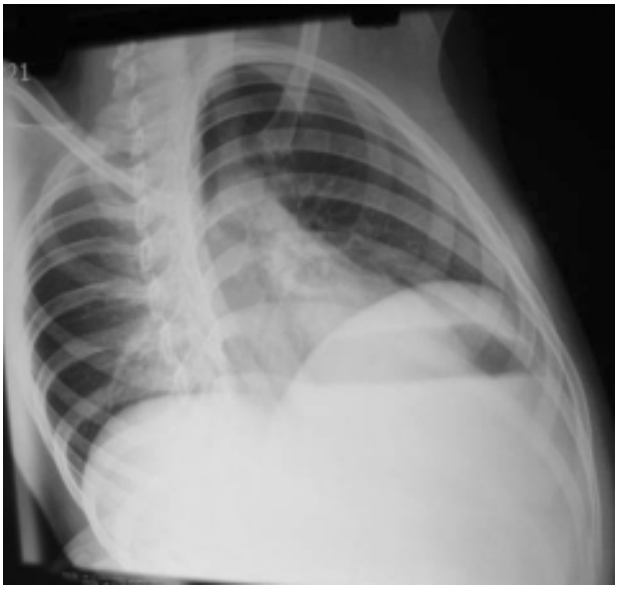


Decrease in lung expansion leads to areas of lung collapse and weakness in abdominals and in muscles of forced expiration results in decreased coughing.

4. Cardiac Involvement

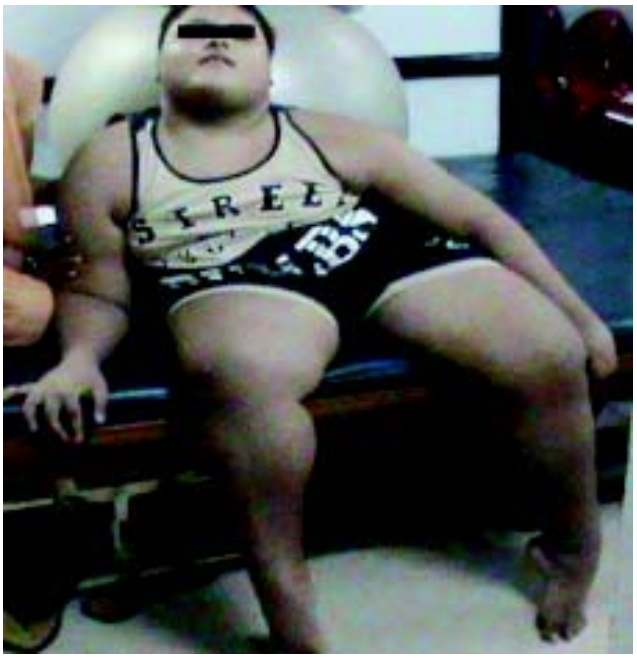
Cardiac smooth muscles are also affected by absent dystrophin protein . Cardiac function can be compromised by scoliosis and respiratory status. It is so progressive that it shows ECG abnormalities, hypertrophic cardiomyopathy and dilated cardiomyopathy. Cardiac abnormalities may also include AV block, atrial paralysis,

atrial fibrillation or flutter, ventricular arrhythmia, conduction defects and reduced ejection fraction.



5. Obesity

As MD patients represent with severe muscular weakness resulting in contractures of the hip flexors and plantar flexors which later interfere with ambulation .And loss of ambulation results in reduced caloric expenditure resulting in obesity .



PHYSICAL THERAPY ASSESSMENT

Pathokinesiology :

Imbalanced muscle weakness, compensatory movement patterns, postural habits and influence of gravity add to progressive muscle weakness in a pattern from proximal to distal.

In Muscular dystrophies, assessment is ongoing process where specific type of muscle weakness, tightness and compensation are identified and interventions should be designed inorder to maximize strength, prevent deformity and provide effective adaptive functioning, depending on the stage in which patient is referred. Assessment includes following parameters:

1. Postural alignment.
2. Range of motion
3. Manual muscle testing
4. Girth Measurement
5. Respiratory status
6. Activities of Daily living
7. Gait
8. Functional Status.
9. Transfers
10. Orthosis/Casting/Bracing
11. Mobility status:
12. Wheelchair mobility: Manual or Motorized
13. Physical environmental and Accessibilty.

Outcome Measures:

1. Vignos Functional Rating Scale.
2. Brooke's clinical protocol.
3. WeeFIM .
4. Pediatric evaluation of disability inventory.
5. Muscle, Pulmonary and ROM testing.
6. GSGC Assessment which includes noting timed tasks in 10 m timed walkng, Stair climbling, sit to stand from chair and rising from floor.(Applicable only for mobile patients)

Rehabilitation Interventions for Muscular Dystrophy:

Physiotherapy in Early stage:

1. Educating the family about the condition and coping strategies
2. Prevention of contractures and deformity which can further lead to disability and pain.

3. Maintenance of maximal strength to prevent disuse atrophy.
4. Maintenance of maximal functional capabilities by using appropriate adaptive equipment
5. Emphasizing home programs.
6. Interventions required to maintain ambulation.

Physiotherapy in Middle stage following loss of ambulation

1. Continuation of early stage program.
2. Spinal care and management to prevent further deformity because of loss of ambulation.
3. Transfers requiring less energy expenditure should be taught.
4. Educating about body mechanics to further prevent the contractures and deformity.
5. Adaptive devices to modified ADLS.

Physiotherapy in Later stage

1. Continuation of above program.
2. Evaluating the endurance and fatigue level required for maintaining any posture or activity.
3. Maximizing Upper limb function .

SHORT TERM GOALS

1. To increase / maintain range of motion.
2. To increase / maintain strength & endurance
3. To promote optimal body alignment & symmetry.
4. To minimize compensatory movement, patterns & position used for function.
5. To prevent the development of scoliosis.
6. To maintain functional ambulation.
7. To maintain sitting ability.
8. To maintain functional (independent) mobility throughout all phases of disease progression.
9. To provide active respiratory program, establish & maintain most effective breathing pattern.
10. To maintain chestwall mobility.
11. To strengthen respiratory muscles & develop endurance.
12. To teach principles of pulmonary hygiene & assisted coughing.
13. To help preserve maximal hand function.
14. To teach caregivers proper handling & transfer techniques

LONG TERM GOALS

1. To prevent deformity & contracture.
2. To maximize, maintain strength & endurance within the limits of fatigue.
3. To maximize & maintain respiratory status.
4. To maintain ambulation.
5. To maintain functional mobility.
6. To maintain highest possible level of functional independence using adaptive equipment & orthotic devices.
7. Provide patient, family & caregivers with timely information helping in overall management of disability.

Exercise has been proven to be beneficial in following ways :

- " increase in strength will improve performance of daily activities such as stair climbing, chair rising, and walking.
- " flexibility program reduces the progression of contractures
- " strengthening of postural muscles may decrease the formation of scoliosis.
- " Also increased energy expenditure due to exercise may reduce the prevalence of obesity as there is no ambulation.

Muscular Strength

General Exercise Guidelines

	Type	Frequency	Intensity	Duration
Flexibility	Passive/Active	Daily	Low	3x (10-30 sec)
Endurance Exercise	Walking, Cycling, Swimming	Variable 1-7 x per week	Low	Variable 1-20 minutes
Muscular Strength	Isokinetic, Concentric, or Eccentric only	Variable 1-5 x per week	Low Low	Variable 1-3 sets 5-15 repetitions

Specific Exercise Guidelines

	Muscle Groups
Flexibility	Hip flexors, Shoulder extensors, Elbow flexors, Plantar flexors, Intrinsic hand flexors, Knee flexors
Endurance Exercise	Muscles used for ambulation
Muscular Strength	Hip extensors, Elbow extensors, Shoulder flexors, Dorsiflexors, Hand and wrist extensors, Back extensors Abdominals.

PRECAUTIONS AND CONTRAINDICATIONS TO EXERCISE

In Muscular Dystrophy patients, due to lack of mature dystrophin the muscle membrane is very fragile, so some forms of exercises are more likely to cause muscle fibre damage by breaking the muscle membrane integrity, especially activities involving high load eccentric exercise.

Eg: downhill running, walking on stairs etc.

Conversely, concentric activities where muscle fibre shorten when they fire, stress on muscles is reduced significantly and are thus advised.

Eg: water exercises, where gravity is eliminated.

Stretching and positioning to prevent deformity:

Effects of chronic positioning, unopposed influence of gravity and imbalanced muscle activity around the joints contribute to development of hypo extensibility, which can be prevented by adequate positioning by daily ROM/ stretching and use of splinting, casting and standing on standing board.

Mostly severe contractures are seen in two joint muscles and those which are postural in function .

In upper limb: Elbow flexors, forearm pronators, wrist and finger flexors.

In Lower limb: Illiotibial band,tensor fascia lata, hip flexors, hamstrings, gastrosoleus and Posterior tibialis

In spine: neck extensors.

Interventions:

1. Passive stretching: should be done daily and is best achieved by standing.
2. PNF- Contract Relax to improve flexibility
3. Joint Mobilization -traction to all joints.
4. Myofascial release techniques.
5. Modalities: Hot packs to increase plasticity and comfort but excessive generalized heat can induce fatigue and reduce strength so should be avoided.

Orthosis and casting :

1. At night or during daytime while taking rest to maintain proper positioning.
2. Ankle foot orthosis(AFO) for stretching plantarflexors.
3. Knee extension splints for stretching knee flexor contractures.
4. Wrist and finger splints for stretching flexors.
5. Serial Casting.

Positioning:

Preferably adviced long hours in prone lying position.

In Supine -Tieing both the thighs to avoid lower limb abductor and external rotator tightness.

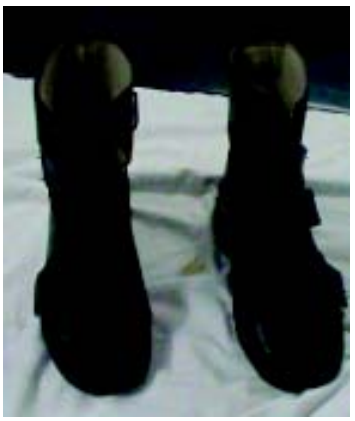
Standing :

With long leg braces (KAFO) on tilt table or standing board to minimize osteoporosis and to prevent lower extremity contractures.

Strengthening can be achieved by

1. Maintaining proper alignment thereby maximizing the muscle work and biomechanical advantage.
2. Positioning and supporting the muscle in their optimal length so that they are functional.
3. Movement facilitation .
4. Submaximal exercises.
5. PNF active assist .
6. Functional movements which are used in ADLS.

Emphasis on Standing and Ambulation with KAFO :



Importance of standing with braces:

- Standing promotes functional status in walking & ADL.
- Lower extremity contractures are stretched resulting in release of stiffness, and flexibility.
- Standing results in minimization of severe osteoporosis as weight bearing improves the bone mineral density.
- Standing provides weight control.
- It improves cardiovascular and cardiopulmonary functions.
- Standing delays the development of scoliosis.

Respiratory Management:

As there is involvement of respiratory muscles, proper respiratory management has to be administrated.

1. To maintain thoracic wall mobility.
2. To maintain strength and endurance in respiratory muscles.
3. To establish proper breathing pattern.
4. To make use of non-invasive inspiratory and expiratory aids.

Interventions:

1. Inspiratory muscle strengthening exercises with Incentive spirometer, blowing whistle,bubbles, sucking through straw .Segmental breathing to improve lung expansion and increase chest wall mobility and to increase the strength of diaphragm muscles.
2. Swimming is advised to improve endurance and breathing patterns.
3. To teach efficient coughing.
4. Postural drainage to remove secretions lobewise should be taught.
5. Inspiratory muscle aids e.g Nocturnal or daytime IPPV with volume ventilator BiPAP if required.
6. Expiratory muscle aids e.g mechanical insufflation - exsufflation.

Spinal Management

1. It is required to prolong ambulation and standing.
2. To promote spinal extension in sitting.
3. To maintain symmetry while sitting in wheelchair.
4. To optimize upper extremity function in symmetrical pattern.

Interventions:

A) Sitting posture:

1. Proper sitting posture in wheelchair should be attained to avoid any compensation happening at spine level. One should be constantly leveling

his pelvis without rotation. Avoiding kyphotic posture, maintaining lower extremity position with no hip abduction and having proper foot placement.

2. Evaluating all functional activities which can produce asymmetrical movement patterns.

B) Standing posture:

1. To help in controlling Lower extremity contracture.
2. To promote spinal extension in standing posture on standing board or tilt tables.
3. To optimize more physiological benefits.

Parents and caregivers should be asked to monitor symmetry and asymmetry posture attained during sitting or standing and correcting those by visual feedback periodically or by changing position or support while maintaining those postures.

Surgical Management:

Segmental instrumentation in spine allows stabilization with immediate postoperative mobilization with no external support required whereas in lower limbs subcutaneous release of Achilles tendons and hamstring muscles and fasciotomy of iliotibial bands. At times, rerouting of tibialis posterior to the dorsal surface of the second or third cuneiform to balance the foot helps, thereby preventing severe varus position of foot.

It is seen that early surgery for contractures followed by intensive physical therapy can prolong brace free ambulation. Gait training can begin within 48 hours after surgery thereby regaining the sense of standing.

OCCUPATIONAL THERAPY FOR MUSCULAR DYSTROPHY

Occupational therapists have a unique ongoing role in supporting and working with patients with muscular dystrophy as the patient's needs and the needs of their caretaker are constantly changing. They need to assess and evaluate an individual's physical, psychological and social needs and focus on maximizing skills, promoting and enabling independence, as well as improving the quality of life of the affected individual and his family.

Assessment

The OT will be responsible for occupational performance areas and components. All

areas assessed will be considered in relation to functional performance and skills in order to identify realistic and client centered treatment goals. The initial step in management of the child with MD involves taking:

1. Medical History with family concerns
2. Aerobic capacity and endurance assessment

Assessments Of Performance Areas :

I. Activities of Daily Living: Basic ADL (BADL) and Instrumental ADL (IADL) skills

BADL:

- Personal care
- Eating and drinking skills
- Dressing
- Bathing
- Toileting
- Bed Mobility
- Transfer: moving and handling, mobility aids used
- Ambulation and stair climbing

IADL:

- Domestic chores
- Transportation
- Banking
- Shopping

II. Play and Leisure Skills

- Recreation
- Hobbies
- Pets
- Sports
- Peer Group

III. Work and Productivity Skills

- School and Nursery assessments
- Pre Vocational testing
- Vocational/ Workplace assessment
- Architectural barriers

Assessment of Performance Components:

The following key performance components need to be assessed.

A. Sensory Processing

Proprioception

B. Neuromusculoskeletal

i.) Reflex
ii.) Range of motion
iii.) Muscle Tone
iv.) Muscle strength
v.) Endurance
vi.) Postural control
vii.) Postural alignment
viii.) Integumentary (when using orthoses, adaptive equipment, or wheelchair)
ix.) Contracture /deformities
x.) Atrophy/ Wasting

C. Motor

i.) Motor control
ii) Gross coordination
ii.) Bilateral integration
iv.) Fine coordination or dextertity

D. Cognitive Integration

i.) Attention span
ii.) Spatial operations
iii.) Problem solving
iv.) Learning
v.) Generalization

E. Psychosocial Skills

i.) Values
ii.) Interests
iii.) Self concept
iv.) Role performance
v.) Social conduct
vi.) Interpersonal skills
vii.) Self expression
viii.) Coping skills
ix.) Time management
x.) Self control

F. Respiratory Status

G. Sleep

H. Need for Assistive and Adaptive Devices and Technologies

I. Home Assessment

J. Wheel Chair Assessment

Frequency of Assessment

An occupational therapy assessment or review of the young person should be carried out systematically and at least annually. More frequent reviews may be necessary at times of change, such as following periods of ill health or after surgery and following loss of ambulation.

Standardised Assessment Tools

The main goal of assessment in occupational therapy is to get a clear understanding of the individual, their social circumstances and their environment, in order to develop a treatment plan which will improve the quality of life of the person and their family. The quality of the assessment carried out will have a direct correlation with the quality of the treatment interventions (Turner et al., 2002). Ideally, in the atmosphere of evidence-based practice, standardised assessments should be used to measure the effectiveness of occupational therapy interventions. Occupational therapists and other professionals have created many standardized tests that could be used to assess certain functions that are problematic for people with muscular dystrophy.

1. ADL Scales : FIM, Barthel Index, WeeFIM,
2. Muscle test (gonimeter, pinchometer, dynamometer, hand functions)
3. Range of Motion (R.O.M.)
4. Vignos Functional Rating Scale.
5. Brooke's clinical protocol.
6. Fall Risk Assessment

PLANNING

Following the assessment process, short and long-term occupational therapy goals have to be set with the individual and the family. These goals must be based on the person's preferences.

INTERVENTIONS

STAGE I & II: Early/pre-symptomatic and Early ambulatory (Walking) Stage

At this stage, education regarding the condition and counseling to the patient and family is of utmost importance. One of the primary considerations in the early management program is to retard the development of contractures. Contractures have not been shown to be preventable, but the progression can be slowed with positioning and an ROM program.

A home ROM program should be emphasized and the family instructed in the stretching exercises. Cycling and swimming are excellent activities for overall conditioning and are often preferred over formal exercise programs Standing or walking for a minimum of 2 to 3 hours daily is highly recommended.

Breathing exercises have been shown to slow the loss of vital capacity and forced expiratory flow rate .Game activities such as inflating balloons or using blow-bottles to maintain pulmonary function can easily be included in a home program and will decrease the severity of symptoms during episodes of colds or other pulmonary infections. Night splints are helpful to slow the progression of ankle contractures.

Play

Play is essential in the psychological development of children. Occupational therapists use play activities in treatment to enhance the developmental and functional skills of a child and to increase the child's enjoyment of play and playfulness .Play can also be a valuable communication tool used by children to communicate their feelings and anxieties . All play activities should be based on the child's interests, not their medical condition. Activities requiring repetitive muscle building types of exercise should be avoided, as they are likely to damage muscle tissue further

Sports

Active exercises and participation in sports activities should be encouraged to help delay the development of contractures. Swimming can be good fun at any age and is an enjoyable form of exercise for people with muscular dystrophy. A child in the early stages of muscular dystrophy will enjoy riding and it is a good exercise for helping him to maintain his balance reactions .

Hobbies

Collecting specialised items is a hobby that fosters social interaction. Shopping, as well as having a functional purpose like buying food or clothes, can also be a social experience at the large shopping malls, the use of computers and video games in occupational therapy treatment programmes is beneficial to people with muscular dystrophy. There are a number of interests that can be carried out with limited upperlimb function; these include reading and creative writing, painting, photography, graphic art and some crafts, such as model-making. People can enjoy leisure pursuits on their own, but Passmore and French . found that social leisure activities were important, as they fostered feelings of self-worth and gave participants a sense of belonging.

Stage III and IV: Late Ambulatory and Early non-ambulatory

Loss of function in personal-care activities is a constant and stark reminder of the progression of muscular dystrophy confronting both the individual and their family in various ways on a daily basis. It is time consuming and physically demanding for all involved personal care is an area that needs to be addressed with the utmost sensitivity. Forward planning is also vital to ensure that the young person's and their family's changing needs are provided for in a timely manner.

In the first stages of loss of function, small independence aids may be useful in maintaining independent self-care skills. As the condition progresses, these aids become more difficult to use and personal-care tasks a more passive experience for the young person. When considering self-care tasks, it is essential to discuss upper-limb function, as this is crucial for independence in this area.

Eating

For the individual with muscular dystrophy, this basic survival task becomes very demanding as muscle weakness progresses, grip strength becomes poor and it becomes increasingly difficult to lift the hands/arms against gravity.

Possible options include:

- lightweight cutlery and cups or mugs with built-up handles
- rocker knife;
- cuffs with inserts for cutlery;
- Plate with a rim to contain the food when scooping;
- non-slip mats;
- mechanical eating aids
- long straw for drinks

Other alternatives such as elevating the plate height, and angled cutlery will minimize the amount of active arm, wrist and hand movement required. Mobile arm supports provides support to the forearm to facilitate eating and drinking.

Grooming

Consideration should be paid to the design features of items of equipment for shaving, combing hair such as long-handled brush/comb, and cleaning teeth, including weight and the type of grip. For grooming tasks normally carried out at the basin, access for a wheelchair to fit underneath (i.e. without a vanity unit, or wall-mounted) together with support for the elbows at each side of the sink is necessary.

Bathing

Bath board and shower aids such as hand held shower, non skid mats, shower chair may be sufficient to provide independence in this area.

Dressing

For postural stability, balance and energy conservation, a seated position with feet firmly on the floor can be helpful for dressing/undressing. As the amount of assistance required increases, small items of equipment such as a dressing stick and reachers may prove useful. Clothing should be comfortable and easy to get on and off: loose, with big head opening and minimal fastenings zips can be made longer to allow easier access for toileting and various sorts of fastenings can be considered, such as Velcro and hooks.

Toileting

Many boys suffer from constipation due to immobility, self-limited diet, reduced

fluid food intake to avoid the need to go to the toilet and slowing of peristaltic movement. A regular toileting routine can help avoid disruption, discomfort and stress, particularly in relation to the school and work environment. Whilst the young person maintains the ability to carry out weight-bearing transfers, rails and a raised toilet seat or a toilet frame may be sufficient. However, as postural control deteriorates, increased support may be necessary in order to allow for a well-supported and relaxed position on the toilet. This type of support generally falls into two categories:

- support which wheels over the toilet;
- frames which fix onto the toilet itself

Transfers

Information and training on how to move and handle an individual can be offered by the occupational therapists, along with advice on equipment that can help when transferring the individual from one position to another . Some of the common moving and handling equipment supplied by therapists are listed below:

- transfer boards;
- hoists and slings;
- sliding sheets;
- handling belts.

Raising the height of beds and chairs from the floor can be useful to the young person in the early stage of the condition as a higher surface requires less muscle power to stand up from, and since the legs can be lowered to the floor in a straight-leg position, rather than trying to rise against gravity from a flexed-knee position. Bed-height adjustment is also helpful if the young person is able to manage to side transfers on/off the bed using a transfer board.

Postural Management

Individuals with muscular dystrophy can develop spinal problems fairly quickly once they stop walking, so they need good postural management interventions to slow down the rate of spinal curvature.Postural management is an approach to the handling, treatment and positioning of children and adults with muscular dystrophy that will reduce the risk of contractures and the development of postural deformities. Passive and active movements of limbs will also slow down the development of contractures.

Good positioning will allow the person to carry out everyday activities with more ease and without adopting abnormal postures. If postural problems are not addressed, it can lead to pain, spinal problems and breathing difficulties. The main pieces of equipment that can help with postural management are:

- sleep systems;
- postural seating;
- wheelchairs with postural seating systems;
- splints/orthotics.

Sleeping

The young person's postural needs must be managed throughout their daily lives which includes overnight positioning. Once pelvic instability is apparent, a postural management plan should be developed to address the sitting, standing and lying positions that the young person will need. This is essential to minimize the risks of deformity, such as the limitations of movement and pain caused by joint contractures or spinal curvatures that impact upon lung capacity and respiratory function.

The young person's postural needs will require regular review and the postural management programme will require to be adjusted accordingly.

Postural Seating

The aims of good seating are: to achieve a good postural position; to maintain functional ability; and to ensure comfort . Seating which promotes a good sitting posture will also promote effective upper-limb function which is essential for a variety of activities, including feeding, writing and play. It is crucial that seating needs are considered from an early age to prevent or delay deformities and promote optimal function . This should be monitored and reviewed on a regular basis to accommodate any changes as the person's condition progresses.

Wheelchairs

Wheelchairs are essential forms of transport for people with muscular dystrophy; they need them to participate in everyday life when they have difficulty walking. They will need different types of wheelchairs at different stages in their illness. Occupational therapists are involved in the assessment and provision of wheelchairs. They may also have to train the individual in how to use their wheelchair. The therapist will have to give recommendations regarding the postural support and pressure relief required for the chair, as well as the type of controls needed to operate the wheelchair.

Transport Issues

Transport is vital to children and adults with muscular dystrophy. They need transport to access education, hospitals, and employment and leisure pursuits. The type of transport needed will change over the course of their illness and the methods of transport used will vary to meet their travel needs. Occupational therapists will often be involved in assessments relating to the transport requirements of people with muscular dystrophy. They need to teach the individuals and their caretakers on how to assist the patient onto different forms of transport. They can also suggest car modifications.

Access To Play Equipment

It is important that young patients with muscular dystrophy have the opportunity to play to develop their skills. Occupational therapists can suggest toys and activities that will help with their development .

IT equipment: hardware and software: If an individual cannot use a standard mouse and keyboard, details of alternative types of keyboards, word-recognition

software and joysticks can be supplied for accessing the internet and playing console games and for socializing and other leisure activities.

Support groups

Many occupational therapists can provide information about and links to support groups for the individuals with muscular dystrophy, their parents or their siblings. Friends and family are the most important factor to maintaining an active social life.

Peer-group friends can provide opportunities for discussion about all topics, including sensitive issues that cannot be easily discussed within the family .

Pets with a loving and protective temperament can also give hours of enjoyment and company to people with muscular dystrophy.

Housing, School And Workplace Adaptations

There are many housing adaptations that the therapist can recommend,that will make life easier for the person with muscular dystrophy and their caretakers. A few are listed below:

- ramps;
- bathroom alterations;
- extensions;
- handrails;
- door alterations;
- hoists;
- lifts.

Equipment

Occupational therapists can advise and provide many pieces of equipment that can help the person to maintain their independence in daily living tasks, school tasks or work tasks. Equipment can also help the caretaker with their care tasks. The following are a minute selection of the equipment that could assist a person with muscular dystrophy:

- hoists and slings;
- shower chairs;
- bath lifts;
- eating aids;
- toilet equipment;
- writing aids.

Written Work / Graphic Skills

Handwriting is a major occupation of education . Once handwriting is established, it is important to assess the following aspects of it:

- Speed of written work? Does speed reduce with sustained effort?
- Effects of gradual postural changes and deterioration
- Legibility of written work? Does legibility deteriorate with sustained effort?
- Effects of writing - does the child experience fatigue and/or cramps in the hands?
- Child's preference - how does the child feel about using technology? Would they prefer to use a scribe/ writer?

Children with Duchenne muscular dystrophy may encounter problems with pencil skills on account of any of the following factors: reduced muscle strength; reduced range of movement; reduced grip strength; reduced stamina; and postural and coordination difficulties. Learning difficulties may also be present and these can further impact on graphic skills. Possible solutions include:

- pencils grips (various types), angled writing boards, resistance provided by both the writing implement and the paper, paper stands/'page-ups' may improve performance in early stages;
- reduction in the amount of writing required, such as by using worksheets on which the child fills in missing words/phrases;
- word-processing technology, including voice-activation programs;
- use of a scribe or writer;
- more oral responses;
- timetabling to allow alternation of passive and active tasks throughout the day to limit fatigue, such as listening activity preceding written work.

Information and computer technology

Word processing: Use of computers should be introduced at an early stage as complimentary to handwriting.

Keyboard alternatives: As power and active movement are lost from the shoulders and upper limbs, it becomes very difficult for the child to extend their arms to the top and edges of the keyboard. Trunk flexion is used to compensate, which is tiring and encourages poor postural positioning. Possible solutions include:

- on-screen keyboard with mouse;
- mouse alternatives, such as touch-pad mouse, joystick, trackball or finger operated integral joystick;
- compact keyboard and or laptops
- Voice-recognition software

Teaching New Methods

Everyone is used to carrying out activities in their own way. An occupational therapist can look at how the individual carries out a task and suggest alternative ways to do it. This may allow the person to complete the task independently. Examples are:

- teaching a person to get dressed on the bed if they have balance problems;

- using a computer to do homework as opposed to having to write it all by hand;
- substitute a battery-operated toothbrush for an ordinary toothbrush.

Pre Vocational Testing

Children need to select subjects that they find motivating and stimulating that could lead to careers that they can pursue. But they also need to be realistic in the courses that they select. Developing a vocational identity is an important part of adolescent development, regardless of their health status. Occupational therapists can have a role by encouraging them to talk about what they want to do when they are older. They can also raise the subject of the boy's expectations regarding employment, as well as establishing what their parents' and their teachers' views are of the boy's work prospects. This will ensure that everyone has a realistic view.

Workplace Assessments

Occupational therapists can also offer practical help in suggesting adaptations to the workplace and work methods to enable the individual to carry out their job. An employment assessment helps to find out what skills a person with muscular dystrophy can bring to an employer. It may also identify skills that have to be developed to improve the person's employment opportunities. The assessment will also discuss the types of work that the person is interested in obtaining and how their medical condition may influence their choice of work.

Fatigue Management

Energy-conservation methods can be used, to reduce fatigue and pain by planning and pacing activities. Some methods of saving energy are listed below:

- If it is not important to the individual to do the task, can someone else do the work?
- Does the task need to be done every day?
- Spread the tasks over the whole day rather than trying to do everything in one time period.
- Can any tools, equipment or adaptations make the tasks easier?
- Stress reduction and relaxation techniques can also help with fatigue and pain management.

Ongoing Assessments

Once the actions and programmes have been put in place, the occupational therapist needs to make sure that these interventions are fulfilling the original goals set by the individual and their caretakers following the assessment process. If their goals have not been met, the therapist will have to re-evaluate their treatment plan and seek alternative ways for the person with muscular dystrophy to achieve their goals.

Stage V & VI: Late non-ambulatory and Palliative Care Stage

As the condition progresses, the individual find that the aids become more difficult to use and personal-care tasks a more passive experience.

Call Systems

A call system should be put in place which can be easily operated by the young person and alerts the caretaker to their needs.

Diet

An immobile individual may gain weight very quickly. This is obviously detrimental to health and increases the physical strains on caretakers. Often, the patient tends to select dry/finger foods in order to avoid the physical difficulties involved in cutting or tearing and reaching the mouth. It is important that the occupational therapist helps the patient make healthy choices.

Transfers: Moving and Handling

Moving and handling needs and the needs of the individual's and caretakers will change over time; therefore, regular reviews need to be carried out. Before any handling task is carried out, it should be explained and consent taken for the move. Postural issues such as trunk and head control have to be assessed to ensure that any equipment or movement approaches used have the right level of support, such as chairs with lateral supports or slings with head supports. The condition of the young person's skin will also influence moving and handling methods. If his skin is vulnerable, make sure that any equipment used will not cause soreness or rubbing.

A profiling bed may be useful as part of a postural management positioning programme. Profiling beds also allow the height of the bed from the floor to be adjusted. Caretakers will also find the ability to raise the bed to an optimum-working height invaluable for transfers, helping with dressing, carrying out stretches or helping the young person to move. The risk of back strain is then minimised.

Occupational therapists can provide advice regarding the number of transfers required and can also advise on how to eliminate unnecessary moves. Several equipment can be utilized to facilitate transfers under different conditions and requirements. For eg.

- Mobile Shower Chairs, Shower Trolleys And Lifting Bath Seats can be used for bathroom and toilet transfers.
- Hoists and Slings are often used for safe transfer of individuals within their home and also in different locations outside. Depending on the hoist design, slings are made with loops, rings or clips to attach to the hoist. Mesh slings are used for bathing, as they dry quickly. Padded slings should be used where the person's skin is vulnerable.
- Stair-climbers and Lifts Stair-climbers and lifts are obviously used to move

people and so they can be deemed manual handling equipment. Stair-climbers are often operated by carers, who therefore need training in how to use them.

Seating

- There are several aspects involved in the assessment for specialised seating, including seat height, width and depth, arm rests, footplates and head rest.
- As the individual becomes more immobile, pressure relief, possibly in the form of a pressure cushion, becomes increasingly important.
- Tilt-in-space facilities in a chair as well as independently adjustable back rests and footrests facilitate a change in position for an individual who may be unable to achieve this himself.

Sleep Management

As the condition progresses, it may be necessary to provide an increased level of support to manage the young person's lying posture effectively. At this stage, a sleep system is worth considering. The aim of a sleep system is to combine symmetrical positioning with a comfortable and supportive position for sleep.

Other sleep systems consist of a mattress overlay that can be moulded, by the positioning of padded supports, to provide contoured all-round body support. For any sleep system, an assessment is required to create an individually customised combination of supports. The following factors would need to be considered:

- the quality of sleep that the person gets and how many times a night the person's and caretaker's sleep is disturbed.
- Establish the cause of sleep disturbances. Is it respiratory, dietary, pain-related or psychological?
- Check whether the bed used is a standard or specialist bed.
- Does it meet the needs of the individual and their caretakers?
- Check whether the mattress has pressure-relieving qualities or whether they are using a sleep system to provide positioning support.

Pain Management

There are a number of interventions that occupational therapists can suggest that can help with pain management. This may be the provision of pressure relief equipment, such as the following:

- mattress;
- seating and wheelchair seating;
- pressure cushions for commodes, shower chairs and baths;
- padded and sheepskin slings.

Skin Protection and Management

It is vital to ensure that any equipment issued will not damage the individual's

skin. If the skin is vulnerable, pressure-relieving materials should be used where the skin comes into contact with the equipment and measures should be taken to limit moving and handling tasks. It is advisable to review how the person is moved and how many times a day he has to be moved, as it may be possible to change the methods of handling to reduce skin contact or to reduce the number of times the person is handled throughout the day. If the individual wears splints, ensure that these are not causing marking or chaffing of the skin. Advice on changing the individual's position when seated in one chair or a bed for long periods of time will also help to prevent skin problems. This can be made easier for the caretaker and the individual by providing adjustable beds and tilt-in-space chairs so that the area that pressure is on can be changed easily with the push of a button.

Sexual Health and Well-Being

Sexuality is fundamental to an individual's health and well-being, irrespective of whether a disability is involved. These needs to be addressed in adults with muscular dystrophy, It is not just about the sexual act. It may be about how medication or incontinence issues affect this aspect of their life. It is also about how they view themselves as a sexual person.

Bereavement and Anticipatory Grief

Individuals with muscular dystrophy experience the loss of muscle strength and associated functions and skills. The loss experienced is ongoing as the condition progresses. This loss is observed but not always understood by the health professional. In addition, in Duchenne's muscular dystrophy as the young man reaches his late teens and early twenties, he becomes acutely aware of his own prognosis. This is compounded by the deterioration and death of his peers. The impact of these deaths and the proximity to the young man himself cannot be underestimated, although it is not always fully recognised. When a realisation or anxiety of impending loss is experienced in advance of the loss, this is anticipatory loss Anticipatory loss can be experienced by people close to the person, too.

Bereavement can be understood to be an emotional and psychological event, which may occur several times in one's life. It affects one's sense of well-being and provokes questions of a spiritual and religious nature, challenging one's existence, sense of meaning and purpose. Bereavement and the associated mourning can also accompany traumatic loss of aspects of oneself, as in paralysis, injury and relationship breakdown. Thought needs to be given to the fragility of one's confidence, self-esteem and identity when a young person is still growing and developing with a deteriorating condition. It is not always recognised that children grieve, as bereavement is often understood to belong to adulthood.

Hospices and Palliative Care

A hospice is defined as a programme, or a facility, to provide palliative care and attend to emotional, physical, spiritual and social needs of terminally ill patients and

their families, at the hospice or within the home. The emphasis is on the relief of pain and promoting quality of life. In this way, it can be seen that hospice care has developed into a concept of care, as it is not limited to the hospice building itself.

The term 'palliative rehabilitation' has been developed in recognition that there is an ongoing adaptation and a re-adjustment to living with a deteriorating condition

Caring for the Caregivers

Occupational therapists also have a duty of care to ensure the needs of the parents and caretakers are addressed separately from those of the person with muscular dystrophy. It is necessary to be both aware and sensitive to the possibility of the different experiences and depths of loss when working with children and young people with muscular dystrophy.

The focus at all times for the occupational therapist is on living and enabling independence but the attitude and approach of the therapist are fundamental to a positive working relationship with the young man and his family. Tact, sensitivity and diplomacy are required by the occupational therapist together with an insight into the difficulties which a family may be experiencing.

SPEECH AND SWALLOWING PROBLEMS AND ITS MANAGEMENT

Speech and language are very essential for daily communication. Any deficit in the process of speech namely respiration, phonation, resonance and articulation affects speech intelligibility. Also, congenital anomalies and mutation to the brain leads to cognitive deficits, thereby causing language problems. Swallowing is a complex function which involves perfect coordination of various stages and muscles. Literature reports difficulties in speech, language and swallowing problems in patients with muscular dystrophy.

Speech and swallowing problems are commonly seen in:

1) ***Congenital muscular dystrophy -***

   These involve severe developmental delay in the brain which leads to mental retardation in many children. These children present with delayed or no verbal communication and severe cognitive issues like difficulties in attention and reasoning. Many of them present with a milder form of deficit like learning disability.

   Language intervention is the most recommended technique in rehabilitation of children with mental retardation. Initially, it is necessary to quantify the degree of deficits in the child and then plan treatment modality accordingly. For example, if the child is verbal to some extent and has borderline functions or milder form of retardation, then language therapy can be carried out with emphasis on increasing the complexity of his language skills. For children with higher level of retardation, an alternated mode of communication has to be chalked out.

2) Facioscapulohumeral muscular dystrophy -

This form of muscular dystrophy involves the muscles of the face, scapula and upper limb. Because of facial involvement, the patient has difficulty in smiling. Poor labial and lingual control is often observed in these patients. These problems lead to dysarthria and dysphagia mainly in the oral phase due to jaw, lips and tongue involvement.

3) Myotonic dystrophy -

Also known as Steinert's disease. It is characterized by weakness of face, neck, shoulder muscles and limbs. Casey and Aminoff (1971) reported a case study of dystrophia myotonica with dysphagia. The patient presented with dysarthric speech of flaccid nature and dysphagia. (443). Difficulty chewing, choking while swallowing, difficulty in swallowing is the commonest eating problems they face.

4) Oculopharyngeal muscular dystrophy -

Classical features of oculopharyngeal dystrophy are ptosis and dysphagia. Commonly seen features are reduced speech intelligibility, poor lingual movements and reduced lingual strength, hypernasality. A study done by Neel et al to estimate the correlation between tongue strength and speech intelligibility concluded that individuals with oculopharyngeal dystrophy required higher lingual strength than normal individuals to carry out speech task and hence had flaccid dysarthria (affected speech due to muscle weakness). Also, dysphagia is seen in some of these patients. Palmer and Neel (2010) reported patients having reduced swallowing functions due to loss of muscle fibres in the pharyngeal and lingual area.

Dysarthria management in terms of improving speech intelligibility and articulatory precision is helpful. Dysphagia has to be monitored very closely in individuals to avoid aspiration. Bolus modification, postural modifications and manuevres are the commonly treatment methods.

Oromotor exercises to improve chewing, lip and tongue control helps in strengthening the function.

.PSYCHOLOGICAL REHABILITATION IN MUSCULAR DYSTROPHY

A patient diagnosed with Muscular Dystrophy goes through a lot of psychological changes. This ranges from having very little knowledge about the disease, then getting to know about not many ways to cure it, or lack treatment plan, deteriorating condition, family issues, social withdrawal, embarrassment about the condition and eventually coming in terms about the issue of death. Hence, as the patients undergo psychological distress they need psychological help which would enhance their overall well being and would help the patient and the family members to cope with the situation in a healthier manner.

In few instances along with Muscular Dystrophy patients are also suffering from few comorbid disorders like Autism, Obsessive Compulsive Disorder, ADHD or poor cognitive functioning.

Emotional Impact in Muscular Dystrophy

These patients go through a lot of emotional changes and for which they need emotional support, understanding, love and patience to ensure their emotional well being. There may be times when it's difficult to keep up with the progression of the disease, anger, frustration, embarrassment, sadness or anxiety. These emotional issues may occur especially during the developmental period or as the disease progresses.

Social Isolation: As the level of mobility decreases, there is a sense of loss of independence and this could lead to social isolation and depression. Patients with late onset in muscular dystrophy may prefer living in isolation if they don't have enough family support to keep them socially isolated. These patients have a low self-esteem and concept which hinders them from socializing.

Depression and Anxiety: According to studies it has been found that as compared to normal people, people suffering from Muscular Dystrophy stand higher chances from suffering from depression and anxiety.

Behavioural Issues: Behaviour problems are quiet common in children who are diagnosed as DMD. Young boys with DMD have more difficulty with impulsivity and emotional control than other children of the same age. Most of them are likely to be inflexible in their thinking which may result into non-compliance or opposition.

Aggression: Patients with muscular dystrophy are at a higher risk of having significant problems with following directions, temper tantrums, problems with arguing and refusing to do what they are asked to do. Behaviour therapist with the help of Behaviour modification therapy would be helpful in developing alternative strategies to modify the likely triggers to negative behaviours.

Family Issues: When the patient's starts showing signs of muscular dystrophy initially the parents overlook the disease but as the disease progresses and after the diagnosis is confirmed, the parents go through an emotional turmoil. As, the patients and family members undergo, emotional stress, frustration, anxiety, depression, etc. they should be given the opportunity to discuss the impending death in an accepting environment with the psychologist who is experienced in handling patients with muscular dystrophy.

Psychological Assessment

The most crucial time to consider assessment includes the time around diagnosis as this is the window period of adjustment after diagnosis for the patients and the family members.

Behavioural, Emotional Adjustment or Coping: Patients with muscular dystrophy should undergo a brief screening of emotional status either in every 6 months or annually, as many of the patients slip into depression and this may worsen their physical condition. Standardised tests like Beck's depression inventory, Hamilton's anxiety rating scale, etc. can be used to evaluate their emotional state.

Neurocognitive: Comprehensive developmental or neuropsychological assessments is recommended at near the time of diagnosis as this would help parents either to go in for a normal school or special school to cater to the special needs of the child. Standardised performance and verbal based tests or rating scales are used to evaluate the IQ or the cognition of the patient like Wechsler's Intelligence Scale for Children, Wechsler's Adult Memory Scale, etc.

Psychopharmacological interventions: This should be considered for the treatment of moderate to severe psychiatric symptoms as a part of multimodal treatment plan that includes appropriate psychotherapies and educational interventions.

- Psychotherapy: Parental management training, where the parents are guided on the ways to help them and the patient cope with the situation and to avoid parent-child conflict which could aggravate and add on to the existing problems.
- Individual Therapy: This is suggested for internalizing behaviours like depression, anxiety, low self- esteem, adjustment and coping difficulties.
- Group Therapy: This is recommended as the patients are mostly socially withdrawn and cuddle into a nutshell, so in order to get them out its necessary that they undergo group therapy which would help them resolve their issues about themselves and help them build confidence.
- Family Therapy: This is quiet important as the patient becomes dependent on the family members for all his needs, which leads to added burden to the family members and a change in their lives. The family members should be well equipped to cope with the situation avoid caregiver's burnout and at the same time help support the patient. Early in the child's life, the family should be guided to encourage the child's independence and to discourage overprotection. It is important to help the child and the family identify realistic goals for independence.
- Applied Behaviour Analysis: This is especially needed if a patient has comorbid, psychological disorders like autism or ADHD.
- Pharmacological Intervention: Selective Serotonin re-uptake inhibitors are prescribed for patients with muscular dystrophy who also suffer from depression, anxiety and obsessive compulsive disorders. Mood stabilisers are prescribed for aggression, anger and emotional dysregulation. Stimulants are prescribed for attention-deficit hyperactivity disorder.

Thus a rehabiliatation team, with their guidance and integrated program can aid in improving quality of life and promoting independence in patients with muscular dystrophy.

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SECTION C

Duchenne Muscular Dystrophy Is Ultimately a Stem Cell Disease, Researchers Find

Science Daily (Dec. 10, 2010) - For years, scientists have tried to understand why children with Duchenne muscular dystrophy experience severe muscle wasting and eventual death. After all, laboratory mice with the same mutation that causes the disease in humans display only a slight weakness. Now research by scientists at the Stanford University School of Medicine, and a new animal model of the disease they developed, points a finger squarely at the inability of human muscle stem cells to keep up with the ongoing damage caused by the disorder.

"Patients with muscular dystrophy experience chronic muscle damage, which initiates a never?ending cycle of repair and wasting," said Helen Blau, PhD, the Donald E. and Delia B. Baxter Professor and a member of Stanford's Institute for Stem Cell Biology and Regenerative Medicine. "We found that in mice the muscle stem cells can keep up with the demands on them to cycle."

The difference is caused, the researchers found, by the fact that mice have significantly longer protective caps on the ends of their chromosomes. The caps, called telomeres, allow the cells to continue to divide and replenish the damaged muscle long after the human cells have reached their capacity for division.

The research marks the first time that muscular dystrophy has been shown definitively to be a stem?cell?based disorder, according to the scientists, who also generated the first?ever mouse model of Duchenne muscular dystrophy that closely mimics the human disease. Similar to human patients, the animals exhibit severe muscle weakness and shortened life span. The mouse model will allow clinicians and researchers to better study the disease and test new therapies.

"The results suggest that treatments directed solely at the muscle fiber will not suffice and could even exacerbate the disease. The muscle stem cells must be taken into consideration," said Blau. Former postdoctoral fellow Jason Pomerantz, MD, co?corresponding author and now an assistant professor at the University of California?San Francisco, said, "if a treatment does not replenish the stem cell compartment, it will likely fail; it would be like pushing the gas pedal to the floor when there is no reserve."

Blau is the senior author of the research, which will be published online Dec. 9 in Cell. Postdoctoral scholars Alessandra Sacco, PhD, and Foteini Mourkioti, PhD, are co?first authors of the work. Sacco is now an assistant professor at the Sanford?Burnham Medical Research Institute.

Duchenne muscular dystrophy is the most prevalent form of the muscular dystrophies. It is caused by a mutation in the dystrophin gene, which connects the interior cytoskeleton of the muscle fiber to the extracellular matrix. Its absence leads to death of the muscle tissue and progressive weakness, which eventually affects a patient's ability to breathe; 10?year?olds are often wheelchair?bound. Death usually occurs by the second or third decade as a result of respiratory and heart problems. The disorder affects about one of every 3,500 boys in the United States, whereas girls are generally spared because the gene lies on the X?chromosome.

Unfortunately, for decades the trusty laboratory mouse failed scientists trying to study the

disease in animals. Mice with the same mutation showed only minimal muscle weakness. This left researchers without an easy way to test drugs and therapies. It also gave them a puzzle: Why were the mice so resistant to the muscle damaged caused by the dystrophin mutation?

Blau, Pomerantz, Sacco and Mourkioti, thought the answer might lie in the muscle stem cells. Like other types of stem cells, the muscle stem cells can divide to both replenish themselves and to make new muscle cell precursors. These precursor cells can replace damaged or dead muscle cells that make up the muscle fiber. But even muscle stem cells have their limits, and in this case, the mouse cells outperform their human counterparts.

The reason, the Stanford researchers found, is in the length of the telomeres on the DNA of the two species. The average length of telomeres in laboratory mice is greater than 40 kilobases; in humans it's about 5 to 15 kilobases. Telomeres serve as protective caps on the ends of chromosomes, buffering them from the gradual shortening that occurs during each round of replication. When the telomeres become too short, the cells are no longer able to divide.

To test their theory, the researchers blocked the expression of a component of the telomerase enzyme, which maintains telomeric DNA. Mice with both the dystrophin mutation and the faulty telomerase expression experienced progressive, debilitating muscle degeneration with age ?? as exhibited by treadmill stamina tests and muscle damage assays ?? and had shorter?than?normal life spans. Muscle stem cells from the mice also had a reduced ability to proliferate, both in the animals and in culture, and were less able to engraft and begin growing when transplanted into wild?type animals.

"What we're seeing is that muscular dystrophy is a multi?factorial disease," said Blau. "The lack of dystrophin causes muscle damage. These damaged muscles are replaced by dividing muscle stem cells, but the repeated rounds of division because the telomeres to shorten until the stem cells can't fix the damage anymore. This is what happens in humans, and in our new mouse model."

The idea that the symptoms of muscular dystrophy reflect an inability of stem cells to repair ongoing damage has some interesting implications. It implies that any successful treatment should begin early, before the stem cell pool is depleted. It also indicates that researchers and clinicians should investigate stem?cell?based therapies as well as those aimed at protecting the muscle fibers themselves. Finally, it suggests that a highly targeted approach to increase telomerase activity in the muscle stem cells could be useful.

"Finding out that this is a stem cell defect is really exciting," said Blau. "In the early 1980s we reported that muscle cells from DMD patients had less capacity to divide but we did not have the tools to figure out why, since muscle stem cells, the dystrophin gene and telomere function had yet to be identified. Finally, now we can get a handle on what is going on, and learn how best to target future therapies. Having a mouse model that mimics the human disease will benefit all in the field and is very exciting for patients."

Other Stanford researchers involved in the work include Rose Tran, now a graduate student; Peggy Kraft, research assistant and Blau lab manager; postdoctoral scholars Jinkuk Choi, PhD, and Marina Shkreli, PhD; research fellow Michael Llewellyn, PhD; Steve Artandi, MD, PhD, associate professor of medicine; and Scott Delp PhD, the James H. Clark Professor of Bioengineering, Mechanical Engineering and Orthopaedic Surgery.

The research was funded by the American Heart Association, the National Institutes of Health, the Muscular Dystrophy Association and the Baxter Foundation.

Case Report - 1

Diagnosis : *Duchenne Muscular Dystrophy*

A case of a 11 year old male, who complained of gradually progressive bilateral lower limb weakness since 5 years. This lead to difficulty in getting up from the floor, climbing stairs and walking. He stopped walking completely about 6 months back. Neurologically, he was hypotonic and hyporeflexic, with bladder/bowel and other sensations intact. He had grade 2+ strength in bilateral lower limbs proximally and grade 3 distally. His upper limb strength proximally was grade 3 and distally was grade 3++. On examination, he had bilateral pseudohypertrophy of calf with bilateral genu valgum and tallipoequinovarus deformity. Functionally, he needed assistance for all his ADL. He was attending regular school, but was wheelchair bound for mobility. On FIM he scored 85. On Brooke and Vignos scale, he scored 3 and 9 respectively.

On investigation, the serum creatine phosphokinase levels were raised, the electrophysiological studies showed evidence of myopathic pattern and muscle biopsy showed effacement of the fascicular architecture with round and hyalinised myofibres. It also showed moderate to marked increase in fibro-fatty tissue, overall revealing histopathology consistent with muscular dystrophy. DNA testing revealed deletions in exons 53-55 of the dystrophin gene, confirming the diagnosis of DMD. MRI of the upper and lower limbs before the stem cell therapy revealed, marked fatty infiltration with volume loss of predominantly the pelvic girdle muscles involving the glutei and the hamstrings, partial fatty infiltration of the leg muscles with the sparing of the extensor compartment and partial fatty infiltration involving the proximal fibers of the biceps.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Quadriceps, Peronei, Tibialis Anterior, Glutei, Abdominals, Back Extensors, Rhomboids, Deltoid, Biceps and Triceps.

Clinical Improvements seen After Stem Cell Therapy

Functionally: At the end of 8 months of follow up , he reported that the effort required to perform the exercises was reduced significantly. His stamina and endurance to sustain exercises had improved significantly as opposed to earlier when he would fatigue easily .His weight also reduced with visible toning of his muscles. Psychologically, he was more confident, alert and responsive as compared to prior therapy. His upper extremity strength increased, and he was able to do over head activities like throwing ball , reach outs , upper body dressing and combing independently , which were all assisted activities prior to the therapy. His trunk strength increased with improved dynamic sitting balance and ability to perform reach outs on the edge of the cot without losing balance. He had stopped walking since 12 months before the therapy, so had developed knee and hip flexor tightness, but post therapy

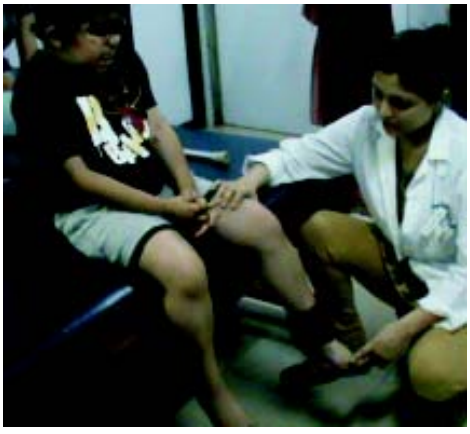
he was made to wear bilateral push knee splints and was taught to walk ,with the aid of the walker .Gradually his lower limb muscles improved in flexibility, strength and he mastered the act of walking .He was the given a KAFO , and taught to walk without an aid (walker), At the end of 3 months , post therapy , he began to walk independently .He could walk 80 steps at a time , which then increased to 500 , at the end of 8 months. His calf muscles which were hypertrophied and hard to feel, on palpation ,also softened up .

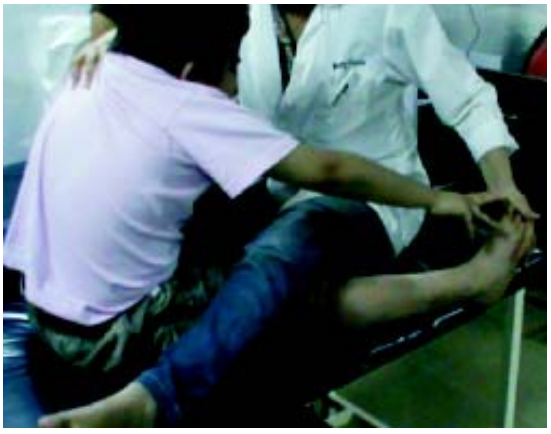
	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	4015 IU	1847 IU
Functional Independence Measure	85	90

Manual Muscle testing : Following muscles showed improved strength

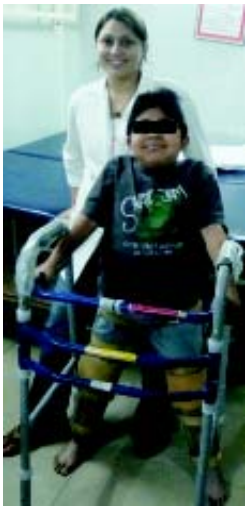
RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
1	2+	Extensors	1	2+
2	3+	Flexors	2	3+
1	2	Adductors	1	2
		KNEE		
2	3-	Extensors	2	3-
		ANKLE		
2	3++	Dorsiflexors	2	3++
2	3+	Evertors	2	3+
		SHOULDER		
3	3+	Extensors	3	3+
3	3+	Flexors	3	3+
3	3++	Abductors	3	3++
3	3+	Triceps	3	3+
2	3+	**ABDOMINALS**	2	3

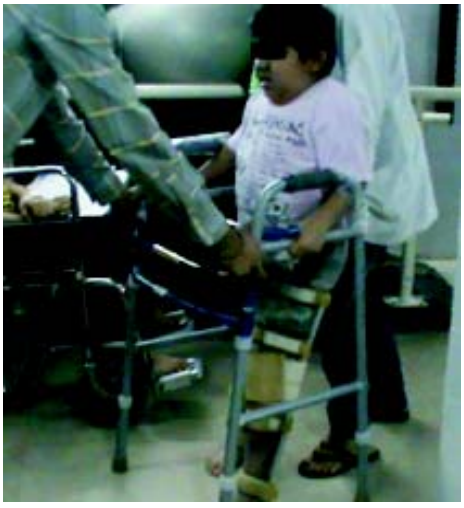
Improved upper limb and trunk strength with ability to perform crawling , and overhead activities with weights.



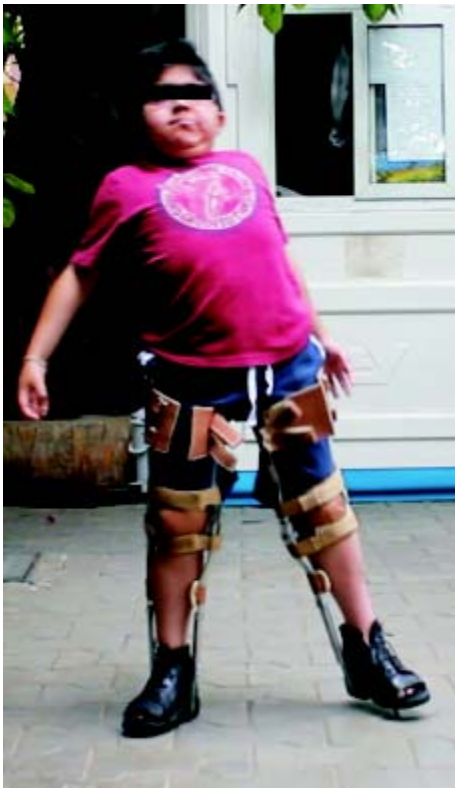


Exercises to strengthen and stretch knee muscles





Standing with bilateral push knee splints and initiation of gait training with the aid of walker



Walking with KAFO inside the parallel bars and gradually walking independently outdoors with no aid.

Case Report - 2

Diagnosis : *Muscular Dystrophy*

18 ½ year old male, a known case of muscular dystrophy since the age of 1 year. It got diagnosed because of family history and increased CPK. He then started developing bilateral lower limb weakness with difficulty in walking and used to walk on toes. He could walk till 15 years of age. Meanwhile upper extremity weakness also developed with difficulty in overhead activities. Neurologically, he was hypotonic and hyporeflexic. He had all sensations intact. He had grade 1 strength in bilateral upper limb and lower limb proximally and grade 3 distally in all 4 limbs. On examination, he had right sided Scoliosis. He was cachexic with poor chest expansion and history of repeated Lower Respiratory Tract Infection. Functionally, he was dependent for ADL and wheelchair bound for mobility. On FIM he scored 63. On Brooke and Vignos scale, he scored 6 and 10 respectively.

On investigation, increased Creatine phoshokinase levels of 1266 IU, Electrophysiological studies revealed primary muscle disease.MRI Musculoskeletal system showed marked fatty infiltration involving muscles of upper arm on both sides with relative sparing of triceps and deltoid muscles. There was generalized marked fatty infilteration of pelvic, thigh and leg muscles.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Quadriceps, Deltoid, Abdominals, Back extensors, Hamstrings, Peronei, Tibialis Anterior, Biceps, Triceps, Brachioradialis.

Clinical Improvements seen After Stem Cell Therapy

Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina. He could sustain exercises for almost 2 hours a day, as opposed to earlier where it was difficult to perform them, for even 15 minutes, due to poor respiratory muscle compliance. His respiratory muscles improved in function with increased lung volume capacity as noted while performing incentive spirometry exercises and also reported by the patient, in evidence of no episode of upper respiratory tract infection / insufficiency post therapy. His trunk and neck musculature increased in strength with ability to hold the neck erect and maintain erect trunk posture. His static sitting balance improved and he could maintain sitting upright independently on the edge of the cot, which was not possible prior to the therapy. Even the caretaker reported that he felt ease in transferring him, as the patient would try and support his body weight because of improving trunk muscles. His upper limb and grip strength also increased. During physiotherapy sessions he was made to stand with bilateral push knee splints on standing board in order to stretch the tight lower limb muscles and improve bone density due to sustain weight bearing. He could initially sustain standing for only 15 minutes with complaints of back pain and knee pain , but gradually he could stand for 60 minutes in a day , without any discomfort.

	Before stem cell therapy	After stem cell therapy
Creatinine Phosphokinase levels	955 IU	460 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		MUSCLES	LEFT	
Before therapy	After therapy	HIP	Before therapy	After therapy
0	1++	Flexors	0	1++
0	1+	Abductors	0	1+
0	1+	Adductors	0	1+
		KNEE		
0	1	Extensors	0	1
		FOOT		
0	1+	Evertors	0	1+
		SHOULDER		
0	1	Flexors	0	1
1	2	Triceps	1	2
0	1+	Biceps	0	1+
		WRIST		
3-	3+	Extensors	3-	3+
1	3	Abductor Pollicis Brevis	1	3
0	1	**ABDOMINALS**	0	1

Radiological Improvements

On repeat MRI of the Musculoskeletal System at the end of 3 months, and comparison of two scans, following changes were documented:

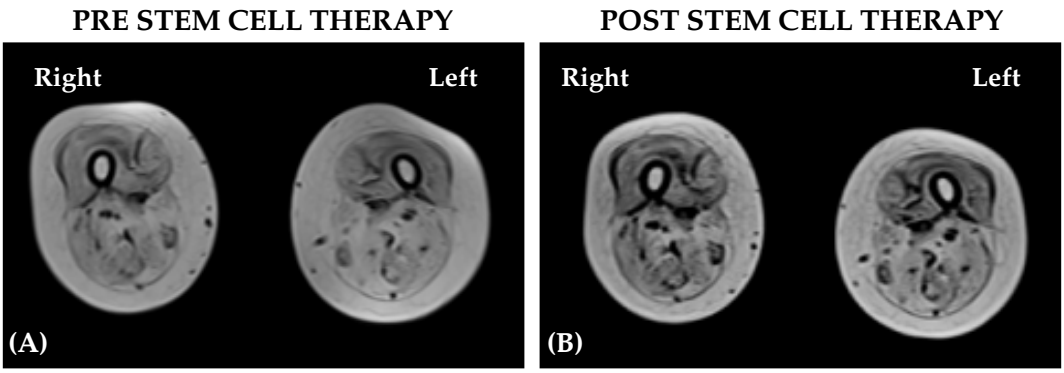
(MRI dated 3/5/2010 and 31/8/2010)

Improvement in the degree of fatty infiltration with minimal possible muscle regeneration is noted in the vastus medialis, vastus lateralis and semi tendinosus muscle in the thigh.

Similar improvement is also noted in the tibialis anterior, medial and lateral head of gastrocnemius muscle in the leg.

In the arm, improvement is noted in the long and lateral head of triceps muscle and biceps brachii muscle.

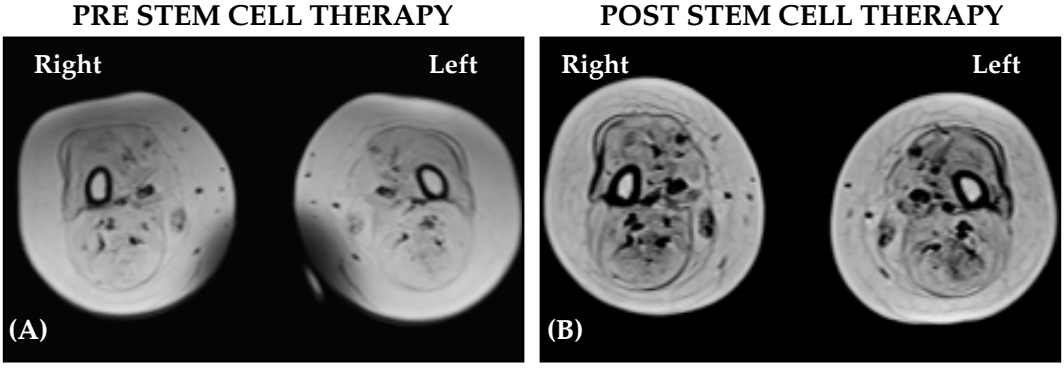
Thus, MRI showed regeneration in the muscles that were injected with stem cells intramuscularly.



Axial T1W images at the level of upper thigh

(A) Pre-stem cell therapy show marked fatty infiltration of the right vastus medials (thick arrow) and lateralis muscle (thin arrow), seen as high signal intensity.

(B) Post-stem cell therapy shows reduced high signal in both the vastus medialis (thick arrow) and lateralis (thin arrow) suggestive of less fatty infiltration and regeneration of muscle fibres

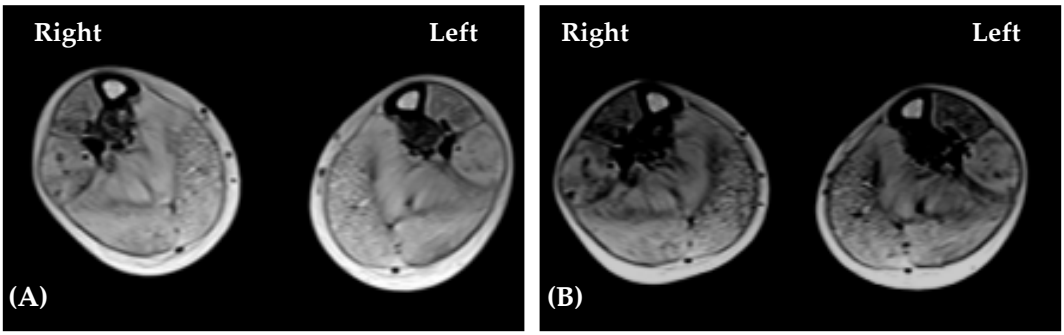


Axial T1W images at the level of upper thigh

(A) Pre-stem cell therapy show marked fatty infiltration of the left semitendinosus (thin arrow) seen as high signal intensity.

(B) Post-stem cell therapy shows reduced high signal in the left semitendinosus (thin arrow) suggestive of less fatty infiltration and regeneration of muscle fibres.

PRE STEM CELL THERAPY **POST STEM CELL THERAPY**

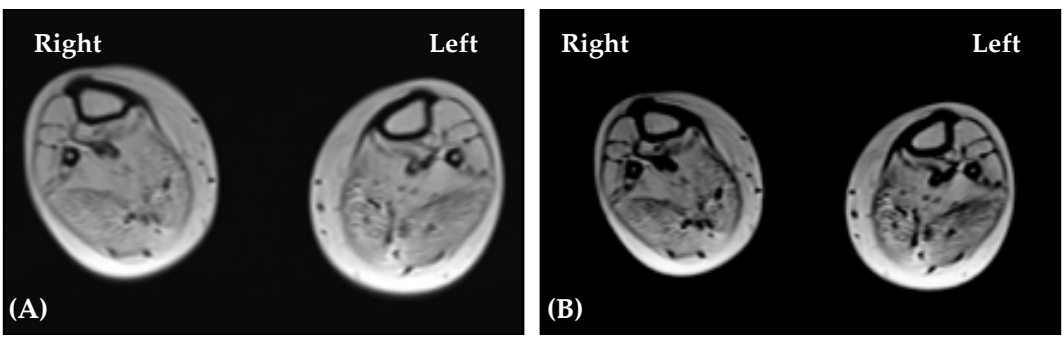


Axial T1W images at the level of the calf

(A) Pre-stem cell therapy show marked fatty infiltration of the bilateral tibialis anterior muscle (thin arrows) seen as high signal intensity.

(B) Post-stem cell therapy shows reduced high signal in bilateral tibialis anterior muscle (thin arrows) suggestive of less fatty infiltration and regeneration of muscle fibres.

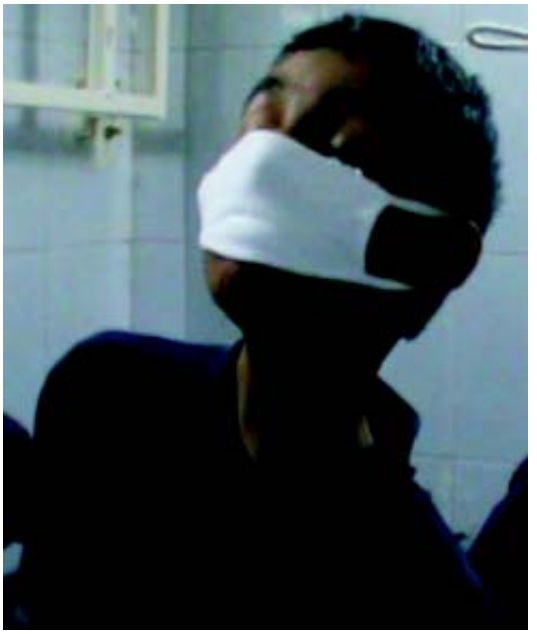
PRE STEM CELL THERAPY **POST STEM CELL THERAPY**

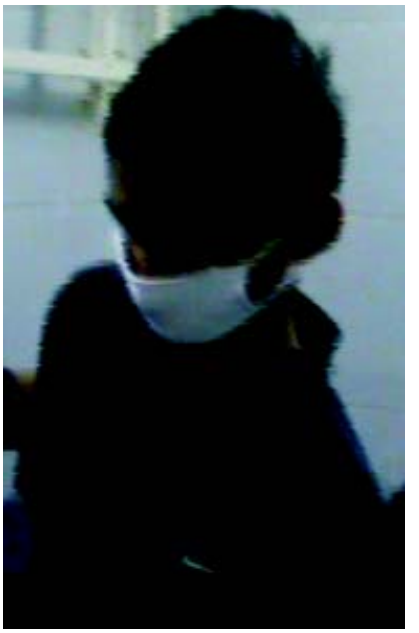


Axial T1W images at the level of the calf

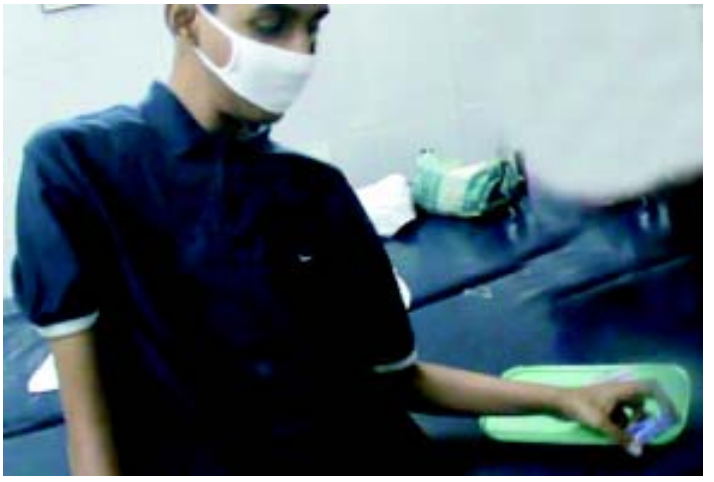
(A) Pre-stem cell therapy show marked fatty infiltration of the left medial (thick arrow)and lateral gastrocnemius muscles (thin arrow)) seen as high signal intensity.

(B) Post-stem cell therapy shows reduced high signal in left medial (thick arrow) and lateral gastrocnemius muscles (thin arrow)suggestive of less fatty infiltration and regeneration of muscle fibres.





Improved neck muscle strength with ability to perform voluntary neck muscle exercises.



Improved grip strength and ability to perform gripping exercises.

Standing on the standing board with bilateral push knee splints

Case Report - 3

Diagnosis: *Limb Girdle Muscular Dystrophy*

A 36 year old businessman gave history of weakness in lower limbs, which started 12 years back. As weakness progressed, he found it difficult to negotiate stairs and get up from squatting position or low seats. Recent progression included difficulty in overhead activities since a year with early fatiguability.

On assessment, he was hypotonic and hyporeflexic with all sensations intact. He had grade 3+ strength in bilateral lower limbs and grade 4 strength in bilateral upper limb with predominantly proximal muscle weakness. He had a Lordotic Tredelenberg Gait with abdominal muscle weakness. Functionally, he was independent in most of his activities of daily living. He had difficulty in climbing stairs and getting up from floor. On FIM he scored 123.

On investigations, the serum creatine phosphokinase levels were raised to 2178 IU. Electromyography studies were suggestive of primary muscle disease, while the muscle biopsy confirmed the diagnosis of muscular dystrophy. MRI of the upper and lower limbs before the stem cell therapy revealed atrophy of muscles in both shoulders, thighs and legs.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally : Rectus Abdominis, Quadriceps, Gastrosoleus and Deltoid.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina. He also reported no fatigue or exhaustion in doing activities. His lower limb and trunk strength had increased with improved gait. Earlier, he used to walk with a hyperlordotic, wide based gait, and would have frequent falls (3-4 times a day).But after the therapy, his stamina, stability and balance while walking improved significantly. He reported significant reduction in frequency of falls while walking (2 times in 4 months), also he reported improved grip of feet on slippery surface while walking. He reported ease and independence in getting up from lower surfaces like commode and sofa , where in earlier he would need a lot of manual assistance to do the same. He also reported improved upper limb strength and ease in performing overhead activities. His trunk strength also increased leading to ease in mat activities like getting up from floor, bridging, coming on all fours, crawling, and kneeling.

	Before stem cell therapy	After stem cell therapy
Creatinine Phosphokinase levels	2178 IU	1222 IU
Functional Independence Measure	123	124

Manual Muscle testing : Following muscles showed improved strength

RIGHT		MUSCLES	LEFT	
Before therapy	After therapy	HIP	Before therapy	After therapy
2+	3+	Internal Rotators	2+	3+
		FOOT		
3	4++	Tibialis Anterior	3	4++

Electrophysiologically: EMG of the right vastus medialis and right tibialis anterior showed myopathic potentials, suggestive of evidence of primary muscle disease. On repeat EMG at the end of 6 months, right tibilais anterior muscle showed improvement in terms of normal voluntary activity with complete Interference pattern and recruitment.

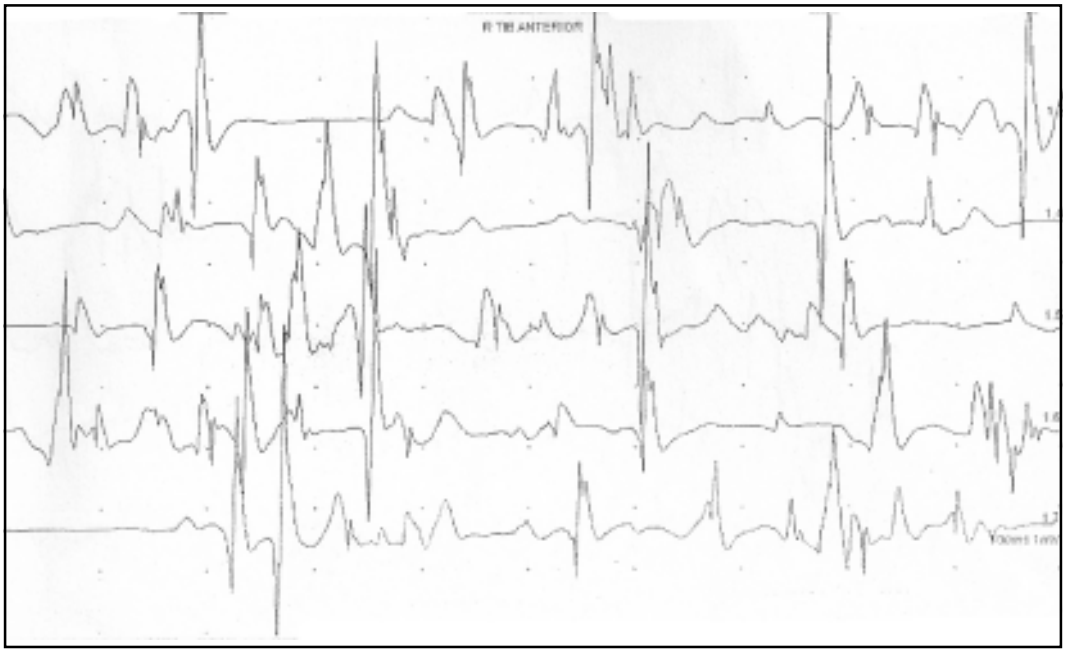
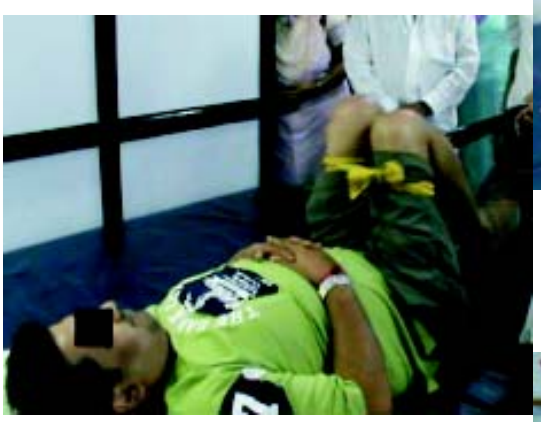


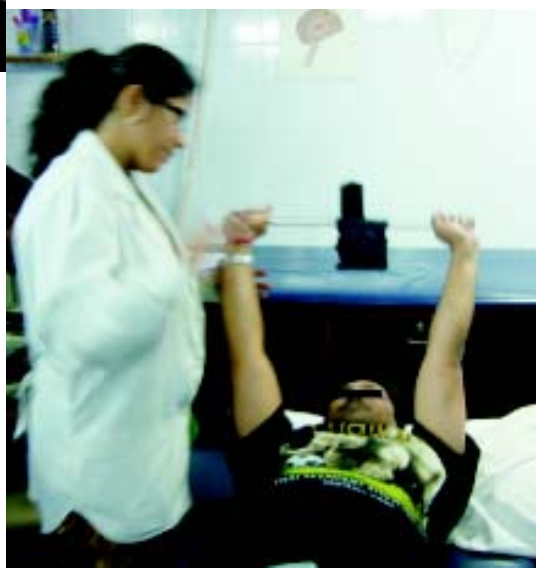
Fig 1: Post therapy EMG of Right Tibialis Anterior Muscle showing normal voluntary muscle activity with complete interference pattern and recruitment.

Improved trunk strength and ability to do bridging.

Improved Trunk Stability and ability to perform All fours and Hip extension.



Improved lower abdomen strength and ability to perform resisted exercises.



Improved upper limb strength and ability to lift weights and perform exercises.

Case Report - 4

Diagnosis : *Muscular Dystrophy*

A 9 year old male, born of non-consanguineous marriage, presented with history of delayed physical milestones. There was difficulty in walking with frequent falls since early childhood and climbing stairs. His speech had been unclear and the overall weakness had been progressive. He was also diagnosed with Attention Deficit Hyperactivity Disorder.

On examination, he had bilateral calf hypertrophy, with exaggerated lumbar lordosis. Gowers' sign was positive. He also had proximal muscle weakness in upper and lower limbs and walked on his toes.

On investigation, his creatine phosphokinase levels were 5600 IU and the electrophysiological studies showed primary muscle disease. The muscle biopsy revealed myopathic changes in the muscle, confirming the diagnosis of muscular dystrophy. No gene deletion was seen for DMD/BMD

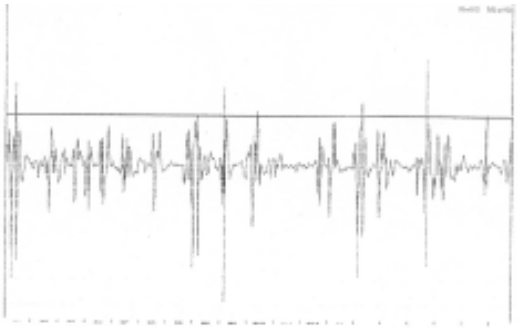
Clinical Improvements seen After Stem Cell transplantation:

Functionally : He reported feeling of wellbeing and improved stamina. His frequency of falls had reduced significantly. His gait had improved ,earlier he used to walk with wide based lordotic equinnus gait , but after 6 months post therapy, he started walking with feet touching the floor completely and improved stability with narrow base of support. His trunk strength had improved, with ease in getting up from lying position and sitting up on bed. While exercising he was able to crawl on the bed, during mat exercises. He could perform pedaling while cycling because of improved quadriceps strength.

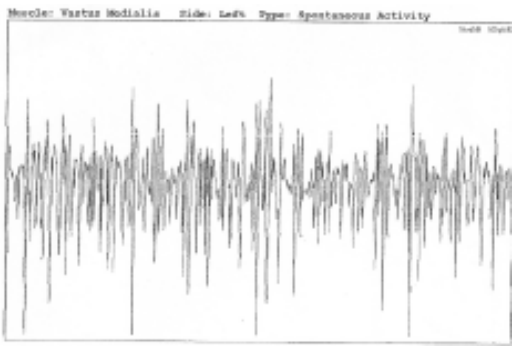
On Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
3	3++	Flexors	3	3++
3-	3++	Abductors	3-	3++
		KNEE		
2	3	Extensors	2	3
2	3	**ABDOMINALS**		

Electrophysiologically : The EMG of Deltoid, Tibialis Anterior, Vastus Medialis, Gastrosoleus muscles showed intrinsic muscle disease but on repeating their EMG after 18 months Vastus Medialis and Gastronemius muscle showed Normal Motor unit potentials with complete interference pattern.



Pre operative EMG showing reduced interference pattern in Vastus Medialis Muscle, with myopathic potentials.



Post operative EMG showed complete interference pattern in Vastus Medialis Muscle with normal motor unit potentials.

Improved crawling ability due to increased quadriceps and hip extensor strength.

Improved gait with feet touching the floor and narrow base of support.

Case Report - 5

Diagnosis : *Muscular Dystrophy*

A 30 year old basketball coach gave history of feeling of heaviness in calf and thigh muscles since 2000. Later, he started encountering difficulty in getting up from low seat as well as walking over rough, uneven surfaces leading to loss of balance while walking. Ability to do overhead activities was also hampered. Overall, stamina was low leading to easy fatiguability while carrying out his official duties.

On assessment, he had grade 3 strength in bilateral lower limbs and grade 3++ in bilateral upper limbs with predominantly proximal muscle weakness more than distal muscles. On examination, he showed pseudohypertrophy of bilateral calf muscles and deltoid. Functionally, he was totally independent in all his activities of daily living. But, he found it difficult to get up from floor and low seat. He walked with a lordotic gait. On FIM he scored 116.

On investigations, the serum creatine phosphokinase levels were raised(6570 IU/ml) Electromyography studies were suggestive of primary muscle disease. MRI of the musculoskeletal system revealed moderate to extensive fatty infiltration in the pelvic girdle and thigh muscles with mild fatty infiltration in the legs, arm and forearm muscles bilaterally.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally : Glutei, Abdominal muscles and Quadriceps.

Clinical Improvements seen After Stem Cell Therapy

Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina, as effort required to perform the activities of daily living was reduced significantly. His profession being a basket ball coach, he is expected to be on the ground for long hours, which was not possible because of the weakness in limbs and fatigue. But after the therapy he was able to sustain standing and coaching for almost 10 hours on the ground, without complaints of exhaustion and weakness. Earlier, he had features of frequent calf muscle cramps, which had resolved completely after the therapy. He reported improved lower limb and trunk strength, with ease in getting up from squatting position and also improved stability while standing and walking. With improved trunk stability his unilateral stance improved, with ease in staircase climbing. His upper limb strength also increased with ease in overhead activities like bathing (especially shampooing his hair) and ability to lift 5-6 kgs of weight, which was not possible before the therapy. He also showed toning of muscles , with improvement in his posture , as it became more erect and upright. Secondary to improvement in his standing tolerance and balance with improved posture, he was able to continue with his chosen and loved vocation, which was being a basketball coach. This had improved his self esteem and self confidence. Also, the financial gains from his work had improved his self pride and stabilized his family financially as he is the sole bread earner. Thus, it all indeed improved his and his family's quality of life.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	1731 IU	846 IU

Manual Muscle testing : Following muscles showed improved strength .

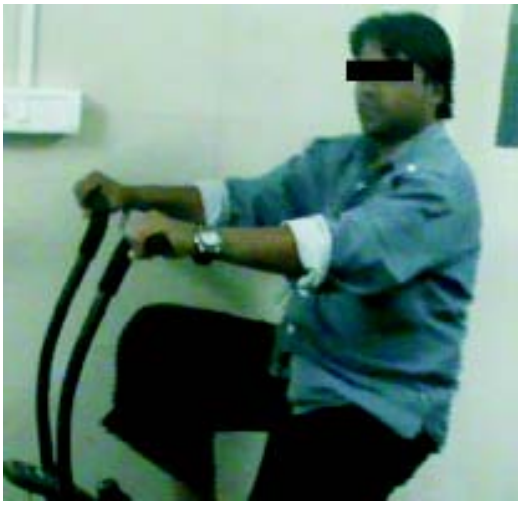
RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
3	3++	Extensors	3	3++
3+	4	Abductors	3+	4
		SHOULDER		
3	3++	Extensors	3	3++
3	3++	Abductors	3	3++
		ELBOW		
3	3++	Triceps	3	3++
3	3++	**ABDOMINALS**		

Electrophysiologically: Motor and Sensory Nerve Study including F wave latency was normal in the nerves tested. Needle EMG showed evidence of active denervation (Fibrillation/positive waves) in Right Gastrocnemius, Right Rectus Femoris, Right FDI with infrequent short duration, small amplitude MUP suggestive of myopathic process. On comparison 6 months after the therapy, repeat EMG of the muscles showed improvement in the MUP amplitudes in all the muscles sampled which were in the range of 500-1500 Uv.

Ability to perform one leg standing, due to improved trunk strength and standing tolerance.

Improved lower limb strength and ability to perform staircase climbing with minimum assistance by the railing.

: Improved trunk control and ability to perform all fours and crawling on bed.



Improved stamina and ability to perform cycling

Case Report - 6

Diagnosis : *Muscular Dystrophy*

A case of a 35 year old male patient, who gave history of pain and cramps in bilateral calf muscles while walking 10 years back. He also had flat foot. With gradual increase in weakness of lower limbs, climbing stairs and getting up from floor became difficult. Thereafter, over 2-3 years, weakness and wasting of bilateral upper limbs and face muscles was also experienced. In 2008, he had history of twisting both ankles while walking leading to fracture of the left ankle. Since then he stopped walking and was wheelchair bound for mobility.

Neurologically, he was hypotonic and hyporeflexic with all sensations intact. He had muscle power of grade 2 in bilateral lower limbs and grade 4 in bilateral upper limb muscles. On examination, he had bilateral equino varus deformity with severe tightness of TA along with pseudohypertrophy of calf muscles. He also complained of increased urgency and frequency of urination. Functionally, he was independent in all his activities of daily living. On FIM he scored 115.

On investigation, the serum creatine phosphokinase level were mildly raised. Electromyography studies were suggestive of primary muscle disease, while the muscle biopsy confirmed the diagnosis of muscular dystrophy.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally Quadriceps, Tibialis Anterior, Peronei, Adductors of hip, Glutei, Triceps, Biceps, Deltoid and Abdominals.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina, as effort required to perform the activities of daily living was reduced significantly. He started to stand with Knee ankle Foot Orthosis (KAFO) and adaptation in the shoe to accommodate the equinnus deformity. Initially, he stood with KAFO, holding the walker and gradually after about 4 months, started to take a few steps with minimal support and lordotic posture. Later, as the muscle strength of his limbs and trunk increased, he could walk independently indoors with KAFO and walker. At the end of 5 months, he started to walk with KAFO and elbow crutches, under supervision of a therapist and could manage to take 15 to 25 steps.

It was observed that the ongoing deterioration in his physical condition had halted completely with an improvement in the muscle power. He reported improvement in his upper extremities and ability to perform overhead activities. Earlier, he had urge incontinence with complaints of increased frequency of urination, but after the therapy, within 3 months, he reported improved bladder control.

	Before stem cell therapy	**After stem cell therapy**
Functional Independence Measure	115	116

Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
2	2++	Extensors	2	2++
3	3+	Abductors	3	3+
2	2++	Adductors	2	2++
		KNEE		
1+	2+	Flexors	1+	2+
3	3++	Extensors	3	3++
		ANKLE		
3	3++	Peronei	3	3++
		SHOULDER		
2+	3+	Extensors	2+	3+
2+	3+	Flexors	2+	3+
2-	2+	Adductors	2-	2+
		ELBOW		
2+	3	Triceps	3	3++
2	3-	**ABDOMINALS**		

Improved trunk and upper extremity strength with ability to stand with KAFO, walker and shoes accommodating the equinus deformity.

Improved standing tolerance, so patient progressed from walker and was taught elbow crutch gait training

Ability to walk with KAFO and minimum assistance.

Improved pinch strength and ability to clip .

Case Report - 7

Diagnosis : *Muscular Dystrophy*

A 23 year old female patient gave a history of bilateral lower limb weakness, difficulty in walking, climbing stairs and getting up from floor since 10 years. Since past 2 years, she had also started developing upper extremity weakness with difficulty in overhead activities. On investigations, the serum creatinine phosphokinase level was raised. Electromyography studies were suggestive of a myopathic process, while the muscle biopsy confirmed the diagnosis of muscular dystrophy. The molecular genetic analysis for mitochondrial mutation was found to be negative. MRI of the upper and lower limbs before the stem cell therapy revealed mild to moderate fatty infiltration of the pelvic girdle muscles and bilateral thigh muscles. Moderate to extensive fatty infiltration was noted in the leg muscles while minimal fatty infiltration was noted in the bilateral arm and forearm.

Neurologically, she was hyporeflexic and hypotonic with intact sensation. She had grade 3+ strength in bilateral upper and lower limbs with proximal muscle weakness more than the distal muscle (distal muscle strength - grade 4). On examination, she had scoliosis of thoracolumbar region. Functionally, she was independent in all activities of daily living, but had difficulty in getting up from floor and climbing stairs along with easy fatiguability. On FIM she scored 110.

On investigations, Electromyography studies and nerve conduction velocity studies were suggestive of a myopathic disorder affecting LL more than UL. Low amplitude CMAPS were seen in bilateral common peroneal nerve due to wasting of external digitorum brevis muscles. Muscle biopsy was suggestive of muscular dystrophy.2D ECHO revealed LVEF of 60%, but electrocardiogram indicated a diffuse ST elevation with an early precordial R/S transition and a normal sinus rhythm. MRI of the musculoskeletal system reveals mild fatty infiltration of the pelvic girdle , the leg, arm and forearm muscles.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally Deltoid,abdominals,quadriceps and glutei.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, she reported feeling of wellbeing and improved stamina, as effort required to perform the activities of daily living was reduced significantly. As strength in her limbs increased, she was able to comb her hair easily and have hair bath independently, without getting fatigue. She was also able to lift heavy objects (approximately 2 kgs) with her upper limbs, which she could not do before. Her lower limb strength also improved, with significant reduction in frequency of falls while walking. She could get up from lower level surface with ease, where in earlier she would need assistance and support from others to lift her. She also reported

more stability while walking and standing, as compared to before as her trunk muscles had improved in strength. Her immunity also improved, as she stopped suffering from frequent episodes of cold, which she always had before the therapy. Also the nasality in her speech reduced, with improved clarity in the speech .She had started to participate in dance thrice a week, one hour each ,as a part of her exercise program ,due to improved strength and stamina in her muscles.

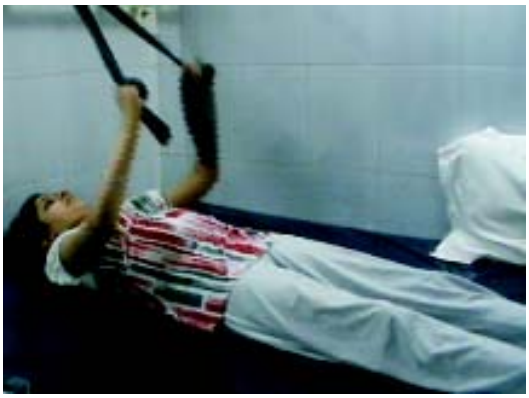
Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
3	3++	Extensors	3	3++
3	3++	Flexors	3	3++
3	3++	Abductors	3	3++
3	3++	Adductors	3	3++
		KNEE		
3	3++	Flexors	3	3++
		ANKLE		
3	3++	Dorsiflexors	3	3++
		SHOULDER		
3	3++	Extensors	3	3++
3	3++	Flexors	3	3++
3	3++	Abductors	3	3++
3	3++	Adductors	3	3++
1+	2+	**ABDOMINALS**		

Electrophysiologically : The EMG of Deltoid, Biceps, Triceps, Glutei, Hamstrings, Quadriceps muscle showed myopathic potentials. On repeating the EMG after 6 months, it showed normal insertional and spontaneous activity with normal motor unit potential duration in Deltoid, Glutei, Hamstrings and Biceps. Thus, findings were indicative of improvement in motor unit potential amplitude duration and voluntary effort.

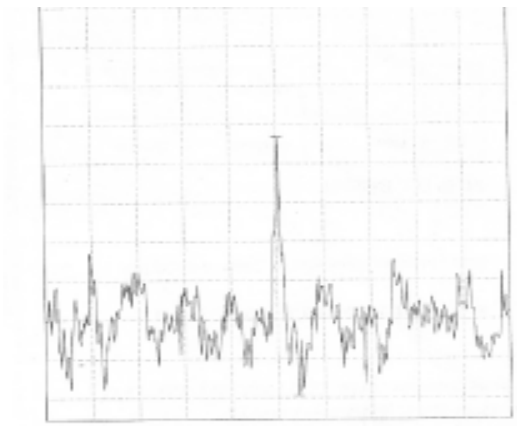
Improved Trunk and lower limb strength, with ability to come on all fours and perform unilateral hip extension

Improved back extensor strength and triceps, with ability to perform push ups.

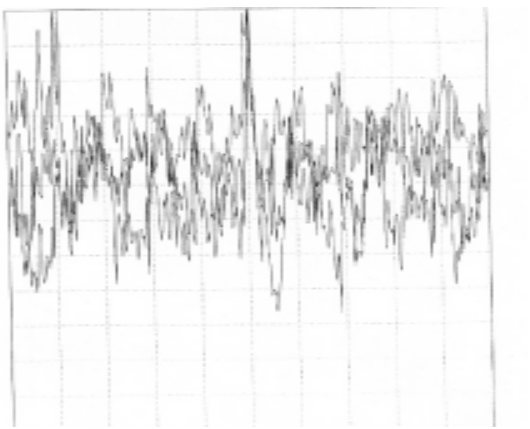


Improved Shoulder extensor strength, thus showing ability to perform resisted upper limb extension movements.

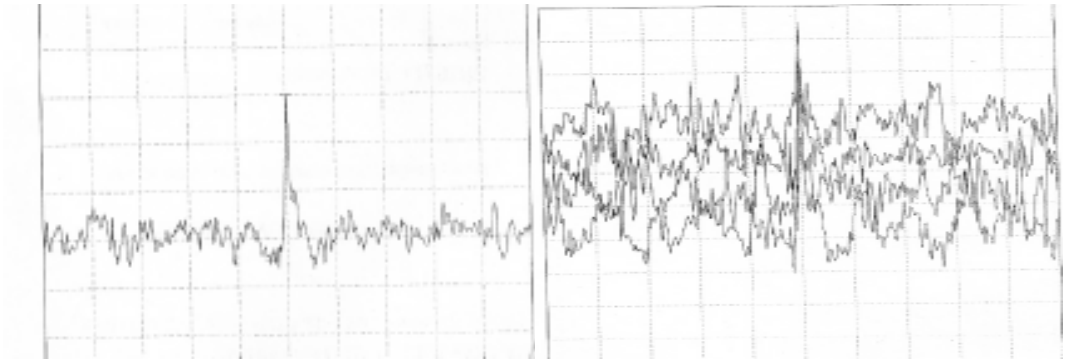
Improved ability to perform side sitting and shifting on the bed.



Pre op EMG Showing reduced interference pattern in Left Deltoid Muscle, with myopathic potentials.



Post op EMG showed complete interference pattern in Deltoid Muscle with normal motor unit potential amplitude duration and voluntary effort.



Pre op EMG Showing reduced interference pattern in Left Glutei Muscle, with myopathic potentials.

Post op EMG showed complete interference pattern in Glutei Muscle with normal motor unit potential amplitude duration and voluntary effort.

Case Report - 8

Diagnosis : *Duchenne's Muscular Dystrophy*

A 7 year old boy presented a history of frequent falls in school and lower extremity weakness. He also had difficulty in climbing stairs and running. So, he got investigated and was diagnosed with DMD.

Neurologically, he was hypotonic and hyporeflexic with all his sensations intact. He had grade 3 muscle power in bilateral lower extremities and grade 3++ in bilateral upper extremities with proximal muscle weakness more than distal. He had pseudohypertrophy of bilateral calf muscles and also showed Gower's maneuver. He walked with a Lordotic wide based gait. Functionally, he was independent in most activities of daily living. On Brooke Scale he scored 1 and on Vignos 2.

On investigation, creatine phosphokinase levels were raised to 8050 IU. Genetic test revealed deletions in exons 46-52 which indicated out-frame mutations confirming DMD. Electromyography studies suggested generalized primary muscle disease. MRI Musculoskeletal showed symmetric atrophy and fatty replacement involving the proximal muscles of both thighs especially the gluteus maximus and the aductor magnus which was consistent with early muscular dystrophy.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Deltoid, Biceps, Triceps, Glutei, Quadriceps, Adductors Tibialis Anterior, Peronei and Abdominals and Back Extensors.

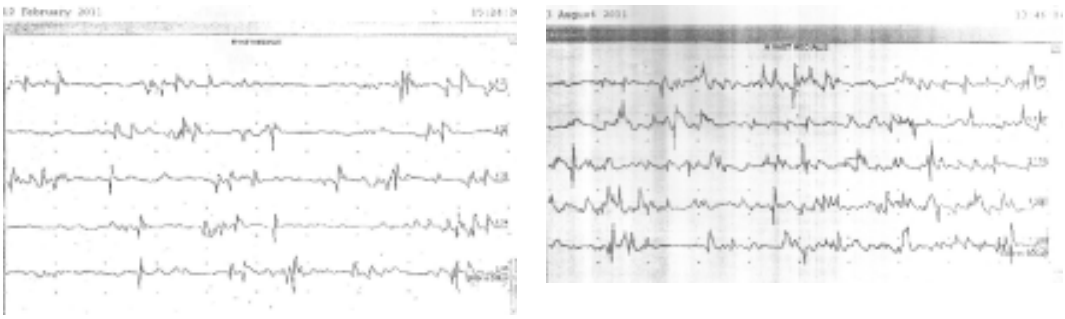
Clinical Improvements seen After Stem Cell Therapy

Functionally : At the end of 3 months, he reported feeling of wellbeing and improved stamina. He could sustain and perform exercises for longer sessions as opposed to earlier when he would feel lethargic and lazy the entire day. He was able to perform mat exercises like kneeling, bridging, quadruped exercises with ease. He was able to perform swimming almost 4-5 laps at a time, which he could not do before therapy. Even the principal and teachers at school reported that he had been more energetic and attentive in school post therapy. His lower limb and trunk strength had increased with ability to bend and pick up objects from floor and tie his shoe lace, which needed assistance before. His ability to squat and get up from floor had also got near normal, which otherwise needed assistance by the mother. His gait had improved in terms of narrowed base of support and plantigrade feet .Earlier he would walk with equinnus wide based gait. His frequency of falls while walking also reduced significantly. Earlier he would fall 4-5 times a day, but post therapy it reduced to almost 2 times a month. He was able to climb stairs independently, where in otherwise he would need aid by the railing. His upper limb and grip strength also increased with improved ability to write, and perform daily activities like bathing, dressing, grooming independently, all of which needed assistance prior to therapy. Over all his confidence and stamina had increased tremendously, because of increased strength in musculature.

	Before stem cell therapy	After stem cell therapy
Creatinine Phosphokinase levels	8050 IU	7666 IU

Electromyography Improvements:

EMG done prior to stem cell therapy showed Generalized Primary Muscle Disease affecting the upper and lower limbs (proximal + semi distal muscles), with severely reduced interference and recruitment pattern in Gastrocnemius and Hamstring muscles. On repeating the EMG of same muscles, EMG of the same muscles showed improved interference pattern in them. The voluntary activity in them also showed normal and areas of small amplitude and short duration motor unit potentials.

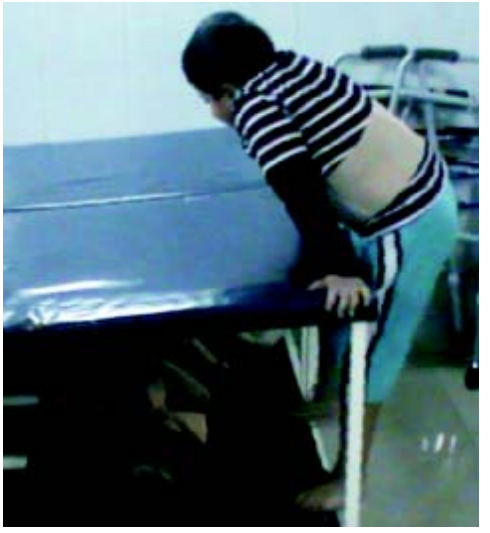


Comparison between pre and post EMG showing increased interference pattern in the muscles.

Improved lower limb and trunk strength with ability to climb stairs independently.

Ability to walk with feet touching the floor and narrow base of support.

Improved trunk strength and ability to get up from floor independently.



Ability to get on the cot independently.

Case Report - 9

Diagnosis : *Muscular Dystrophy*

A 40 year old female patient gave history of bilateral lower extremities weakness with complaints of frequent falls while walking and difficulty in climbing stairs since 2005. Gradually weakness progressed with inability to get up from a low level surface.

Neurologically, she was hypotonic and hyporeflexic. All her sensations were intact. On examination, she had grade 2+ muscle power in bilateral lower extremities proximally and grade 3++ distally in lower extremities and upper extremities(proximal >> distal). She reports no family history of the same. Functionally, she was independent in most ADL. She walked with a wide base of support but couldn't climb stairs and had difficulty in getting up from floor. On FIM she scored 113.

On investigations,the serum creatine phosphokinase levels were raised. Electromyography studies were suggestive of primary muscle disease. MRI of the upper and lower limbs before the stem cell therapy revealed severe atrophy with fatty infiltration of the hamstring muscles,moderate atrophy of the gluteal and adductor magnus muscles with focal areas of mild atrophy and fatty infiltration in biceps and triceps .

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Quadriceps, Gastrosoleus, Deltoid and Abdominals.

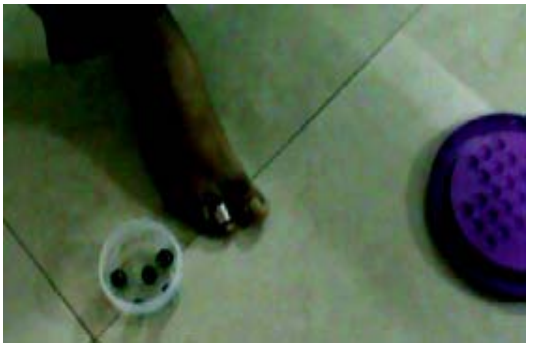
Clinical Improvements seen After Stem Cell Therapy.

Functionally: On follow up, at the end of 3 months, she reported feeling of wellbeing and improved stamina. Her lower limb and trunk strength had increased with improved gait. She reported improved stability and balance while walking as compared to prior therapy. Also transfer activities like getting up from low level surfaces, which earlier needed assistance , got independent post therapy.

	Before stem cell therapy	After stem cell therapy
Creatinine Phosphokinase levels	4909 IU	2937 IU

Increased trunk strength and ability to perform corner shifting

Increased trunk strength and ability to sit up , on the egde of the bed from lying position independently



Increased intrinsic foot muscle strength and ability to pick up marbles .

Increased trunk strength and ability to perform crawling

Ability to perform kneeling and kneel walking

Case Report - 10

Diagnosis : *Muscular Dystrophy*

A 64 year old female, with history of slowly progressing muscle weakness since 1986, reported difficulty in lifting her child and doing overhead activities. Later, weakness progressed to both lower limbs with episodes of frequent falls. In 2009, she suffered a left fracture neck femur and was operated for the same with steel plate fixation. Following another fall in 2009, she stopped walking completely. She was completely wheelchair bound thereafter. Gradually, she also developed facial muscle weakness leading to difficulty in closing the mouth fully, leading to mouth breathing and extremely poor exercise tolerance.

Neurologically, she was hypotonic and hyporeflexic with an intact sensory system. She had grade 2++ strength in bilateral lower limbs and grade 3 in bilateral upper limbs with predominantly proximal muscle weakness. On examination, she was osteoporotic with severe wasting of bilateral upper and lower limb muscles. Functionally, she was dependent on the caregiver for all activities of daily living and was wheelchair bound for mobility. On FIM she scored 53.

On investigations,electromyography studies were suggestive of generalised primary muscle disease, while the muscle biopsy confirmed the diagnosis of muscular dystrophy.MRI of the upper and lower limbs revealed extensive fatty infiltration in the muscles of the pelvic girdle,thighs and legs bilaterally. Forearm and muscles showed moderate fatty infiltration.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally Orbicularis oris, Rhizorius, Deltoid, Biceps, Triceps, Brachioradialis, Adductors, Trapezius, Rhomboids, Tibialis Anterior, Peronei, EDL, Abdominals and Back Extensors.

Clinical Improvements seen After Stem Cell Therapy

Functionally: At the end of 3 months, she reported feeling of wellbeing and improved stamina, as effort required to perform the activities of daily living had reduced significantly. Her exercise tolerance had increased. She also reported improved self confidence and contentment, as her insomnia had reduced and she could sleep peacefully for about 7 hours without any medications, which she could not do earlier. Her upper limb and grip strength had increased bilaterally with ability to extend her fingers. She was able to use her fingers functionally for daily activities like feeding herself by breaking chapattis into pieces, for which earlier, she required assistance. She was able to lift up a 100 ml bottle to drink water by herself. Her bed mobility also improved, in terms of getting up independently from bed to sitting position, wherein earlier she had to be lifted up by the maid. During exercise sessions she was made to stand on standing board, which she could sustain for 1 hour thereby, leading to improved bone density and toning of muscles.

She had weak facial muscles and could not close her lips completely thereby leading to unclear speech. But, after stem cell therapy her facial musculature improved with ability to close her lips and improved clarity of speech.

Six months post therapy, exercise sessions progressed and she was made to stand with one push knee splint and walker, as her trunk strength had improved and could sustain standing with a walker. Initially, she was taught to take a few steps and within a month, she could walk with the walker. Gradually, even the walker was weaned off and she could manage to walk without any assistive device. She could independently perform day to day activities like brushing, bathing, dressing, walking up to the washroom and toilet activities. Her ability to walk improved her participation in household help like cooking, all of which was earlier impossible for her. She was able to stand (slightly resting against the kitchen platform) and cut vegetables, roll chapattis and roast it on the griddle, she could also cook vegetables, etc as she could stand for 45 minutes to one hour at a stretch in the kitchen. She started preparing meals for the entire family and was able to independently clean the kitchen.

She even started pursuing her leisure activities like stitching, hemming and embroidery. Her Quality of Life improved significantly, with productive participation in the family.

	Before stem cell therapy	**After stem cell therapy**
Functional Independence Measure	53	61

Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
2	3	Flexors	2	3
2	2++	Abductors	2	2++
		KNEE		
3	3++	Extensors	3	3++
		ANKLE		
3	3++	Dorsiflexors	3	3++
		SHOULDER		
1	1++	Extensors	1	1++
2-	2++	Flexors	2-	2++
		WRIST		
2	3+	Interossei	2	3+
2	3+	Lumbrical	2	3+
1+	2+	**ABDOMINALS**		

Initiation of standing, with the help of standing board.

Progression to standing with the assistance of the walker.

Ability to walk independently indoors, with assistance of the walker.

Ability to perform cooking, mainly making chapattis in the kitchen, while standing independently with no assistive device.

Improved upper limb strength and ability to speak on phone with lips closed and clear speech.

Improved pinch strength and ability to put clips on the clothes to dry them, while performing house hold activities.

Case Report - 11

Diagnosis: *Duchenne Muscular Dystrophy*

An 8 ½ year old male, diagnosed case of DMD since 5 years of age had history of lower limb weakness with complaints of difficulty in climbing stairs and frequent falls while walking. Gradually weakness had been progressive with complaints of early fatigue and difficulty in getting up from the floor. Neurologically, he was hypotonic and hyporeflexic. He had grade 2+ strength in bilateral lower limb and grade 3+ in bilateral upper limb with predominant proximal muscle weakness. On examination, he had pseudohypertrophy of bilateral calf and deltoid muscles. Functionally, he needed assistance in few activities of daily living. He walked with a Lordotic Equinnus Gait. On FIM he scored 96.

On investigation, the serum creatine phosphokinase levels were raised to 4689 IU and EMG report shows evidence of myopathic process. Genetic analysis showed deletions in exons 8-13, 17 and 19 which indicated out frame mutations consistent with DMD. MRI of the musculoskeletal system showed moderate to extensive fatty infiltration in the pelvic girdle muscles and bilateral thighs while mild infiltration in the leg muscles. The medial and long head of triceps muscle showed mild fatty infiltration with rest of the muscles of the arm, forearm and supinator well maintained.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei and Rectus abdominis

Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he required significantly less assistance to perform the day to day activities. Strength of his limb and trunk muscles also increased. He could transfer himself from bed to stool, have bath by himself and was able to dress up independently, earlier he was dependent on the mother for the same. He also improved in his overhead activities like throwing and catching up of the ball. His exercise tolerance had improved and he could sustain exercise sessions for 3-4 hours a day. He could climb the stairs without any support and with alternate feet on each step at a time which was not possible before the therapy.

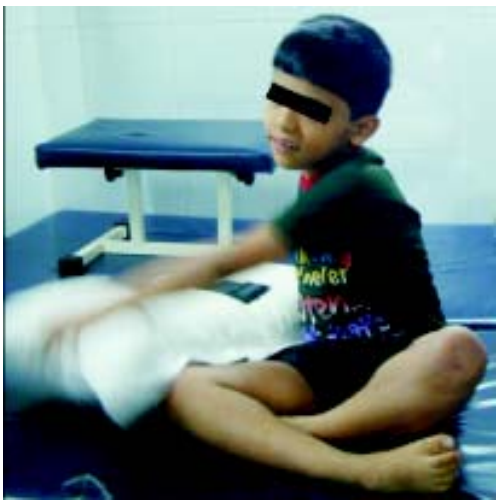
	Before stem cell therapy	After stem cell therapy
Functional Independence Measure	96	108
Creatinine Phosphokinase levels	4689 IU	4236 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		MUSCLES	LEFT	
Before therapy	After therapy	**KNEE**	Before therapy	After therapy
2++	3++	Extensors	2++	3++
		SHOULDER		
2+	3++	Extensors	2+	3++
3	3++	Abductors	3	3++
		ELBOW		
3	3+	Triceps	3	3+
1	2++	**ABDOMINALS**		

Improved ability to climb up the stairs, with one foot on the floor at a time.

Improved upper limb strength and ability to perform resistive theraband exercises.



Improved upper limb strength and ability to perform rotation activities with lifting up weights in hands.

Case Report - 12

Diagnosis : Duchenne Muscular Dystrophy

A 10 year old male, complained of bilateral lower limb pain and cramps since 2-3 years of age. He also had increased frequency of falls while walking. He then developed Equinnus Gait. He stopped walking since last 6 months, could walk till December 2009 and could pedal a cycle and go to school. He gradually started developing upper extremity weakness with difficulty in overhead activities since last 1 year.

Neurologically, he was hypotonic and hyporeflexic. He had 3- strength in bilateral upper limb and grade 2 strength in bilateral lower limb with predominant proximal muscle weakness. On examination, he showed pseudohypertrophy of calf muscles. Functionally, he needed assistance for all his activities of daily living. On FIM he scored 67. On Brooke and Vignos scale he scored 2 and 9 respectively.

On investigation, the serum creatine phosphokinase levels were raised to 5050 IU Electromyography studies revealed primary muscle disease. Muscle biopsy also confirmed the diagnosis of muscular dystrophy. Genetic testing did not reveal any deletions in any of the 79 exons of dystrophin gene. MRI of upper and lower limbs showed moderate to extensive fatty infiltration of the pelvic girdle muscles, moderate fatty infiltration in bilateral thighs, mild to moderate fatty infiltration in leg muscles and bilateral arm muscles. The muscles of the flexor and extensor compartments of the forearm were well maintained.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Quadriceps, Abdominals, Back Extensors, Biceps, Deltoid.

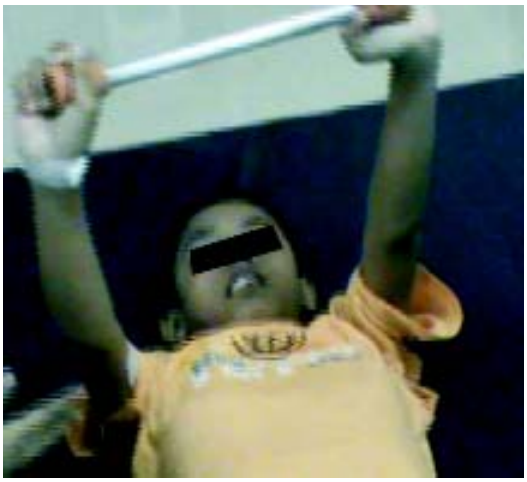
Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported that the effort required to perform exercises was reduced and his stamina had increased tremendously. His trunk strength had improved, with ability to sit erect on the dining table and have his meals, as opposed to earlier when he would always sit in stooped posture. His upper limb strength also increased and could perform activities of daily living like eating, dressing, bathing, etc independently. He could also perform overhead activities like reach outs easily. Also, while exercising he could perform crawling, and come on all fours, which he could not do before due to buckling of his elbows (weak triceps).His grip and pinch strength had improved since he performed fine motor activities like buttoning, writing , etc efficiently, which were very difficult earlier. He was then given bilateral push knee splints and made to stand with the help of the walker and manual assistance, which he could maintain for about half an hour. Gradually as the strength of his lower limbs increased, he began to walk about 30 steps at a time, at the end of 5 months.

	Before stem cell therapy	After stem cell therapy
Creatinine Phosphokinase levels	5050 IU	1244 IU

Manual Muscle testing : Following muscles showed improved strength

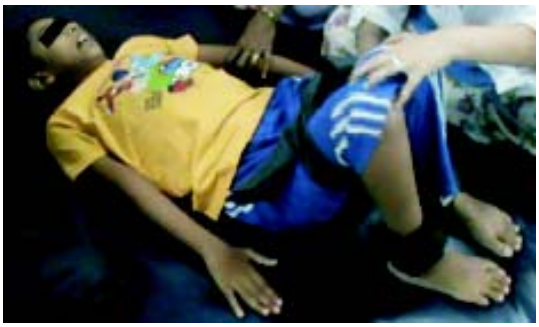
RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
2	2++	Flexors	2	2++
1	1++	Adductors	1	1++
		ANKLE		
3	3++	Dorsiflexors	3	3++
2	2+	Evertors	2	2+
2	3+	**ABDOMINALS**		



Increased upper limb, triceps muscle strength and ability to raise a rod (extend his elbow)

Improved trunk control and ability to sit erect on uneven surface.

Improved lower limb strength and ability to walk with bilateral push knee splints, independently.



Improved trunk control and ability to perform bridging .

Case Report - 13

Diagnosis : *Duchenne Muscular Dystrophy*

A 21 year old male, case of DMD, whose symptoms started at the age of 3 years with bilateral lower limb weakness and frequent falls while walking. He could walk till the age of 16 but thereafter he was wheelchair bound. He even developed bilateral upper limb weakness.

Neurologically, he was hypotonic and hyporeflexic. All his sensations were intact. He had grade 1++ strength in bilateral lower limb and grade 1 in bilateral upper limb with proximal muscle weakness more than distal muscles. On examination, he had pseudohypertrophy of bilateral calf muscles. He had bilateral knee flexion as well as wrist contractures. Functionally, he was dependent on caregiver for all ADL. He was wheelchair bound for mobility. On FIM he scored 62. On Brooke and Vignos scale he scored 4 and 7 respectively.

On investigation, DNA analysis revealed deletion in dystrophin gene involving exon 2. Serum creatine phosphokinase levels were raised to 3359 IU. EMG and Muscle Biopsy showed myopathic process and confirmed the diagnosis of muscular dystrophy. MRI revealed marked fatty infiltration of the pelvic gluteal, bilateral thigh muscles and leg muscles.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Deltoid, Biceps, Brachioradialis, Glutei, Quadriceps, Adductors, Tibialis Anterior and Peronei.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported that the effort required to perform the exercises was reduced significantly. Earlier he would feel fatigued out and lethargic the entire day. His trunk control and sitting balance improved, with ability to sit on the edge of the bed independently, earlier he would fall frequently due to poor trunk balance. He also improved in his bed mobility with independence in activities like getting up and lying back on the bed. He gradually got independent in his day to day activities like eating, combing, brushing and dressing for which he used to be dependent on his mother. As his upper extremity strength improved, he got independent in his personal hygiene and toilet activities. Also as he started bearing most of his weight by himself, transfers by the caretaker got easier and with least effort. He had multiple joint contractures in lower limbs like bilateral knee flexor contracture with bilateral talipes equino varus deformities, so he was made to stand on tilt table during therapy sessions, with bilateral push knee splints and stretched tendoachilles thereby leading to improved bone density and toning of muscles.

He could sustain standing for 20 minutes initially which then increased to 60 minutes. He also shifted from tilt table to assisted standing on the treadmill with harness.

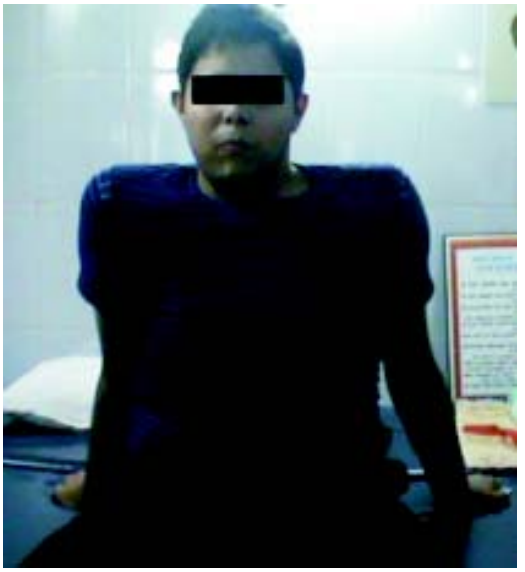
Gradually due to sustained weight bearing on lower limbs, his bilateral knee contracture and ankle contracture started stretching and opening up. Gradually, his back extensor strength increased further and he could sustain sitting activities. During therapy sessions he was then given serial casting for both his ankles and they straightened up almost completely.

	Before stem cell therapy	After stem cell therapy
Creatinine Phosphokinase levels	3359 IU	1450 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
1	2+	Extensors	1	2+
1	2+	Flexors	1	2+
1	2+	Abductors	1	2+
1	2+	Adductors	1	2+
		KNEE		
3	3+	Flexors	3	3+
1	2+	Extensors	1	2+
		SHOULDER		
1	2+	Flexors	1	2+
3++	3	Triceps	3++	3

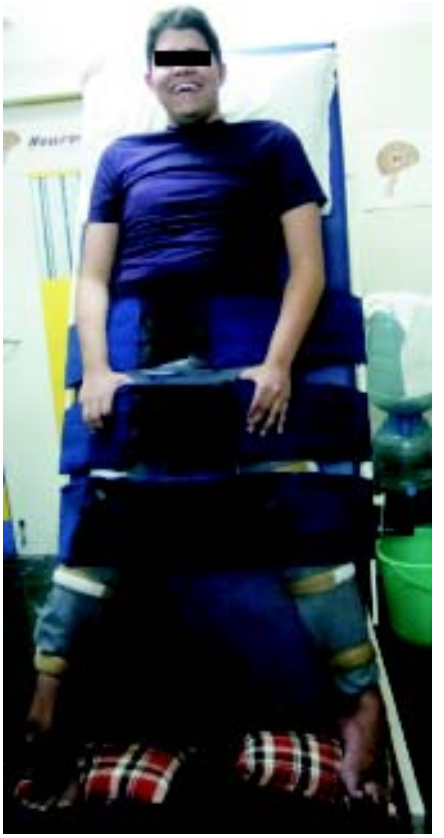
Radiological Improvement: On Comparing the MRI of Musculoskeletal system of both upper and lower limb muscles, at the interval of 6 months. The medial and lateral head of gastrocnemius showed less marked fatty infiltration, as compared to previous scans. Of all the muscles, improvement was more marked in the medial head of Gastronemius.



Improved trunk strength and ability to sit independently on the edge of the cot .

Improved abdominal strength and ability to perform crunches.

Improved abdominal strength and ability to perform Swiss ball exercise to strengthen them further.



Standing on the tilt table with bilateral push knee splints to stretch knee and ankle joints, improve the bone mineral density and toning of muscles.

Case Report - 14

Admission diagnosis : *Duchenne's Muscular Dystrophy*

A 9 year old male, known case of DMD since the age of 6. It started with history of bilateral lower limb muscle weakness and difficulty in climbing stairs and getting up from floor. Thereafter, he started walking on toes and having frequent falls. He had stopped walking since a year. Neurologically, he was hypotonic and hyporeflexic. He had all sensations intact. He had grade 1+ strength in bilateral lower limb and grade 3 in bilateral upper limb with predominant proximal muscle weakness. On examination,he had pseudohypertrophy of bilateral calf. Functionally, he was totally dependent on mother for all ADL and wheelchair bound for mobility. On FIM he scored 81. On Brooke scales, he scored 3 and on Vignos scale 9.

On investigation, the serum creatine phosphokinase levels were raised to 3076 IU and EMG showed myopathic units in the proximal muscles with early and full recruitment suggestive of a myopathic process. Genetic analysis showed deletions in 46,47 and 48 exons which indicated out frame mutations consistent with DMD. MRI of the musculoskeletal system showed marked fatty infiltration in the pelvic girdle muscles ,gluteal and bilateral thighs with relative sparing of the leg muscles. There is very early medial and long head of triceps muscle showed mild fatty infiltration with rest of the muscles of the arm and forearm muscles.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Deltoid, Biceps, Triceps, Glutei, Quadriceps, Adductors, Hamstrings, Abdominals and Back Extensors.

Clinical Improvements seen After Stem Cell Therapy

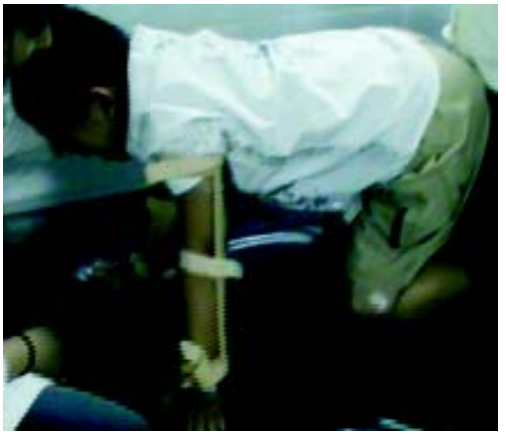
Functionally: On follow up at the end of 3 months, he reported feeling of wellbeing and improved stamina, with ease in all exercises. His trunk strength had improved with ability to perform bed mobility activities with ease like getting up from lying position to sitting, rolling, side lying, etc independently, earlier all of which needed assistance by the mother. Also his dynamic sitting balance had improved with ability to sustain balance on uneven surface like a Swiss ball. His upper limb and grip strength had increased with independence in activities of daily living like eating, bathing, dressing, washing up after toilet activities; opening tap, etc .He could also lift up his upper extremities with 1 kilogram of weights. Earlier overhead activities were not possible at all. He had bilateral knee flexor muscle tightness and knee flexion contracture of about 30 ° (restricted range of motion as assessed by Goniometer) .So during rehabilitation he was advised to wear bilateral push knee splints for sustained stretching of knee flexors. Gradually his knee muscles started loosening up with increased range of motion at the knee. He was also made to stand with splints on the standing board. He could sustain standing for 30 minutes initially but gradually progressed to 60 minutes. Mean while his trunk strength increased further, he was then taught to stand

with the walker. At the end of 8 months post therapy , he was able to stand independently , with the aid of the walker for about 60 mins , and gait training was initiated. On Brooke scales, he improved from 3 to2 2 and on Vignos scale , he showed a change from 9 to 8, after the stem cell therapy.

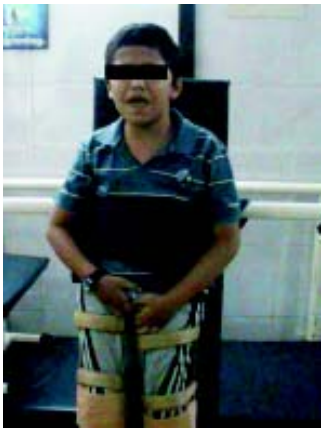
	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	3076 IU	2870 IU

Manual Muscle testing : Following muscles showed improved strength

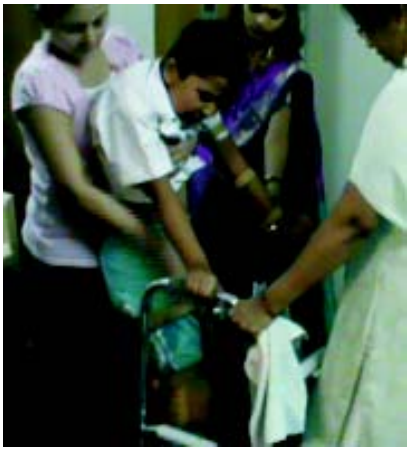
RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
1	2	Extensors	1	2
1	2++	Flexors	1	2++
1	2+	Adductors	1	2+
		KNEE		
3	3+	Flexors	3	3+
		SHOULDER		
2	3	Extensors	2	3
3	3+	Flexors	3	3+
2	3+	External Rotators	2	3+
3	3+	Triceps	3	3+
3	3+	Rhomboids	3	3+
3	3+	Serratus Anterior	3	3+
1	2-	**ABDOMINALS**	1	2-

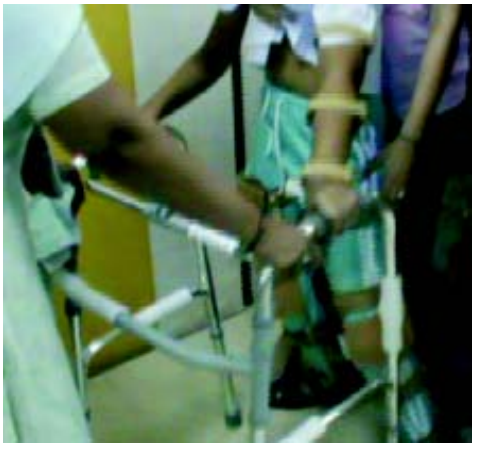


Improved upper limb and trunk strength, with ability to perform all fours, and raise upper extremities overhead.



Standing with bilateral push knee splints on standing board and gradually progressing to standing in parallel bars independently.





Initiation of gait training, with assistance of bilateral push knee splints and walker.

Case Report - 15

Diagnosis : *Muscular Dystrophy*

Clinical presentation: A 36 year old male gave history of progressive bilateral lower limb weakness since the age of 16. He could manage walking till the age of 21. Later, upper extremity weakness developed which progressed to weakening of chest, trunk and neck muscles leading to spinal deformities and neck drop.

Neurologically, he was hypotonic and hyporeflexic with intact sensations. He had grade zero muscle power in bilateral lower limbs(proximal as well as distal) .In the upper limbs, power was grade zero proximally and grade 2+ distally. On examination he had gross wasting and weakness of all muscles. He had right IT band contracture and lordotic contracture of entire spine. Functionally, he was totally dependent for all ADL and wheelchair bound for mobility. On FIM he scored 48.

On investigations, the serum creative phosphokinase levels were mildly raised. Electromyography studies were suggestive of primary muscle disease, while the muscle biopsy confirmed the diagnosis of muscular dystrophy. MRI of the upper and lower limbs before the stem cell therapy revealed moderate to extensive fatty infiltration in most muscles of the pelvic girdle, thigh, leg, arm and forearm muscles bilaterally.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally Abdominals, Quadriceps, Glutei, Tibialis Anterior, Peronei, Deltoid, Biceps, Triceps, Ext. Digitorum

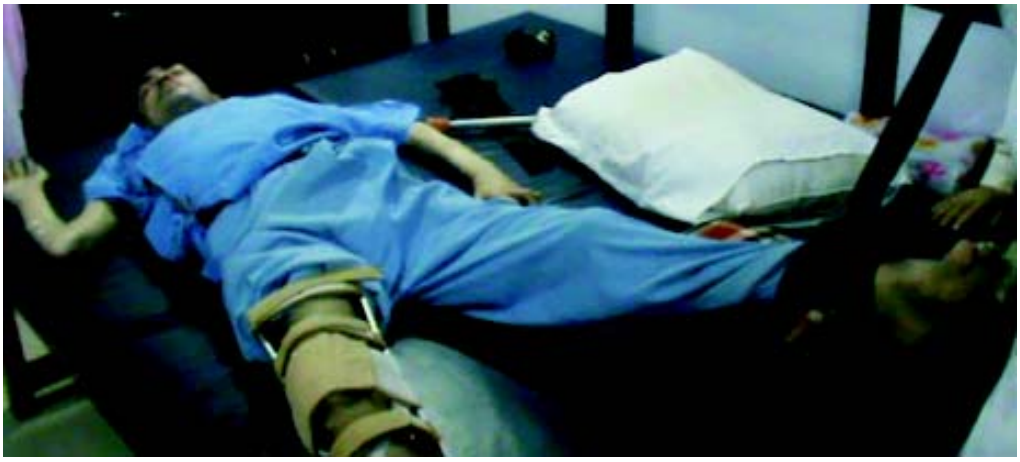
Clinical Improvements seen After Stem Cell Therapy.

Functionally: On follow up, at the end of 3 months, he reported feeling of wellbeing and improved stamina. He also reported no fatigue or exhaustion in doing activities. His trunk strength increased with ability to hold his neck erect and upright independently, as opposed to neck drop, which he had prior therapy. His dynamic sitting balance had improved, with ability to sit on the edge of the cot and perform reach outs. His upper limb and grip strength had also increased with ease in performing activities of daily living like brushing, bathing, eating, etc. He could hold a pen and was able to write post therapy, which was not possible at all before. His lower limb musculature also improved in strength. He had knee flexor muscle tightness, but due to sustain stretching, his knee flexors improved in flexibility with increased knee joint range of motion.

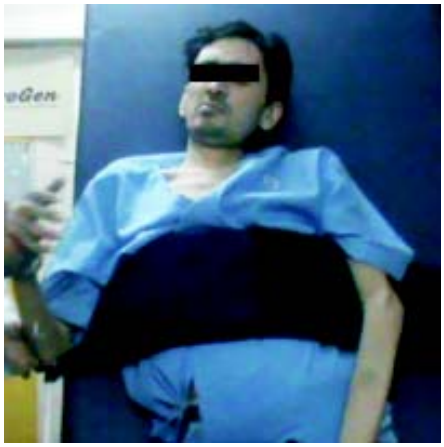
Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
0	1	Extensors	0	1
0	1	Flexors	0	1
0	1	Abductors	0	1
		KNEE		
1	1++	Extensors	1	1++
		ANKLE		
0	1+	Dorsiflexors	0	1+
0	1+	Evertors	0	1+
		SHOULDER		
0	1+	Abductors	0	1+
0	1+	Triceps	0	1+
		WRIST		
0	1+	Extensors	0	1+
		NECK		
1	2++	Extensors	1	2++
1	2++	Rotators	1	2++
0	1++	**ABDOMINALS**	0	1++

Neck muscle strengthening exercises and gradually independent neck holding.



Lower extremity strengthening suspension exercises.



Upper limb strengthening exercises on the tilt table

Case Report - 16

Diagnosis : *Becker's Muscular Dystrophy*

A young male aged 19 years, gave history of bilateral lower limb weakness with difficulty in walking and getting up from floor, climbing stairs since 2001. He continued to walk but with a waddling gait till 2008.

Neurologically, he was hypotonic and hyporeflexic with intact sensations. He had grade 1+ strength in all 4 limbs proximally and grade 3 in all 4 limbs distally. On examination, he had pseudohypertrophy of bilateral calf muscles. Proximal muscles were predominantly affected than distal. Functionally, he needed assistance in most ADL. He was wheelchair bound for mobility. On FIM he scored 65.

On investigations, the serum creatine phosphokinase levels were raised. Electromyography studies were suggestive of primary muscle disease.Muscle biopsy was suggestive of muscular dystrophy with immunohistochemical staining to dystrophin showing discontinuous labeling in about 50% of the fibres. Some fibres showed total absence while others showed well preserved staining along the sarcolemma, suggestive of a Becker's muscular dystrophy. MRI of the upper and lower limbs before the stem cell therapy revealed moderate to extensive fatty infiltration of the most of the pelvic girdle, thigh,leg,arm and forearm muscles.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally Deltoid, Biceps, Brachioradialis, Quadriceps, Glutei, Peronei, Tibialis Anterior and Abdominals.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina. He could sustain exercises for longer hours as opposed to earlier ,when he would complain of fatigue the entire day. His trunk muscle strength and dynamic sitting balance had improved significantly. Also his upper extremity and grip strength increased with independence in activities of daily living like dressing, bathing, combing, feeding and assisting in transferring himself He was able to hold a cup or bottle of water and drink by himself. He was also able to cut / trim his nails as his pinch and grip strength had increased which was documented while performing resisted exercises with the springs in the gripper. Earlier he would perform them with one spring (resistance), but gradually he increased to three springs, at a time. Also he could move his wheel chair and apply brakes to them independently, thus enhancing wheel chair controlled mobility. Flexibility of his muscles had increased and he could sustain stretching with bilateral push knee splints, with ease. Initially he was made to stand with bilateral push knee splints and high boots on standing board in order to stretch tendoachilles and improve bone density along with toning of muscles. But once he began standing comfortably for 45 minutes at a stretch and his trunk muscles also

increased in strength he was taught gait training, with the aid of splints and walker. He could perform assisted walking for about 20 steps at a time and was adapted to it.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	1713 IU	906 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
1	2+	Extensors	1	2+
1	2++	Flexors	1	2++
2	2++	Abductors	2	2++
2	3+	Ankle Plantarflexors	2	3+
		KNEE		
1	2-	Extensors	1	2-
2-	2+	Triceps	2-	2+

Ability to stand on standing board with bilateral push knee splints and perform gripper exercises.

Ability to perform assisted walking with the help of bilateral push knee splints and high boots with posterior steel shank.

Improved trunk strength and ability to sit independently on the edge of the bed, showing improved dynamic sitting balance.

Case Report - 17

Diagnosis : *Muscular Dystrophy*

A 55 years old female, a diagnosed case of neurogenic/muscular dystrophy gave history of progressive weakness in both lower limbs since 1991 (right>>left). She also complained of inability to squat and climb stairs. She could get up from squatting position, only with the help of support - climbing on oneself (Gower's sign). She had mild cardiac arrythmias and was on warfarin (5 mg) for the same.

Clinically, she had wasting of mainly the right lower limb muscles, such as, adductor magnus, adductor brevis, semimembranosus and semitendinosus muscles. Also there was marked atrophy of bilateral gastrocnemius and soleus muscles. She had absent reflexes and motor power in right lower limb being Grade 4. Her gait was waddling type with wide base of support and Lordotic back posture. No sensory complaints were noted.

Her muscle biopsy was suggestive of neurogenic atrophy without features of reinnervation and electrophysiology was suggestive of chronic myopathic changes

Clinical Improvements seen After Stem Cell Therapy

Functionally: On follow up, at the end of 3 months, she reported feeling of wellbeing and improved stamina. She also reported no fatigue or exhaustion in doing daily household activities, which was her major complaint prior therapy. She could swim easily around 12 laps where in earlier she was able to do just 3 laps.

Her trunk and lower limb muscles improved in strength and she was able to get up independently from lower level surfaces / squatting position, which was not possible before therapy .Also her frequency of falls while walking had almost become negligible, and her stability for walking increased significantly. She could also lift up objects without bending from the trunk , which was very difficult prior to the therapy .All her mat activities like kneeling, kneel walking, quadruped position are now easily performed. Her ability to climb stairs had also improved, with no assistance from the railing. Her calf muscle consistency, improved to near normal, as opposed to earlier when she had stiff and rigid calf muscle, on palpation. Her thigh muscle, which was wasted also increased in girth by 1 inch.

Improved trunk strength and ability to get up from the floor independently .

Ability to climb stairs independently

Improved upper limb, trunk strength and ability to perform over head task with weights

Case Report - 18

Diagnosis : *Limb Girdle Dystrophy*

A 20 year old female presented a history of progressive weakness in her limbs and girdle muscles since the age of 9 years. She initially had difficulty in climbing stairs and getting up from the floor indicating Gowers' maneuver.

She could walk with support till 2004-05, but gradually weakness progressed, such that at present, she is wheelchair bound. Neurologically, she was hypotonic and hyporeflexic. Her sensations were intact. Power in the distal muscles of both her upper and lower limbs was grade 4, while proximal muscle groups had power of Grade 2. On FIM, she scored 62

on investigation, her CPK levels were 5509 1 U/L and electromyography (EMG) indicated generalized intrinsic muscle disease.

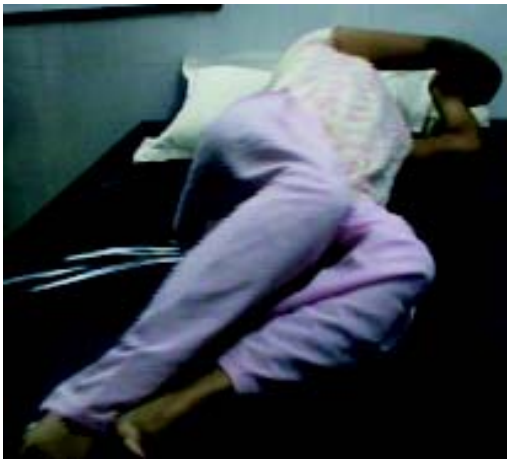
Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Hamstings, Calf Muscles, Glutei Muscle, Triceps, Biceps, Trapezius and Deltoid.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: On follow up, after 3 months, she reported feeling of wellbeing and improved stamina, as effort required to perform exercises was reduced. Her trunk strength had increased as she could perform bridging and abdominal crunches with ease. She was also made to stand with bilateral push knee splints on a standing board, thereby leading to improved bone density and toning of muscles. Gradually, strength in her upper limbs improved as she could bend her elbows independently, so activities of daily living like combing, eating had all become independent. At the end of 6 months, she was able to walk with KAFO's for about 15 - 20 steps at a time indicating that the strength in her lower limbs had also increased. The caretaker reported ease in handling and transferring her, as she could take the weight of her body and assist in performing the act, which was not possible before.

Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
1	2-	Extensors	1	2-
1	2-	Flexors	1	2-
		ANKLE		
3	4+	Plantarflexors	3	4+
		ELBOW		
2	2+	Biceps	2	2+
2	2++	Triceps	2	2++
2	2++	**ABDOMINALS**		



Ability to roll independently on bed as strength of trunk muscles had increased.

Improved trunk stability and dynamic sitting balance, with ability to weight shifts in sitting cross legged.

Ability to stand with bilateral push knee splints inside the parallel bars

Gait training, with bilateral push knee splints and walker.

Case Report - 19

Diagnosis : Limb Girdle Dystrophy

A 28 year old male presented with a history of progressive weakness in his limbs and girdle muscles since the age of 13 years. He initially had difficulty in climbing stairs and getting up from floor displaying Gowers' sign. He also gave history of frequent falls and difficulty in walking. He stopped walking in 2002 while, stopped standing since last 3-4 years. Weakness also progressed to his upper limbs, such that now he was totally dependent on his caregivers for all activities of daily living.

Neurologically, he was hypotonic and hyporeflexic. All his sensations were intact. Power in the distal muscles of both his upper and lower limbs was grade 3, while proximal muscle groups had power of Grade 1. These muscles also showed muscle wasting. On FIM, he scored 53

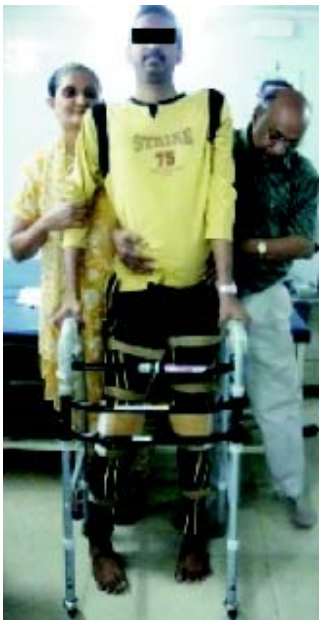
His CPK levels were raised to 5509 IU and electromyography (EMG) indicated a generalized muscle disease. The muscle biopsy further confirmed the diagnosis by reporting severe myopathy.

Clinical Improvements seen After Stem Cell Therapy

Functionally: At the end of 3 months, he reported that the effort required to perform the exercises was reduced significantly. Earlier, he would feel fatigued out and lethargic throughout the day, but post therapy he showed increased stamina and endurance to sustain the entire day. His upper limb strength had increased as he could perform his activities of daily living like eating, combing etc easily. Also, he could use his upper limb to move his wheel chair independently, which was not possible earlier. His trunk strength had improved with improved dynamic sitting balance. Post therapy, he also started standing with bilateral push knee splints on standing board for about 30 minutes a day, thereby leading to improved bone density and toning of muscles.

Manual Muscle testing : Following muscles showed improved strength

RIGHT		MUSCLES	LEFT	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
1	2	Extensors	1	2
1	2	Abductors	1	2
		KNEE		
0	2+	Extensors	0	2+
		ANKLE		
3	4+	Plantarflexors	3	4+
		SHOULDER		
1	2	Flexors	1	2
1	2	Abductors	1	2
0	2	Biceps	0	2
1	2	Triceps	1	2
0	2	Brachioradialis	0	2



Ability to stand with bilateral push knee splints and walker, with the help of a therapist.

Ability to eat independently, while being seated on a chair, thus showing improved functional ability to do ADL.

Case Report - 20

Diagnosis: *Limb Girdle Dystrophy*

A 27 year old male, known case of Limb Girdle Muscular Dystrophy, had a history of progressive weakness in his limbs and girdle muscles since the age of 4 years. He initially had difficulty in climbing stairs and getting up from the floor with a positive Gowers' sign.

Neurologically, he was hypotonic & hyporeflexic with intact sensations and bladder and bowel control. He had Grade 3+ muscle strength in bilateral upper limbs & Grade 2+ muscle strength in bilateral lower limbs. On palpation, bilateral calf & deltoid muscles showed pseudohypertrophy. Functionally, he was independent in all his activities of daily living, but did them in a modified manner. He walked with a lordotic gait & wide base of support. Electromyography studies showed myopathic process in Left Deltoid, Tibialis Anterior and Vastus Medialis .

On investigation, serum creatinine phosphokinase was raised to 610 IU/ml. Electromyography studies showed primary muscle disease.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally deltoid, triceps, biceps, adductors of shoulder, glutei, quadriceps, adductors of hip and abdominals.

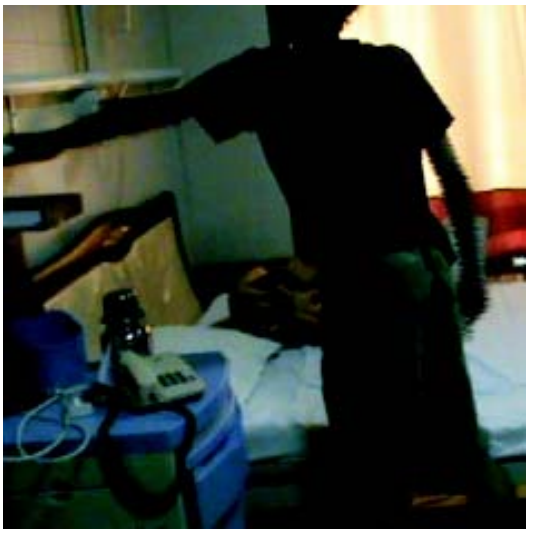
Clinical Improvements seen After Stem Cell Therapy

Functionally: At the end of 6 months, he reported feeling of wellbeing and improved stamina, as effort required to perform the activities of daily living was reduced significantly. He reported that the ongoing deterioration in his muscle strength had halted completely. He reported improved trunk muscle tone and strength with ability to stand upright with an erect posture as opposed to earlier when he would stand with hyperlordotic wide based stance. He also reported increased lower limb strength, with no feeling of fatigue even while standing for longer hours at work. Earlier he would take multiple breaks and rest due to exhaustion. His frequency of falls had reduced significantly, earlier he would buckle from knees quite often, but now due to improved lower limb and trunk strength his ability to walk steadily has improved significantly with increased standing tolerance and stability. His gait had improved with reduced waddling while walking. He reported ease and independence in getting up from lower level surfaces, where in earlier he would require a lot of assistance to do the same.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	610 IU	568 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
1	2++	Extensors	1	2++
1	2++	Flexors	1	2++
3-	3+	Abductors	3-	3+
1+	2++	Adductors	1+	2++
1+	2+	Internal Rotators	1+	2+
		KNEE		
2-	3	Extensors	2-	3
		ANKLE		
3	4	Dorsiflexors	3	4
		SHOULDER		
3	3++	Flexors	3	3++
		ELBOW		
3	3++	Biceps	3	3++
3	3++	Triceps	3	3++
2+	3++	**ABDOMINALS**	2+	3++



Improved trunk control and ability to get up from lower level surface or cot independently.

Improved stance with reduced lordosis and erect upright posture.

Improved trunk strength and dynamic sitting balance to perform lower body dressing with ease and independence.

Case Report - 21

Diagnosis : *Duchenne Muscular Dystrophy*

A 14 year old male, noticed sudden onset of bilateral lower limb weakness which was progressive since 2002. He had difficulty in getting up from the floor, climbing stairs & complained of frequent falls. Gradually upper limbs also started to get weak. He had stopped walking since 2 years.

Neurologically, he was hypotonic and hyporeflexic. He had Grade 0 muscle power in bilateral lower limbs and Grade 1 in proximal upper limb muscles and Grade 3 in distal muscles of upper limb. His proximal muscles were weaker compared to distal muscles. His sensations were intact and bladder and bowel control was normal. Functionally, he was dependent on his mother for all his activities of daily living. He was attending regular school and could write normally due to good distal muscle strength. He was wheel chair bound for mobility. On FIM he scored 54

On investigation, his creatine phophokinase levels were raised to 18200 IU and the electrophysiological studies revealed a primary muscle disease.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Quadriceps, Tibialis Anterior, Peronei, Glutei, Deltoid, Triceps, Biceps, Back Extensors and Abdominals.

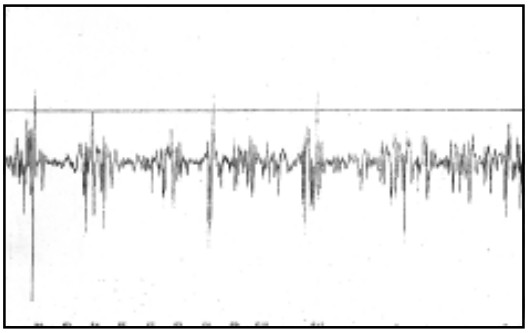
Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina, as effort required to perform the activities of daily living was reduced significantly. His trunk strength had increased with improved dynamic sitting balance and tolerance to sit upright without any support. Neck control had improved with ability to sustain the neck erect for longer periods without any support. Fine motor activity like pinch strength had improved so his handwriting improved, due to firmer grip. He started standing with calipers, independently with good trunk control and with both heels almost touching the ground thereby, leading to improved bone density and toning of muscles. His ankle dorsiflexor strength had improved with better ability to dorsiflex, evert and bring the foot to neutral position, as it would earlier remain in an attitude of inversion and plantar flexion, leading to tightness of tendoachilles tendon. Thus, post therapy while standing his heel would then touch the floor completely.

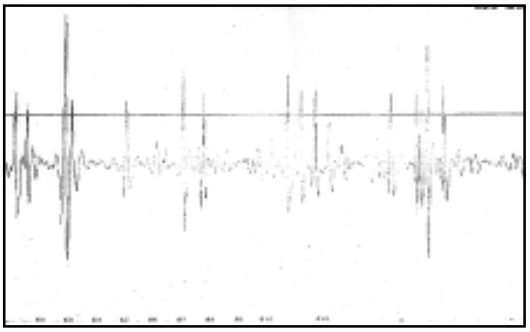
Manual Muscle testing : Following muscles showed improved strength

RIGHT		MUSCLES	LEFT	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
0	1	Abductors	0	1
0	1	Adductors	0	1
		KNEE		
0	1+	Flexors	0	1+
		ANKLE		
0	1+	Dorsiflexors (Tibialis Anterior)	0	1+
0	1	Everters (Peronei longus and Brevis)	0	1
0	3++	Plantarflexors	0	3++
		SHOULDER		
0	1+	Extensors	0	1+
0	2	Flexors	0	2+
0	1	Biceps	0	1++
0	2-	Brachioradialis	0	2-
3	3++	Intrinsic Muscle of Hand	3	3++

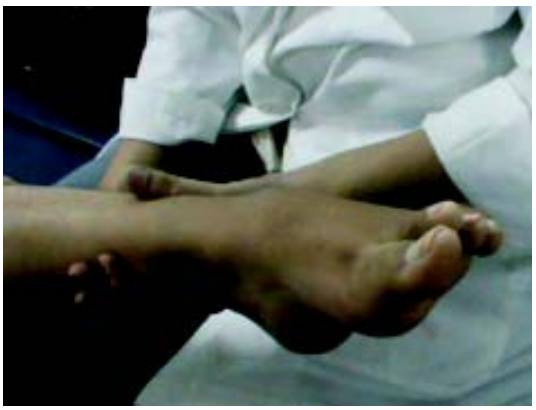
Electrophysiologically : The EMG of Left TA, Gastrocnemius, Deltoid and Biceps Brachii showed polyphasic, short duration myopathic potentials. On repeat EMG 6 months post therapy Left Gastrocnemius muscle showed normal needle EMG findings, which correlated with the clinical findings of improved Plantar flexor strength in bilateral feet.



Pre therapy EMG of Left Gastrocnemius showing , polyphasic, short duration Myopathic Potentials.

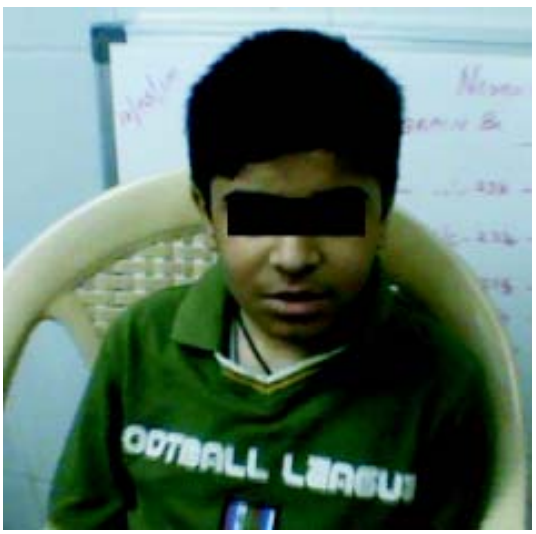


Post therapy EMG of Left Gastrocnemius showing, normal needle EMG findings, with complete interference pattern.



Improved strength of everters and ability to perform ankle dorsiflexion and eversion

Improved ability of neck control and maintaining it erect



Improved ability to stand with bilateral push knee splints with minimum assistance.

Case Report - 22

Diagnosis : *Facio Scapulo Humeral Dystrophy*

A 25 year old male, a known case of Facio Scapulo Humeral Muscular Dystrophy since 8 years, with history of sudden onset of weakness in his upper limbs which was progressive in nature. Later, he also developed bilateral lower limb weakness.

Neurologically, he was hypotonic & hyporeflexic with intact sensations and bladder /bowel control. He had Grade 3+ muscle strength in bilateral upper limbs and Grade 2+ muscle strength in bilateral lower limbs. On palpation, bilateral calf and deltoid muscles showed pseudohypertrophy. Functionally, he was independent in all his activities of daily living, but did them in a modified manner. He walked with a lordotic gait and a wide base of support. Functionally, he was mobile but had difficulty in climbing stairs, getting up from the floor and do overhead activities using upper extremities. He had a waddling gait and showed Tredelenberg's sign. On FIM, he scored 118.

On Investigation, his creatine phosphokinase was found to be 260 U/L. Muscle biopsy showed features of muscular dystrophy compatible with facioscapulohumeral muscular dystrophy. Electromyography studies showed primary muscle disease with proximal muscles most affected.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Anterior, middle and posterior fibres in Deltoid, Rectus femoris, Vastus lateralis and vastus medialis in Quadriceps, Glutei and rectus abdominis in abdominal muscles.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina, as effort required to perform the activities of daily living was reduced significantly, with ability to perform exercises for 4-5 hours daily.

He reported improved strength in his trunk muscles and ability to bend forwards and pick up objects from floor, while sitting on the cot, earlier he was unable to bend from trunk, due to fear of fall. He reported ease and independence in getting up from lower surfaces as opposed to earlier, when he would need manual assistance from his father to lift him up from cot and other lower surfaces. His lower limb strength had improved and he could squat, climb stairs and walk on slopes independently, where in earlier he needed lot of manual assistance. His level of confidence had increased and posture improved, which was earlier hyperlordotic while standing which had normalized to being upright and erect. His waddling while walking had reduced with increased stability and near normal gait. He could stand and perform spot marching, which was impossible earlier for him, as he had increased hip abductor strength after

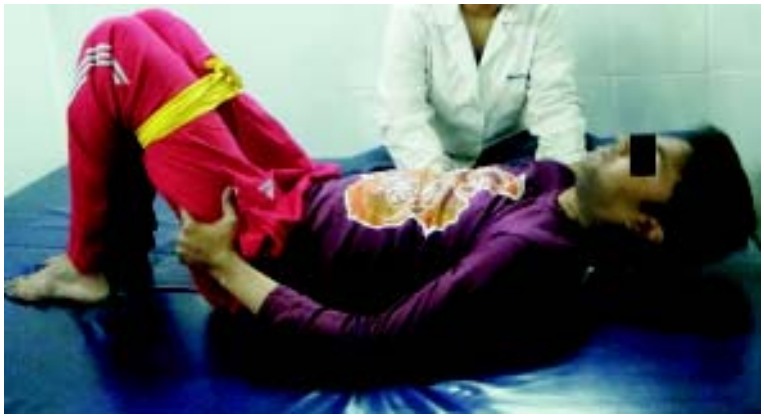
the therapy, giving him stability to perform unilateral stance. He showed toning of all his muscles. He also felt increased upper limb strength and ability to do pushups, which was not possible earlier due to fatigue and weakness in upper limbs.

Manual Muscle Testing: Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
1+	2++	Extensors	1+	2++
1+	2+	Flexors	1+	2+
1+	2+	Abductors	1+	2+
1+	2+	Adductors	1+	2+
		KNEE		
2	3++	Flexors	2	3++
3-	3	Extensors	3-	3
		SHOULDER		
1	2+	Extensors	1	2+
2	2+	Flexors	2	2+
2	2++	Abductors	2	2++
		ELBOW		
3	3++	Triceps	3	4+
2	3+	**ABDOMINALS**		

Improved gait, with reduced waddling and narrow base of support.

Improved ability to get up from lower level surfaces, with minimum assistance by the care taker.



Improved upper abdominal strength and ability to perform sit ups.

Case Report - 23

Diagnosis : *Duchenne Muscular Dystrophy*

A 19 year old male, a case of DMD gave history of sudden onset of lower limb weakness and pseudohypertrophy of calf muscles as noticed by parents. He could walk till the age of 7-8 years of age. Presently, he was wheel chair bound for mobility. Now, even upper extremity weakness had set in and was progressive. Neurologically, he was hypotonic and hyporeflexic. He had all sensations intact. On examination, the only muscles working were bilateral gastronemius, tibialis posterior and toe flexors but rest all trunk, neck and limb muscles were hardly functional. He had scoliosis of thoracic region and severe contractures of bilateral upper extremity and lower extremity due to immobility.He had bilateral elbow, wrist, hip, knee and ankle contractures. Functionally, he was dependent on the caregiver for all his activities of daily living. On FIM scale he scored 48.

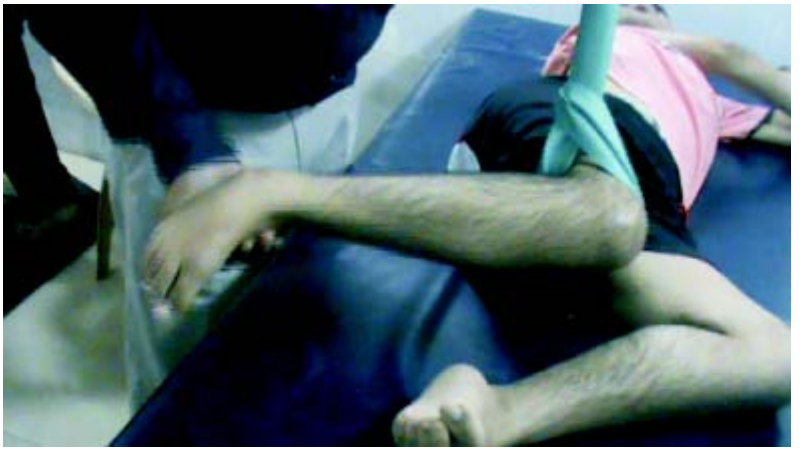
His serum creatinephosphokinase levels were raised to 335 IU/ml. Electromyography and Nerve Conduction Study suggested generalized muscle disorder. Muscle biopsy reported some fibres were totally replaced by fibrous tissue. The DNA analysis showed deletion in exons 47-52 of the dystrophin gene, further confirming the diagnosis of muscular dystrophy.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: On follow up after 3 months, he reported that his stamina had improved and the effort required to perform the exercises was reduced significantly. His trunk control improved and his dynamic sitting balance also improved, with ability to sit on the edge of the bed for about 15 minutes, which he could not do before. His respiratory muscle strength had increased, with improved chest expansion and reduced frequency of respiratory tract infection as compared to before. An objective assessment of which being his ability to perform and increase in incentive spirometer exercises from 200 cc to 400 cc comfortably. His neck musculature strength had increased dramatically, earlier he would have a neck drop, but post therapy, he could hold his neck upright for almost half an hour without fatigue. He had multiple contractures like bilateral hip knee and elbow contracture, with kyphoscoliotic spine, but post therapy, due to sustained stretching, his knee flexion contracture opened up from 45 ° of flexion to 35° (as assessed and documented by a goniometer).

Improved sitting balance and trunk control

Improved neck control and neck holding capacity.



Reduced knee flexion contracture, and suspension exercises for knee extensor strengthening.

Case Report - 24

Diagnosis : *Ducchenne Muscular Dystrophy*

A 13 year old male was diagnosed with Muscular Dystrophy at the age of 8 yrs, as he had difficulty in walking with lower limb weakness. After 2-3 years, he had difficulty in getting up from the floor. Gradually, the weakness progressed to the upper extremity with difficulty in overhead activities.

Neurologically, he was hypotonic and hyporeflexic. All his sensations were intact. He had grade 3, strength in bilateral lower limb and grade 3++, in bilateral upper limb with predominantly proximal muscle weakness more than distal muscles. On examination, he had pseudohypertrophy of bilateral calf and deltoid muscles. Bebinski was depressed.

Functionally, he was independent in his activities of daily living, but found difficulty in getting up from floor and low seat. He walked with a lordotic waddling gait with wide base of support with a tendency for Talipo equinovarus deformity. On FIM he scored 79 & On Brooke and Vignos Scale he scored 1 and 9 respectively on admission.

On investigation, the serum creatine phosphokinase levels were raised to 4774 IU. Electromyography/ NCV showed primary muscle disease in right upper limb and right lower limb. Muscles were examined with concentric needle electrode and showed spontaneous activity absent at rest and voluntary contraction in right vastus medialis, right tibialis anterior and right deltoid showed short duration low amplitude motor unit potentials intermixed with normal motor unit potential. While right vastus medialis, right tibialis anterior and right deltoid was complete. Right sural nerve, right and left peroneal nerves, right tibial nerve, right median nerve and right ulnar nerve showed normal findings. F-wave in both lower limbs and right upper limb and H-reflex in both lower limbs showed normal latency. DNA testing revealed deletions in exons 45, 46,47,48,49 of the dystrophin gene, confirming the diagnosis of DMD. 2-D Echo cardiography: LVEF-60%

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei and Abdominal muscles

Clinical Improvements seen After Stem Cell Transplant:

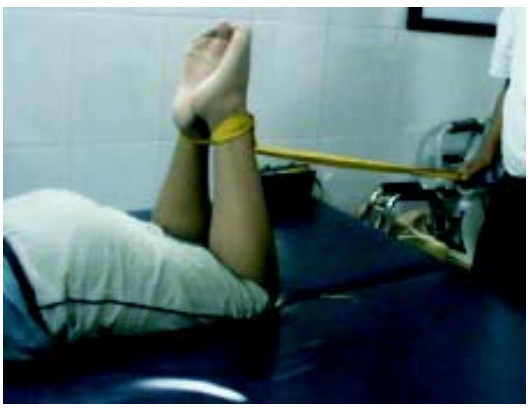
Functionally : At the end of 3 months, he reported feeling of wellbeing and improved stamina, as effort required to perform exercises was reduced significantly, as opposed to earlier when he would fatigue and feel lethargic most part of the day. His lower limbs and trunk muscle strength had increased and the frequency of his falls while walking had reduced considerably . Parents reported that his gait had normalized, while earlier he would walk with wide based gait. His stance stability had also improved. They also reported that his overall participation in school activities had

increased such as, participation in school sports like cricket. Also his upper limb strength had increased with ease in performing overhead activities and play sports like throw ball. He also became independent in all his activities of daily living like bathing, dressing, etc, which required a lot of assistance earlier.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels (MB)	35 IU	15 IU

Upper extremity strengthening activity and ability to lift 2 kilograms weight

Improved trunk stability and ability to bend and pick up objects.



Improved hamstring strength and ability to perform resisted knee flexor exercises.

Case Report - 25

Diagnosis : *Duchenne Muscular Dystrophy*

An 8 year old male, diagnosed as a case of Duchenne Muscular Dystrophy at 4 yrs of age due to difficulty in walking and complains of frequent falls. He also had difficulty in getting up from the floor and climbing stairs.

Neurologically, he was hypotonic and hyporeflexic. All his sensations were intact. He had grade 3+ strength in bilateral upper limb and lower limb with predominant proximal muscle weakness more than the distal muscles.

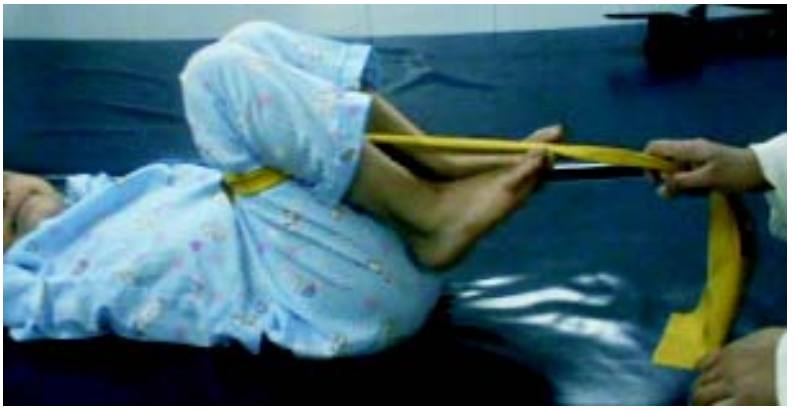
On examination, he showed pseudohypertrophy of bilateral calf and deltoid. Functionally, he was independent in all his activities of daily living. He walked with a Lordotic Waddling Gait with a wide base of support and had Gowers' maneuver. On FIM he scores 90 & on Brooke and Vignos scale he scored 2 & 3 respectively.

On investigation, the serum creatine phosphokinase levels were raised to 5415 IU. Electromyography studies and Nerve Conduction Velocity revealed myopathic disease with no spontaneous activity and polyphasia and early recruitment in tibialis anterior, gastrocnemius, vastus lateralis, brachioradialis and deltoid muscles. Motor nerve conduction studies showed reduced CMAP amplitude in bilateral CP nerves with normal conductions in PT, right median and Ulnar nerves. Genetic testing revealed deletions in exons 48, 49 and 50 of the dystrophin gene. X-Ray Chest showed normal cardiac size and configuration. 2-D Echo Cardiography showed LVEF-55%. Electrocardiogram showed Left Ventricular Hypertrophy.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Quadriceps and Glutei.

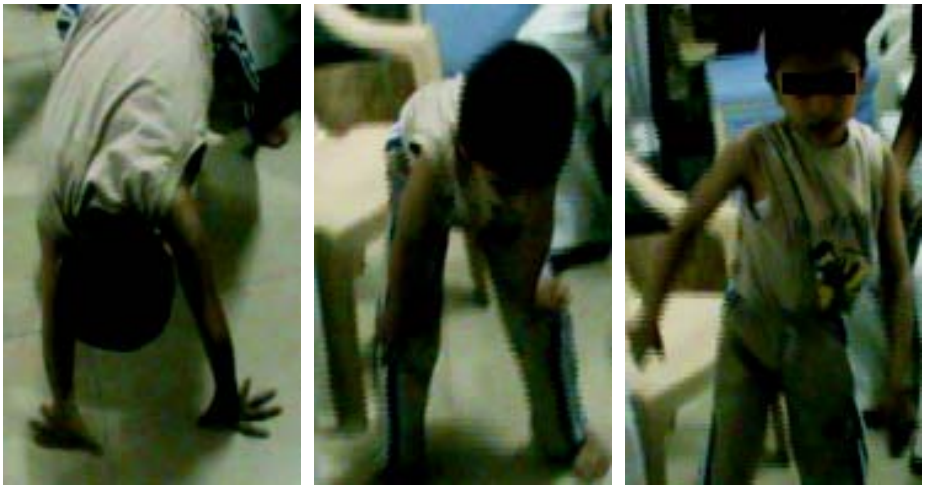
Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina, as effort required to perform the activities of daily living was reduced significantly. He could exercise for longer duration without complaints of fatigue. His bed mobility had also improved, with ease and independence in sitting upright on the bed, for which he earlier needed assistance. He had wide based waddling equinnus gait earlier, but after the therapy, as strength of his trunk and lower limb muscles improved, he was able to walk with heels touching the ground and relatively normal gait. His frequency of falls while walking had reduced significantly. Mother reported that, after the therapy, he fell may be once in a month, as opposed to earlier when he would fall 3-4 times a day. He could get up from the floor independently, where in earlier he would need manual assistance to lift him from the floor.



Improved lower abdomen strength and ability to perform resisted strengthening exercises.

Improved trunk stability and ability to perform reach outs in all fours position



Improved ability to get up from floor without any manual assistance

Case Report - 26

Diagnosis : *Muscular Dystrophy*

A case of a 37 year old muscular dystrophy patient, since the past 18 years whose problem began with bilateral lower limb weakness which was progressive. He could walk for 12-15 years, but later stopped completely. Since the last 5 years, weakness has progressed to both his upper limbs leading to difficulty in performing overhead activities.

Neurologically, he was hypotonic and hyporeflexic with intact sensations. He had grade zero strength in bilateral lower limbs and grade 1+ strength in bilateral upper limb with predominant proximal muscle weakness more than the distal muscles in bilateral upper limb. On examination, he had gross wasting in all the four limb muscles. Functionally, he was totally dependent on his caregiver for his activities of daily living. He was wheelchair bound for mobility. On FIM he scored 88.

On investigations, the serum creatine phosphokinase levels were 335 IU. Electromyography findings were suggestive of myogenic involvement in right lower limbs as well as right deltoid and right abductor digiti minimi, while the muscle biopsy confirmed the diagnosis of muscular dystrophy. MRI of the musculoskeletal system revealed moderate to extensive fatty infiltration of pelvic girdle, thighs, legs, arm and forearm muscles.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally Deltoid, Biceps, Triceps, Adductor pollicis, Flexor pollicis, Brachioradialis, Palmar Interossei, Dorsal Interossei, Abdominals, Back Extensors, Glutei, Quadriceps.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: On follow up, at 6 months post therapy, his dynamic sitting balance and tolerance had improved significantly, as his trunk muscle strength had increased so he could sit for long hours. His upper limb strength had improved and he could initiate movements in his shoulders bilaterally, which were totally absent before the therapy. His neck musculature also improved with improved ability to hold the neck upright. His lower limb strength had also increased minimally. He had started standing with bilateral push knee splints, on the standing board thereby, leading to improved bone density and toning of muscles. He reported feeling of wellbeing and improved stamina, along with a halt in the ongoing deterioration of his physical condition.

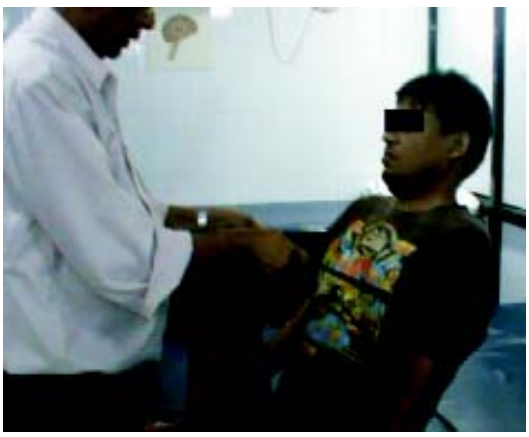
Creatinine Phosphokinase levels	Before stem cell therapy	After stem cell therapy
Total	335 IU	135 IU
MB	30 IU	12 IU

Manual Muscle testing : Following muscles showed improved strength

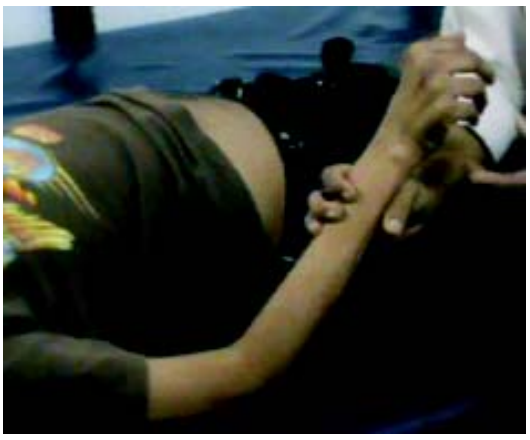
RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
0	1+	Extensors	0	1+
0	1+	Flexors	0	1+
0	1+	Abductors	0	2+
0	1+	Adductors	0	1
		KNEE		
0	1	Extensors	0	1
		SHOULDER		
2	2+	Extensors	2	2+
1	2+	Flexors	1	2+
1+	2+	Abductors	1+	2+
2	2++	Adductors	2	2++
		ELBOW		
2+	3++	Supinator	2+	3++
2+	3+	Lumbricals	2+	3+
1	2+	**ABDOMINALS**		

Improved ability to raise shoulders due to increased shoulder girdle strength.

Improved neck muscle strength and ability to raise the neck over the bed.



Improved strength of trunk muscle, with the ability to perform abdominal crunches.



Improved wrist extensor strength and ability to perform wrist extension.

Case Report - 27

Diagnosis : *Muscular Dystrophy*

A 32 year old female, a case of muscular dystrophy since past 12 years, gave a history of bilateral lower limb weakness with difficulty in walking and frequent falls. She also complained of difficulty in climbing stairs and getting up after a fall. Later, since about a year, she noticed difficulty in overhead activities, indicating progression of weakness to her upper limbs.

Neurologically, she was hypotonic and hyporeflexic with intact sensations. She had grade 2+ strength in bilateral lower limbs and grade 3^{-} strength in bilateral upper limb proximally and grade 4 distally in bilateral upper limbs. She walked with a lordotic gait with wide base of support and assistance. Functionally, she was independent in all her activities of daily living, but had difficulty in walking, climbing stairs and overhead activities. On FIM, she scored 99.

On investigations, the serum creatine phosphokinase levels were raised. Electromyography studies were suggestive of primary muscle disease, while the muscle biopsy confirmed the diagnosis of muscular dystrophy.

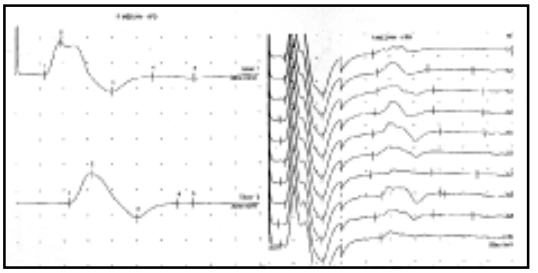
Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Quadriceps, Abdominal muscles and Deltoid.

Clinical Improvements seen After Stem Cell Therapy

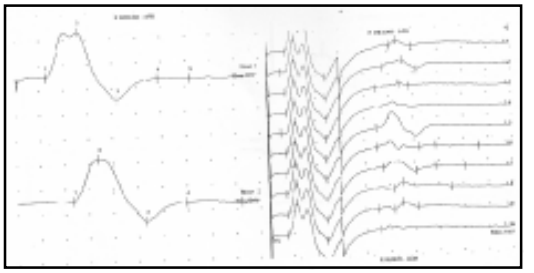
Functionally: On follow up, at 6 months post therapy, she reported feeling of wellbeing and improved stamina, as effort required to perform the activities of daily living was reduced significantly along with a halt in the ongoing deterioration of her physical condition. Although her Manual Muscle testing did not show any significant change, her functional abilities had improved. Also her CPK levels had changed.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	3072 IU	436 IU

Electrophysiologically : The EMG of Deltoid, Vastus Medialis ,Tibilais Anterior muscle showed myogenic involvement in the muscles. On repeating the EMG of same muscles after 6 months, readings showed marginal improvement in compound muscle action potentials.



Pre-Operative Deltoid Muscle EMG Showing Myogenic Involvement



Post operative Deltoid Muscle EMG Showing marginal improvement in latency, Compound Muscle Action Potentials and in motor velocity.

Improved Trunk Control and ability to perform all fours position.

Improved ability to get up from lying position to sit up independently.

Improved ability to perform trunk rotation with weights in the hands.

Improved upper limb strength and ability to perform upper limbs strengthening exercises with theraband.

Case Report - 28

Diagnosis : *Duchenne Muscular Dystrophy*

A 16 year old male, gave a history of bilateral lower limb weakness and frequent falls while walking since the age of 6 years. Gradually, his weakness progressed to upper limbs also. He could walk till the age of 13. He had a family history wherein his elder brother being afflicted similarly, had succumbed to respiratory distress 6 months ago.

Neurologically, he was hypotonic and hyporeflexic. He had all sensations intact. He had grade 0 strength in bilateral lower limb and grade 1+ in bilateral upper limb muscles with proximal muscle weakness more than the distal muscles. On examination, he had right sided scoliosis with bilateral elbow and knee flexion contracture and bilateral TEV. Functionally, he was totally dependent on his mother for all his activities of daily living. He was wheelchair bound for mobility. On FIM he scored 58.

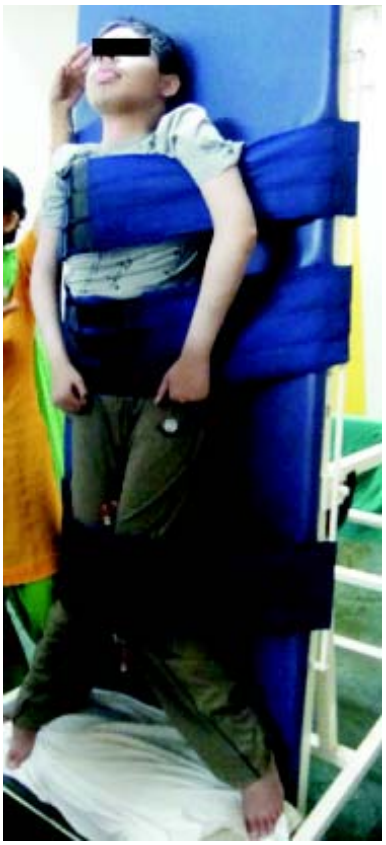
On investigation, the serum creatine phosphokinase levels were raised to 1767 IU The electromyography studies and muscle biopsy indicated primary muscle disease.MRI of musculoskeletal system done before the therapy showed almost complete fatty infiltration of all the muscles of both the upper and lower limbs with no volume loss in muscle bulk and relative sparing of the sartorius muscle.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Deltoid, Biceps, Triceps and Abdominals.

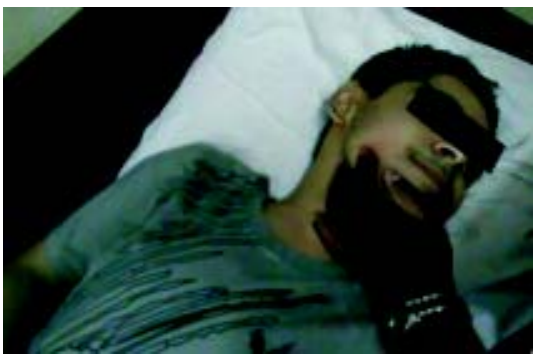
Clinical Improvements seen After Stem Cell Therapy

Functionally: At the end of 3 months after the stem cell transplantation, he reported feeling of wellbeing and improved stamina. His appetite had increased and he would feel energetic the entire day. He had multiple contractures like bilateral hip - knee flexion, elbow flexion contracture and right sided scoliosis. With regular sustained stretching, he reported reduction in tightness and improved flexibility of joints. He was made to stand on the tilt table , which he could sustain for almost 30 minutes a day , with the aim of stretching tight muscles and leading to weight bearing of joints thereby improving bone mineral density and toning up of weak muscles. His trunk control improved, with ability to sit independently on the edge of the cot, without any support. An observation made by the parents and patient himself was that the deterioration and fast progression of his disease was brought to an arrest.

	Before stem cell therapy	After stem cell therapy
Creatinine Phosphokinase levels	1767 IU	805 IU



Standing on the tilt table to improve weight bearing on the joints (passively)



Passive Stretching of the neck side flexors.

Passive stretching of the Hip Flexors and Knee flexors , with the aid of weight cuffs and gravity.

Case Report - 29

Diagnosis : *Becker's Muscular Dystrophy*

A 33 year old male, case of Becker's Muscular Dystrophy was diagnosed at the age of 12 years as he gave a history of frequent falls while walking. The weakness in his bilateral lower limbs progressed gradually along with the upper limbs which led to difficulty in overhead activities. He was totally wheelchair bound since 11 years. His parents had a consanguineous marriage. He also had a family history wherein his brother expired at age of 25 due to muscular dystrophy.

Neurologically, he was hypotonic and hyporeflexic, all his sensations were intact. He had grade 2 strength in bilateral lower limbs and grade 1+ in bilateral upper limbs. On examination, he had gross wasting of all 4 limbs and trunk muscles. He had hip and knee contractures with slight scoliosis. Functionally, he was totally dependent on the caregiver for most of his activities of daily living. On FIM he scored 65.

On investigation, serum creatine phosphokinase levels were raised to 853 IU EMG revealed primary muscle disorder and right common peroneal nerve. Genetic testing for mutations in the dystrophin gene revealed deletion of exon 12 Muscle biopsy showed collagenisation of muscle bundles with fatty infiltration and compensatory hypertrophy. There was no infiltration of inflammatory cells and the sample was consistent with muscular dystrophy. 2D ECHO revealed modified LV dysfunction with EF of 40%.

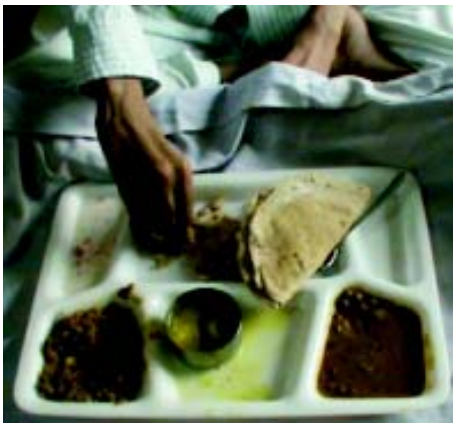
Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Rectus Abdominis, Quadriceps and Peronei

Clinical Improvements seen After Stem Cell Therapy.

Functionally: On follow up at the end of 3 months, he reported feeling of wellbeing and improved stamina. He improved in his trunk strength and could sustain sitting on the edge of the cot for 20 minutes, which he could not do before. Due to sustain stretching of the tight muscles, he could open up his hands and move his fingers with ease thereby, improving his hand function like eating. He was made to stand with bilateral push knee splints on the tilt table thereby, stretching the lower limb contractures, toning of muscles and improve the bone mineral density.

	Before stem cell therapy	After stem cell therapy
Functional Independence Measure	65	69
Creatinine Phosphokinase levels	853 IU	487 IU

Standing on the tilt table with bilateral push knee splints, to stretch contractures and other benefits of standing like toning of muscles and improving bone mineral density.



Independence in eating despite having finger flexion contracture

Improved sitting balance and ability to sit cross legged without any support.

Case Report - 30

Diagnosis : *Muscular Dystrophy*

A 38 year old male with history of bilateral calf muscle heaviness and difficulty in climbing stairs, since 2000, had gradually progressive lower limb weakness. His problems started with difficulty in getting up from the floor along with frequent loss of balance and falls while walking. He also complained of difficulty in lifting weights for prolonged period of time.

Neurologically, he was hypotonic and hyporeflexic with intact sensations. He had grade 3 strength in bilateral lower limbs and grade 4 in bilateral upper limbs with predominant proximal muscle weakness. On examination, he had hypertrophy of bilateral calf muscles. Functionally, he was independent in most of his activities of daily living. He walked with a Trendelenburg's and lordotic waddling gait. On FIM he scores 107.

On investigations, the serum creatine phosphokinase levels were raised to 4088 IU. Electromyography studies were suggestive of primary muscle disease, while the muscle biopsy confirmed the diagnosis of muscular dystrophy.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Rectus Abdominis, Quadriceps and Peronei.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina. Earlier he always complained of fatigue on any activity, but gradually his endurance improved and he could sustain exercises for longer duration. His trunk strength had improved and functionally, he was able to get up from the bed independently. Earlier, he needed a lot of assistance from the caretaker to do the same. He had waddling hyperlordotic wide based Equinnus gait but as the strength in his lower limbs improved, post therapy, his gait improved to plantigrade normal base gait (increased lower limb abductor strength), with improved stability during stance phase. He had also reduced 5 kgs body weight and could appreciate the filling up and toning of previously wasted muscles e.g.: quadriceps bilaterally.

	Before stem cell therapy	**After stem cell therapy**
Functional Independence Measure	107	109
Creatinine Phosphokinase levels	4088 IU	1335 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	HIP	Before therapy	After therapy
2	3+	Extensors	2	3+

Increased upper limb strength and ability to lift weights and hold.

Improved trunk control and ability to come to all fours independently.

Improved upper limb strength and ability to perform upper limb strengthening exercises with 2 kgs weights.

Improved gait with no waddling and normal base of support with plantigrade stance.

Case Report - 31

Diagnosis : *Duchenne Muscular Dystrophy*

A 6 year old boy, diagnosed with DMD at the age of 3 years as had a history of delayed walking as a milestone (achieved at 2 years of age). He also had difficulty in getting up from the floor and climbing stairs. He gradually developed difficulty in doing overhead heavy activities. He had a family history, wherein his maternal cousin also suffered from muscular dystrophy.

Neurologically, he was hypotonic and hyporeflexic with all the sensations intact. He had grade 3+ strength in bilateral lower limb muscles and grade 3++ in bilateral upper limb with predominantly proximal muscle weakness more than distal. On examination, he had hypertrophy of bilateral calf and deltoid muscles. Functionally, he was independent in most activities of daily living but needed assistance from mother. He showed Gowers' sign and equinnus lordotic gait. On FIM he scored 106. On Brooke and Vignos scale he scored 1 and 2 respectively.

On investigation, the serum creatine phosphokinase levels were raised to 9850 IU Electromyography studies revealed primary muscle disease. DNA testing revealed deletions in exons 48,49,50 of the dystrophin gene, confirming diagnosis of DMD .

MRI upper and lower limbs showed marked fatty infiltration of pelvic girdle muscles, less marked fatty infiltration in the gastrocnemii and soleus muscles, minimal fatty infiltration of the biceps and triceps was also noted.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Quadriceps, Abdominals, Deltoid and Triceps

Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported that the effort required to perform the exercises was reduced significantly. His lower limb and trunk strength increased. He was able to climb stairs with ease. Also, while performing mat exercises like bridging, crawling and kneel walking on the bed, his performance had improved. Over all his stamina and endurance had increased tremendously, as mother reported that he was very active in the school, post therapy.

	Before stem cell therapy	After stem cell therapy
Creatinine Phosphokinase levels	9850 IU	9657 IU

Improved lower limb strength and ability to perform kneel walking.

Improved trunk control and ability to come to all fours and maintain it, along with performing upper limb weight transfers.

Improved upper limb strength and ability to perform overhead activities like throwing a ball.

Improved lower limb strength and trunk stability with ability to climb stairs independently.

Case Report - 32

Diagnosis : *Duchenne Muscular Dystrophy*

A 13 year old male, who had bilateral lower limb weakness with difficulty in climbing stairs, walking and getting up from floor since the age of 5 years. Gradually, weakness progressed and he stopped walking at the age of 11 yrs. He also noticed upper limb weakness since 2 years with difficulty in overhead activities.

Neurologically, he was hypotonic and hyporeflexic with all his sensations intact. He had grade 1 strength in bilateral lower limbs and grade 2+ in bilateral upper limb with predominant proximal muscle weakness more than distal. On examination, he had hypertrophy of bilateral calf and deltoid muscles. He had right sided kyphoscoliosis and bilateral TEV deformity in foot. Functionally, he was dependent on caregiver for most of his activities of daily living. He was wheelchair bound for mobility. On FIM he scored 52. On Brooke and Vignos scale he scored 4 and 9 respectively.

On investigations, the serum creatine phosphokinase levels were 7500 IU. Electromyography/Nerve Conduction Studies suggested primary muscle disease.

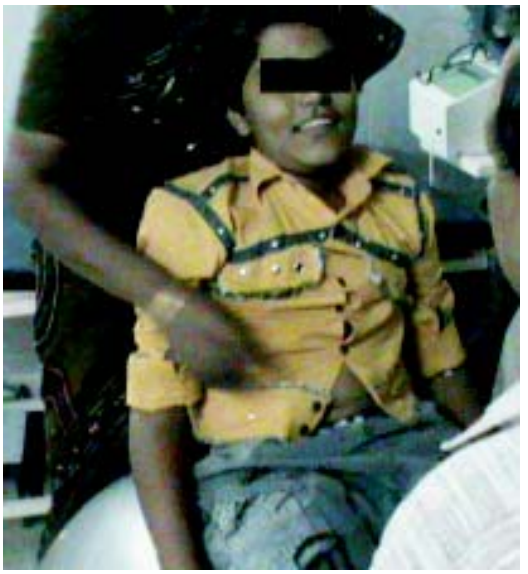
Muscle Biopsy suggested of muscular dystrophy. It showed a random variation in size of muscle fibres which showed angulated outlines, atrophy and hyaline at places vacuolated, cytoplasm. Centralization of nuclei was seen and there was an increase in inter-fascicular connective tissue. 2-D Echo: LVEF-70%. PFT: severe restrictive abnormality.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Quadriceps, Peronei, Abdominals and Deltoid.

Clinical Improvements seen After Stem Cell Therapy

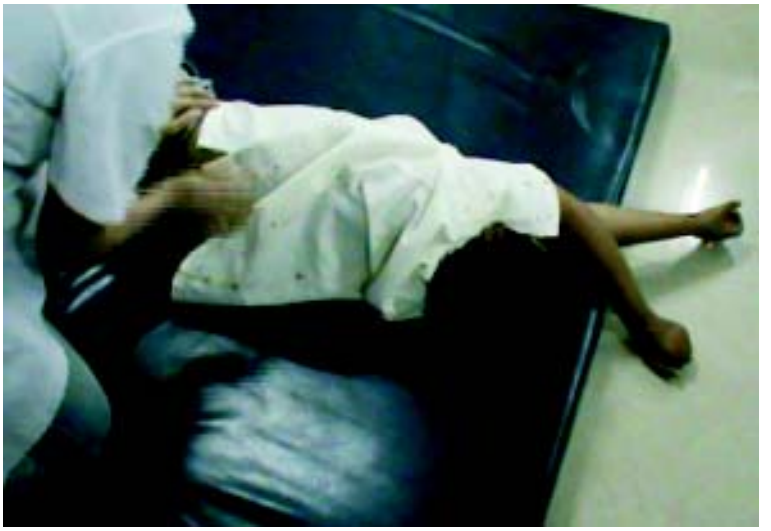
Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina. He reported ease in performing all exercise and during physiotherapy sessions he would not fatigue, wherein, previously, he would feel lethargic and tired the entire day. He was trained for dressing activities and had started to attempt it with minimum assistance. Most of his muscles had started toning up.

	Before stem cell therapy	After stem cell therapy
Creatinine Phosphokinase levels	1177 IU	782 IU



Training for sitting balance on uneven surface to train dynamic sitting balance.

Training for back extensor muscles to improve trunk strength.



Training for mat exercises and independent rolling activity.

Case Report - 33

Diagnosis : *Ducchenne Muscular Dystrophy*

An 11 year old male, reported bilateral lower limb weakness and difficulty in walking and climbing stairs since the age of 3 years. At the age of 8 years, he also complained of difficulty in getting up from the floor and early fatigue. His speed of walking had also reduced.

Neurologically, he was hypotonic and hyporeflexic with all his sensations intact. He had grade 2+ strength in bilateral lower limb and grade 3++ in bilateral upper limb with predominant proximal muscle weakness more than distal. On examination, he had hypertrophy of bilateral calf and deltoid muscles. Functionally, he needed assistance in a few activities of daily living. He had a lordotic gait with abdominal muscle weakness. He had difficulty in getting up from floor and climbing stairs. On FIM he scores 114. On Brooke and Vignos scale he scored 1 and 3 respectively.

On investigation, the serum creatine phosphokinase levels were raised to 4877 IU .Genetic analysis showed deletion in the dystrophin gene involving multiple exons (8-19). Muscle biopsy showed marked degenerative changes in many fibres, necrotic fibres engulfed by macrophages, variation in fibre size and excess sarcolemmal nuclei suggesting of muscular dystrophy. Electromyography studies and nerve conduction velocity confirmed diagnosis of primary muscle disease in all the muscles examines. 2 D-Echo: mildly dilated LV with mild generalized LV hypokinesia with LVEF- 40-45%

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Quadriceps and Abdominals.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported improved strength in both his lower limbs and trunk with improved stability in walking. His gait had improved with ability to keep both his heels on the ground while walking unlike before where he would walk with equinnus gait. Also, he would climb stairs with lot of ease. He was able to get up from floor or lower level surfaces with ease, while before the therapy his father would lift him up from the floor. He performed all the exercises with significantly less effort than before. He was overweight prior to the therapy, but 3 months post therapy, with intensive exercise program and under the supervision of the dietician, he had healthy weight loss and showed toning up of his muscles.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	4877 IU	4812 IU
Brooke and Vignos scale	1& 3	1& 2

Improved upper abdomen strength and ability to perform sit ups.

Improved hip extensor strength and ability to perform all fours and unilateral hip extension .

Training for trunk extensor strengthening and ability to perform back extension with ease while exercising

Improved trunk strength and ability to perform side sitting, during mat exercises.

Case Report - 34

Diagnosis : *Duchenne Muscular Dystrophy*

A 9 year old male was diagnosed with DMD at the age of 4 years. It began with difficulty in climbing stairs and getting up from the floor. There had been gradual progressive lower limb weakness with difficulty in walking. He had stopped walking independently at the age of 7 years. He also had difficulty in performing overhead activities. Neurologically, he was hypotonic and hyporeflexic. All his sensations were intact. He had grade 2+ strength in bilateral lower limb and grade 3+ strength in bilateral upper limb with proximal muscle weakness more than the distal muscles. On examination, he had hypertrophy of bilateral calf and deltoid. Functionally, he required assistance for his activities of daily living. He was wheelchair bound for mobility. On FIM he scored 85.

On investigation, the serum creatine phosphokinase levels were raised to 5144 IU Genetic analysis revealed exons deletions (51 & 52) in the dystrophin gene EMG revealed generalized intrinsic muscle disease. The examination showed an excess of myopathic potentials at all the sites. Spontaneous positive potentials were noted in the right medial Gastrocnemius and right Biceps.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Rectus Abdominis, Quadriceps and Peronei.

Clinical Improvements seen After Stem Cell Therapy

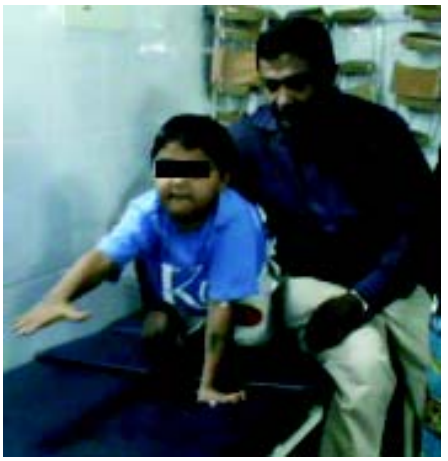
Functionally : On follow up at the end of 4 months, he reported feeling of wellbeing and improved stamina. He had developed TendoAchilles tightness and attitude of equinnus feet bilaterally, so he was given serial casting to stretch it and it released TA , thereby improving ankle dorsiflexion range. He reported improved strength in his limbs and trunk muscles. He could stand with the help of bilateral push knee splints and high boots with posterior steel shank and walker, thereby leading to improved bone density and toning of muscles. Also his knee strength had improved and he could hold his knees erect in 90 °, while sitting on the edge of the cot, therby showing improved knee musculature strength. FIM score has improved from 85 to 92.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	5144 IU	3878 IU

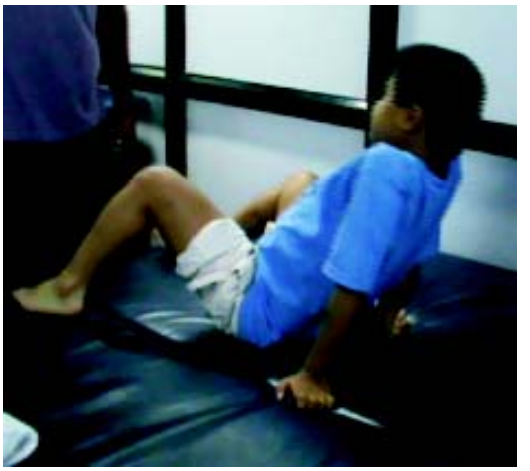
Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	HIP	Before therapy	After therapy
1	2+	Extensors	1	2+
2	2++	Abductors	2	2++
2	2++	Adductors	2	2++
		KNEE		
3	3+	Flexors	3	3+
3-	3+	Extensors	3-	3+
2	2++	ABDOMINALS		

Electrophysiologically : Pre therapy EMG of right vastus medialis, right medial gastrocnemius, right deltoid, right biceps, left gluteus maximus and left lateral hamstrings showed an excess of myopathic potentials at all sites of examination. On repeating the EMG of all muscles again at the end of 6 months, right vastus medialis and right medial gastrocnemius showed improvement in terms of normal motor unit potentials with complete interference pattern.



Improved ability to perform all fours and reach outs, thus showing improved trunk control.

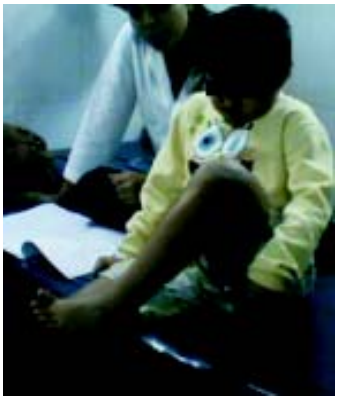


Improved ability to perform shifting on the cot .

Improved lower extremity and lower abdomen strength, and ability to perform lower leg raising.

Improved trunk strength and ability to stand with bilateral push knee splints with minimum assistance of the wall.

Standing with Splints



Improved hip flexor strength and ability to raise hip in sitting on the edge of the cot.

Case Report - 35

Diagnosis : *Duchenne's Muscular Dystrophy*

A 12 year old patient, gave history of bilateral lower limb weakness since the age of 3 years. He reported that he experienced difficulty in getting up from the floor and climbing stairs. Initially, which later progressed to walking on toes and increasing frequency of falls. Gradually the upper limb weakness also developed leading to decreased ability to perform overhead activities. Neurologically, he was hypotonic and hyporeflexic with intact sensations. Manual muscle assessment revealed that he had grade 3 strength in bilateral lower limbs and grade 3++ in bilateral upper limbs with predominantly proximal muscle weakness . On examination, he had pseudohypertrophy of bilateral calf muscles and bilateral knee flexion contracture ~ 40° and Tallipo Equino Varus attitude of foot. Functionally, he needed assistance for a few ADL. He walked with a bilateral flexed knee and wide base of support and Trendelenberg's Gait (i.e. in a modified way, with hands in his pocket).He was currently on a very low dose steroid. On FIM, he scored 110. On Brookes scale, he scored 2 and on Vignos scale 3.

On investigation, raised serum creatinine phosphokinase levels and EMG revealed primary muscle etiology. DNA analysis of the dystrophin gene revealed deletions in the promoter region confirming the diagnosis of DMD. MRI of the upper and lower limbs before the stem cell therapy revealed: diffuse fatty infiltration of the muscles of the trunk, pelvis,thighs and legs, with maximal involvement of the gluteal muscles, adductor magnus and vasti, with partial involvement of other muscle groups.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Quadriceps, Abdominals, Adductors, Tibialis Anterior, Peronei.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: On follow up, at the end of 3 months, he reported feeling of wellbeing and improved stamina. Earlier he would fatigue out, during the day, but post therapy, he could sustain exercises, without any complaints of tiredness. His trunk and lower limb strength increased with increased stability while walking. Earlier he would walk with flexed knees and wide base of support with episodes of frequent falls while walking, but post therapy as he was recommended, bilateral push knee splints and elbow crutches, he was able to walk with improved stability and for longer distance, without fear of fall. His base of support had reduced and he would walk on plantigrade feet.

	Before stem cell therapy	After stem cell therapy
Creatinine Phosphokinase levels	8856 IU	3950 IU

Improved Upper Limb strength and ability to perform overhead activity with weights.

Exercises to improve trunk strength and perform squatting exercises.

Improved Gait and ability to walk with bilateral push knee splints and elbow crutches, and finally walking without aid.

Case Report - 36

Diagnosis : *Muscular Dystrophy*

A 22 year old musician/guitar player gave history of delayed motor milestones with early fatigability while "toddling". Parents noticed that he used to walk in an abnormal pattern, with stiff knees, slightly bent and on toes. He also had inability to squat down or get up from that position since the age of 7. Gradual progressions in weakness lead to difficulty in climbing stairs as well as in walking. He experienced breathlessness on exertion, most probably, due to his cardiomyopathy and low LV function(EF-35%).He also had multiple contracture in both upper and lower limbs(listed below), due to which walking was more difficult. He met with an accident (2003) which leads to an injury to his right knee joint, due to which he had stopped walking. He also had mild weakness in his upper limb muscles.

Neurologically, he was hypotonic and hyporeflexic. On examination all sensations were intact. He had grade 3++ muscle power in bilateral upper extremities and grade 3 in bilateral lower extremities with grade 2 trunk muscle strength. On examination he had the following contractures bilaterally, such as, knee flexion ,hip extension,elbow flexion and pronator contracture, with TA tightness. He could walk independently till the age of 15 years. Functionally, he needed assistance in few ADL and used modified chair for mobility. On FIM he scored 108.

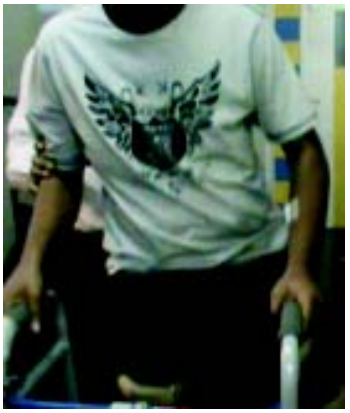
On investigations,the serum creatine phosphokinase levels was slightly raised. Electromyography studies were suggestive of primary muscle disease, while the muscle biopsy done at the age of 5 years (from gastronemius Muscle) did not reveal any anamoly. MRI of the upper and lower limbs before the stem cell therapy revealed diffuse severe fatty infiltration of all visualized muscles of both UL and LL with decreased muscle bulk.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally Quadriceps, Adductors, Glutei, Triceps and Abdominals.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina, with ability to sustain exercises for longer. He also reported significantly reduced fatigue, which was his common compliant prior to the therapy. His trunk strength had improved with ability to perform crawling and back extensions with ease during exercise sessions. He was recommended bilateral push knee splints and walker, and he could easily walk with it for almost 20 -30 steps at a time, after 6 months of immobility. Gradually he progressed and began to walk with push knee splints alone. He also reported improved flexibility of all joints with increased range of motion in them.

Improved upper limb strength and ability to do resisted theraband exercises.



Walking with bilateral push knee splints and walker.

Back extensor strengthening activity on swiss ball.

Improved trunk strength and ability to perform quadruped position.

Case Report - 37

Diagnosis : *Limb Girdle Muscular Dystrophy*

Clinical presentation : A 24 year old, college going female gave a history of hypertrophied calf muscles, noticed on routine evaluation at the age of 16 years. On investigation, serum CPK was found to be high and muscle biopsy was suggestive of mitochondrial myopathy. Gradually, she started developing lower extremity weakness at the age of 14-15 years with difficulty in climbing stairs and running.

Neurologically, she was hypotonic and hyporeflexic with intact sensations. On examination, she had grade 2++ strength in bilateral lower extremities and bilateral upper extremities with proximal muscle weakness more than distal. She had pseudohypertrophy of bilateral calf muscles and bilateral genu recurvatum on standing. She reported no family history of muscular dystrophy. Functionally, she was independent in most ADL and needed assistance while squatting and getting up from bed. She had stopped climbing stairs since 2 years. On FIM she scored 109.

On investigations,the serum creatine phosphokinase level was raised. Electromyography studies revealed myopathic changes, while the muscle biopsy was suggestive of mitochondrial myopathy.

MRI of the upper and lower limbs before the stem cell therapy revealed extensive fatty infiltration of most muscles of the pelvic girdle, thighs , legs with mild infiltration of the upper limb muscles.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Deltoid, Glutei, Quadriceps, Hamstrings, Peronei, Tibialis Anterior, Back extensors and Abdominals.

Clinical Improvements seen After Stem Cell Therapy.

Functionally : At the end of 3 months, she reported feeling of wellbeing and improved stamina, as effort required to perform the activities of daily living was reduced significantly. Her trunk control and lower limb muscles increased in strength with improved stability in standing .She even reported reduction in frequency of falls while walking. She also felt ease and independence in standing from lower level surfaces, like chair or sofa , which were totally dependent prior to the therapy. Her upper limb strength had increased with ability to perform overhead activities like bathing ,upper body dressing, etc.

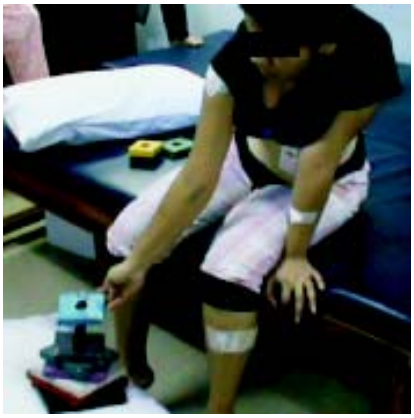
	Before stem cell therapy	After stem cell therapy
Creatinine Phosphokinase levels	563 IU	154 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		MUSCLES	LEFT	
Before therapy	After therapy	HIP	Before therapy	After therapy
1	2+	Extensors	1	2+
2	2++	Abductors	2	2++
2	2++	Adductors	2	2++
		ANKLE		
2	3++	Evertors	2	3++
3	3++	Plantarflexors	3	3++
1	2++	ABDOMINALS	1	2++

Improved trunk strength and ability to perform activities in quadruped position

Exercises to improve abdominal strength.



Exercises to improve dynamic sitting balance and reach out activities

Improved trunk strength and ability to perform crawling on bed.

Case Report - 38

Diagnosis : *Muscular Dystrophy*

Clinical Presentation: A case of a 30 year old male patient with history of bilateral lower extremities muscle weakness and wide based gait since 2002. He also started noticing grip strength weakness. He had stopped walking independently since about a year ago. He also had history of convulsions since 2001, which had not been treated adequately, hence still had episodes of seizures at the frequency of once per 4 months. He also had a coincidental finding of a syrinx at C3 to D2 although there were corresponding symptoms .

Neurologically, he was hypotonic and hyporeflexic. On examination, he had no sensory symptoms or signs. On motor system evaluation, he had grade 2 muscle power in bilateral lower as well as upper extremities, with predominantly proximal muscle weakness . He had hypertrophy of bilateral calf muscles. He had severely decreased grip strength. Functionally, he was dependent for most of his ADL and transfers. He was wheelchair bound for mobility, but he could walk indoors with 2 person's support and a waddling gait. On FIM he scored 81.

On investigation, the serum creatine phosphokinase levels were raised mildly to 441 IU. EMG was suggestive of primary muscle disease affecting proximal more than distal muscles of upper extremities. NCV study of all four limbs done which showed marked reduced CMAPs and CV in all major motor nerves of all 4 limbs, while SNCV study was normal. MRI musculoskeletal system showed fatty infiltration in muscles and MRI spine showed syrinx extending from C3 to D2.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Deltoid, Triceps ,Biceps, Brachialis, Brachioradialis, Wrist Extensors, Extensor Indicis, Lumbricals, Glutei, Hamstrings, Tibialis Anterior, Peronei, Gastrosoleus, Abdominals and Back Extensors.

Clinical Improvements seen After Stem Cell Therapy.

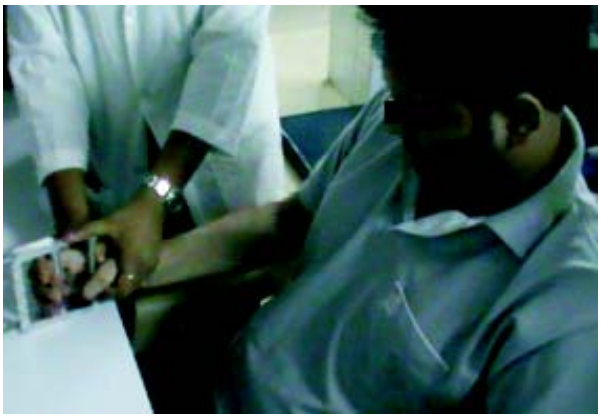
Functionally: On follow up, at the end of 3 months, he reported that the effort required to perform the exercises was reduced significantly. Earlier he would feel fatigued out and lethargic the entire day. His trunk strength improved with toning of his lower limb muscles, so his gait improved in terms of stability. Earlier he would walk with wide based equinnus gait, but post therapy he was recommended high boots with posterior steel shank and his gait got near normal. Gradually his grip strength also increased significantly.

	Before stem cell therapy	After stem cell therapy
Functional Independence Measure	81	82

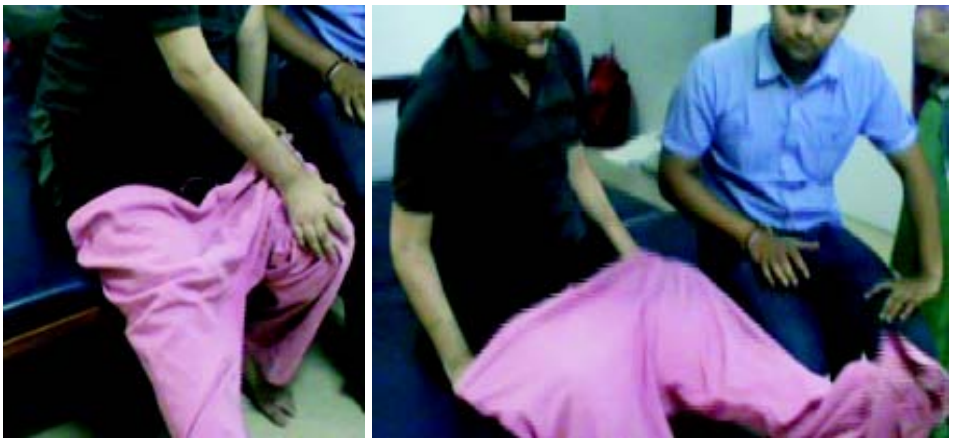
Note: On follow up, at the end of 7 months, his hand intrinsic muscles showed slight deterioration, although the trunk and lower limb muscles sustained the improvement in strength.

Manual Muscle testing : Following muscles showed improved strength

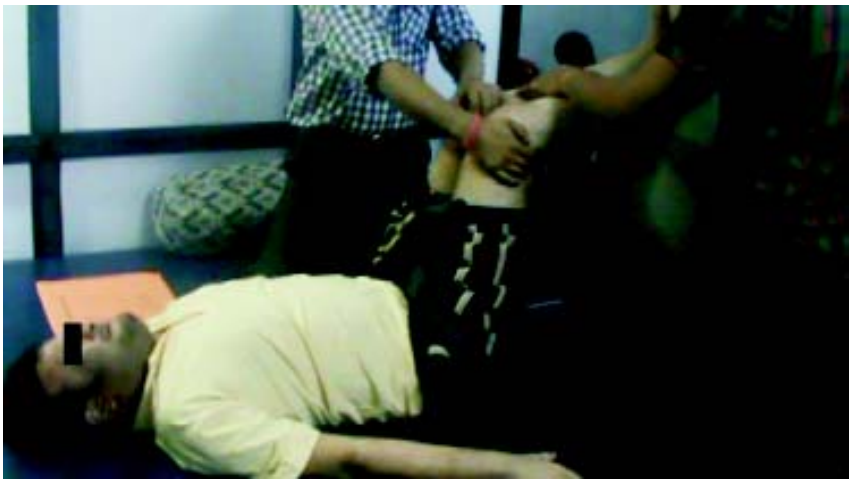
RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**ANKLE**	Before therapy	After therapy
1	2	Evertors	1	2
		SHOULDER		
2	2+	Abductors	2	2+
		WRIST		
1	1++	Extensors	1	1++
3	3+	Opponens Pollicis	3	3+



Exercises to improve grip strength and performing of assisted gripping exercises.



Improved limb and trunk strength with ability to perform lower body dressing independently



Improved lower limb strength and ability to perform lower abdominal strengthening Swiss ball activity.

Case Report - 39

Diagnosis : *Congenital Muscular Dystrophy*

Clinical presentation : A 6 year old female born of a consanguineous marriage , with a history of full term C-section twin delivery had history of delayed milestones with neck holding achieved at 9 months of age and sitting balance at 1 ½ years. The child never crawled, stood and walked. On consulting a paediatric neurologist and upon investigations, she was diagnosed as a CMD. Her twin sibling (identical twin) also was found to be afflicted with the same disease.

Neurologically, she was hypotonic and hyporeflexic. On examination, she had intact sensations. She had grade 1 muscle power in bilateral lower extremities and grade 2 in bilateral upper extremities with proximal muscle weakness more than distal with good grip. She had attitude of lower extremities being in hip abduction and external rotation with knee flexion. She had congenital hip dislocation with hip ligament laxity. Functionally, she was dependent on her mother for all ADL and mobility. On FIM she scored 48.

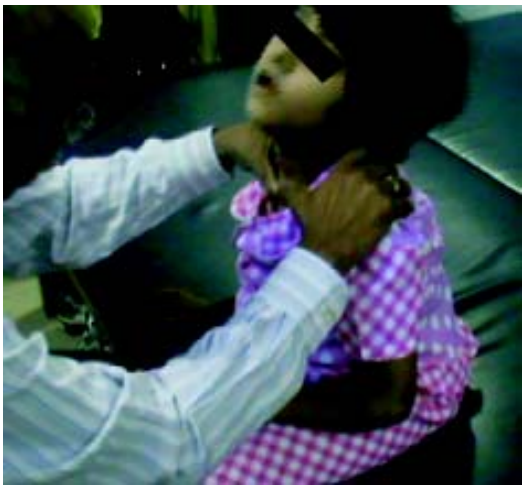
On investigations,the serum creatine phosphokinase levels was raised to 1187 IU. Electromyography studies were suggestive of primary muscle disease. Muscle biopsy showed presence of primary muscle disease as the histological report depicted that the fascicular architecture was partly effaced and there was hyalinization, necrosis, myophagocytosis and an occasional regenerating fibre was present along with moderate numbers of hypertrophic fibers. Immunostaining with monoclonal antibodies confirmed the diagnosis. MRI of the upper and lower limbs before the stem cell therapy revealed variable fatty infiltration along with loss of muscle volume.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Deltoid, Biceps, Triceps, Glutei, Quadriceps, Abdominals and Back Extensors.

Clinical Improvements seen After Stem Cell Therapy.

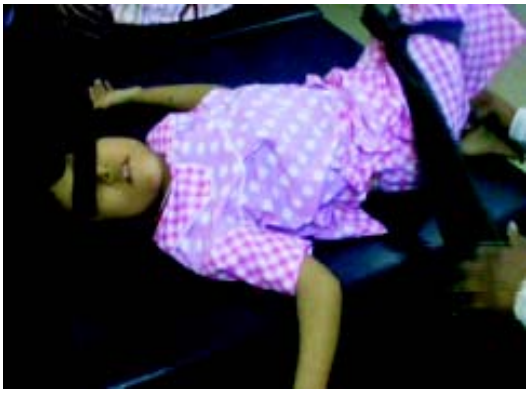
Functionally: At the end of 3 months, mother reported feeling of wellbeing and improved stamina in child , with ability to sustain exercises for longer. Her neck musculature increased in strength with improved neck holding. Her grip strength had increased with ability to perform peg activities with ease, which she could not do prior to the therapy. Her trunk control and strength had increased and mother reported that she started to sit erect and for longer duration, post therapy, thus showing improved sitting balance. Overall her body musculature improved with toning of all muscles.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	1187 IU	1100 IU

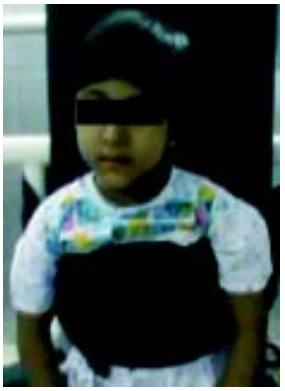


Neck Muscle strengthening exercises.

Upper limb strengthening exercises, to improve overhead activities



Exercises to strengthen trunk muscles.



Standing on the standing board, showing improved neck holding .

Case Report - 40

Diagnosis : *Congenital Muscular Dystrophy*

A 6 year old female born of a consanguineous marriage, with a history of full term C-section twin delivery had history of delayed milestones with neck holding achieved at 9 months of age and sitting balance at 1 ½ years. No crawling, standing, walking was noticed. On consulting a pediatric neurologist and upon investigations, she was diagnosed as a CMD. Her twin sibling (identical twin) also was found to be afflicted with the same disease.

Neurologically, she was hypotonic and hyporeflexic. On examination, she had intact sensations. She had grade 1 muscle power in bilateral lower extremities and grade 2 in bilateral upper extremities with proximal muscle weakness more than distal with good grip. She had attitude of lower extremities being in hip abduction and external rotation with knee flexion. She had congenital hip dislocation with hip ligament laxity. Functionally, she was dependent on her mother for all ADL and mobility. On FIM she scored 49.

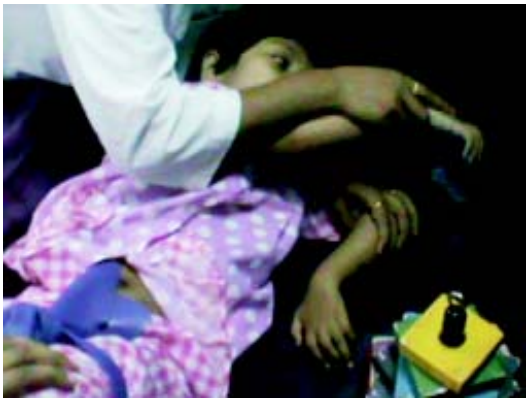
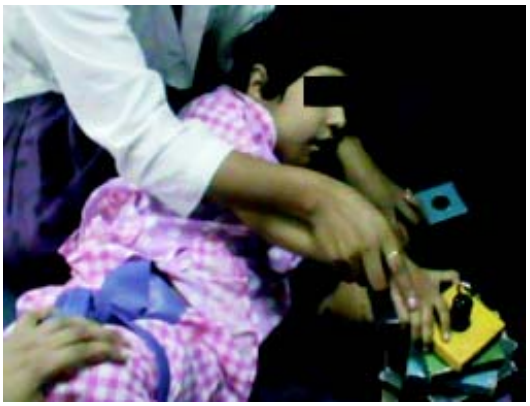
On investigations,the serum creatine phosphokinase levels was raised. Electromyography studies were suggestive of primary muscle disease, while the muscle biopsy immunostaining reveals Merosin positive Congenital muscular dystrophy. MRI of the upper and lower limbs before the stem cell therapy revealed extensive fatty infiltration of the pelvic girdle, thigh, leg muscles and moderate fatty infiltration in the upper limb muscles.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally Glutei, Quadriceps, Deltoid, Biceps, Triceps, Abdominals and Back Extensors.

Clinical Improvements seen After Stem Cell Therapy

Functionally: At the end of 3 months, mother reported feeling of wellbeing and improved stamina in child, with ability to sustain exercises for longer. Her neck musculature increased in strength with improved neck holding. Her trunk strength also improved with ability to sit independently on the edge of the cot, without any support. Also the caretaker reported ease in transferring her, which was difficult prior to the therapy. Her grip strength increased with ability to hold objects easily and harder. She was also able to perform over head activities with ease. Mother reported that all her muscles were more toned as compared to prior therapy.

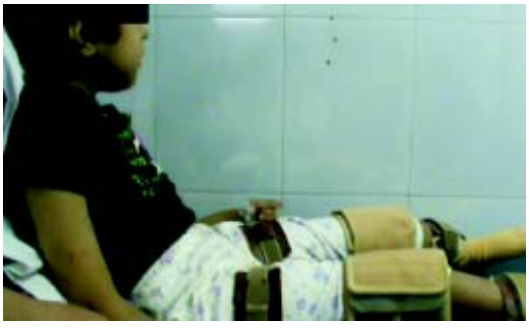
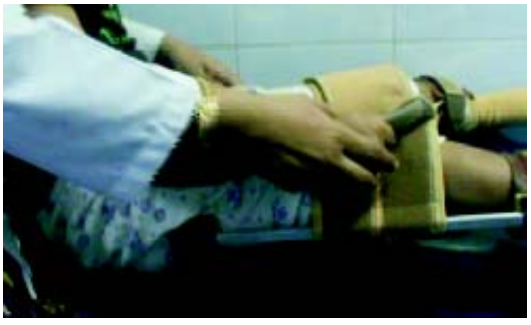
	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	1125 IU	720 IU

Improved upper limb and grip strength, with ability to grasp objects.

Increased upper limb strength and ability to perform resisted theraband exercises.

Improved neck control and ability to hold neck erect in sitting position.

Improved trunk strength and upper limb strength with ability to remove calipers with assistance.

Case Report - 41

Diagnosis : *Muscular Dystrophy*

A 30 year old male diagnosed with muscular dystrophy since past 10 years. It began with sudden onset of weakness in bilateral lower limb.

Neurologically, he was hypotonic & hyporeflexic. He had Grade 2 strength in his shoulder & pelvic girdle muscles & Grade 4 strength in his bilateral upper limb & lower limb distal muscles. He had intact sensory system with bladder and bowel control. Attitude of his bilateral lower limb is hyperextension of knees of approximately 20 degree in standing. His bilateral quadriceps shows tightness with knee flexion RDM of about 40 degree. Functionally, he needed assistance in all his activities of daily living except bathing. Presently, he was wheelchair bound. On FIM he scored 70

On Investigation, electromyography studies suggested myopathic process which was further confirmed by muscle biopsy which showed fibrofatty tissue with no muscle.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Biceps, Anterior and Middle Fibers of Deltoid.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: On follow up, at the end of 3 months, he reported feeling of wellbeing and improved stamina. He could perform all exercises with ease.

His upper extremity strength improved and he got independent in activities of daily living like dressing, combing and feeding himself. He improved in his socio-economic and vocational conditions, as post therapy he was able to go to his workplace by driving on a scooter with two extra wheels fitted on the sides. He was able to transfer to his seat straight from the scooter without anybody's help. But, needed assistance to get back to his house. He even reported improved lower limb strength. His functional status and his confidence increased tremendously, thereby leading to improved quality of living.

	Before stem cell therapy	**After stem cell therapy**
Functional Independence Measure	70	72

Manual Muscle testing : Following muscles showed improved strength

RIGHT		MUSCLES	LEFT	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
1	2	Abductors	1	2
1	2	Adductors	1	2
		KNEE		
1	2	Flexors	1	2
0	2	Extensors	0	2
		SHOULDER		
2	3	Triceps	2	3

Improved Upper limb strength and independence in upper body dressing.

Case Report - 42

Diagnosis : *Muscular Dystrophy*

A 40 year old female, case of LGMD, since 1986 gave history of sudden onset of lower limb weakness leading to difficulty in walking, which progressed to weakness in upper limbs.

Neurologically, she was hypotonic, hyporeflexic with intact sensations, including bladder and bowel control. She had Grade 2 power in bilateral proximal shoulder and hip girdle muscles and Grade 4 strength in distal muscles of both upper and lower limbs. She had an attitude of hyperextension (approximately 45 degree) in bilateral knees on standing. Functionally, she was dependent on her husband for all her activities of daily living, except eating and was wheelchair bound for mobility. On FIM she scored 94

On Investigation, the electromyography and nerve conduction studies showed generalized primary muscle disease affecting the proximal and semidistal muscles of upper and lower limbs. The muscle biopsy of left quadriceps showed myopathic change which was severe and of very long duration with excessive replacement fibrosis.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Anterior, middle and posterior fibers of Biceps and Deltoid muscles, Glutei muscles, Vastus medialis, Rectus femoris in Quadriceps muscles, Gastronemius and Soleus.

Clinical Improvements seen After Stem Cell Therapy

Functionally: on follow up after 3 months, she reported feeling of wellbeing and improved stamina. Gradually, her endurance had improved with ability to sustain exercises without complaints of fatigue. Her trunk and upper limb musculature improved in strength, with ability to perform activities like sitting on the edge of the cot without assistance and cutting vegetables. Also, her mobility in the bed like rolling, getting up from lying to sitting had become independent.

Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
3	3+	Abductors	3	3+
		ANKLE		
0	1+	Peronei (Evertors)	0	1+
		SHOULDER		
2	2+	Abductors	2	2+
1	3	Internal Rotators	1	3
1	3	External Rotators	1	3
0	1+	Brachialis	0	1+

Improved trunk control and upper limb strength, with ability to dress upper body independently.

Improved dynamic sitting balance and upper limb strength, with ability to comb and groom independently.

Case Report - 43

Diagnosis : *Duchenne Muscular Dystrophy*

A 13 year old male diagnosed with DMD, which started with difficulty in walking, climbing stairs and frequent falls. Gradually, the weakness became progressive. From past 3 years, he had stopped walking. Neurologically, he was hypotonic and hyporeflexic with intact sensations. He had grade 1 muscle power in his bilateral lower limb muscles and grade 2++ in his bilateral upper extremity muscles. He had bilateral equino varus deformity in his foot. On examination, he showed pseudohypertrophy of bilateral calf muscles and generalized obesity. Functionally, he was dependent on the caregiver for all his activities of daily living. He attended a regular school and continued with his education. He was wheel chair bound for mobility. On FIM, he scored 53. On Brooke and Vignos scale he scored 3 and 9 respectively.

On investigation, his electromyography and nerve conduction studies suggested of myopathic pattern, without any signs of active denervation.

Clinical Improvements seen After Stem Cell Therapy.

Functionally : At the end of 3 months, he reported that the effort required to perform the exercises was reduced and his stamina had increased. He also had increased trunk strength and could perform dynamic sitting balance on an uneven surface like a Swiss ball. Also his mat activities like rolling and turning on bed had become independent, which was very difficult for him earlier.

Improved trunk control and ability to sit without any assistance.

Improved mat exercise endurance, with ease in performing exercises.

Case Report - 44

Diagnosis : *Muscular Dystrophy*

A 20 year old male presented with a history of sudden onset of bilateral calf pain and weakness in legs in 2002. Following which he was diagnosed to be suffering from a primary muscle disease. He had difficulty in walking, climbing stairs and getting up from floor. He also had a history of frequent falls while walking due to buckling of legs.

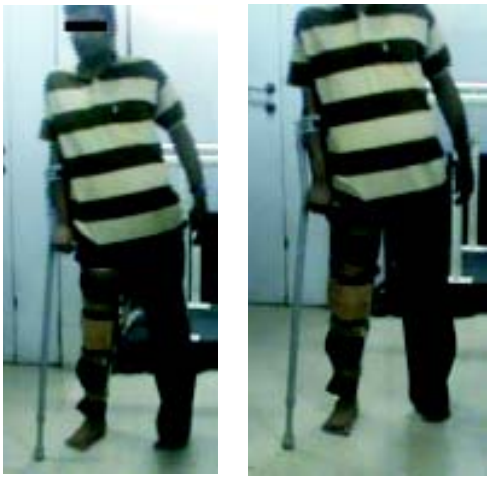
On assessment, neurologically, he was hypotonic and hyperreflexic with intact sensations. He had grade 3++ strength in both upper and lower limb muscles, with predominant antigravity muscle weakness. On examination, he showed hypertrophy of bilateral calf and deltoid muscles. He had bilateral tendoachilles tightness. Functionally, he was independent in all his activities of daily living but had difficulty in getting up from floor. He could walk independently, with a wide base gait or with minimal assistance, e.g. walking by holding walls. On FIM he scored 119.

On investigation, serum creatine phosphokinase levels were raised to 8140 IU/ml and muscle biopsy showed evidence of primary muscle disease.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei and Rectus Femoris, Vastus Medialis and Vastus Lateralis in Quadriceps Muscles.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported that the effort required to perform the exercises was reduced. Earlier, he would feel fatigued out and lethargic throughout the day. His trunk strength improved with ability to perform bridging and crawling activities independently. Since, he had wide based hyperlordotic equinnus gait prior to the therapy and he would walk only indoors due to scare of fall, his social life was severely affected. During physical therapy sessions he was recommended an elbow crutch and one push knee splint, to prevent falls due to buckling of knees. Improved stability in walking with elbow crutch enabled him to socialize outdoors, without fear of fall, and improved his quality of life.



Walking with one elbow crutch and push knee splint, giving stability and mobility to patient.

Improved trunk control and ability to perform bridging.

Improved trunk control and ability to perform crawling .

Case Report - 45

Diagnosis : *Muscular Dystrophy*

A 10 year old male presented with a history of progressive bilateral lower limb weakness since 3 years. He had difficulty in walking, climbing stairs, getting up from the floor and frequent falls while walking.

Neurologically, he was hypotonic and hyporeflexic with intact sensations. He had grade 2 strength in bilateral lower limbs and grade 3+ in bilateral upper limbs with predominant abdominal weakness. On examination, he showed pseudohypertrophy of bilateral calf muscles.

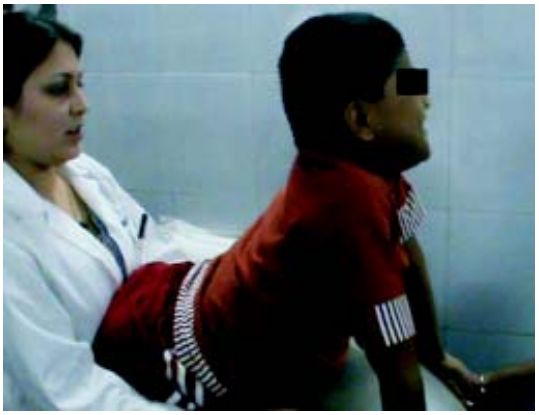
Functionally, he was independent in all his activities of daily living, but needed a little longer time to complete them. He moved about in the house, by crawling on all fours, otherwise he was wheel chair bound for mobility. On FIM, he scored 102.

On investigations, the serum creatine phosphokinase levels were raised to 5026 IU. Electromyography studies were suggestive of primary muscle disease.

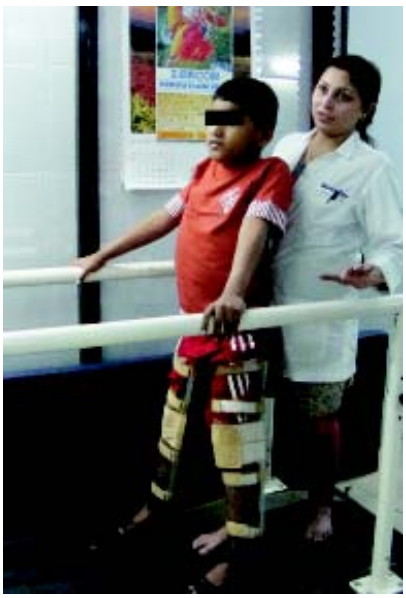
Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina, as effort required to perform the activities of daily living was reduced significantly. He reported improved upper limb strength and ease in performing overhead activities, as opposed to earlier when he would fatigue out in activities like combing ,shampooing his hair and reach outs for things on overhead shelves. He had never received any formal rehabilitation and due to progressive weakness in limbs, had stopped walking completely, since 6 months prior to the therapy. He had also started developing Talipo Equino Varus deformity of both feet and bilateral knee flexor tightness. Immediately after the therapy he was prescribed knee ankle foot orthosis (KAFO) and was given extensive gait training along with muscle strengthening exercises and stretching for tight muscles. Within one and half month post therapy, he showed increased lower limb and trunk strength and had started to walk independently with KAFO.

Improved Upper limb strength and ability to perform overhead activity, like throwing and catching ball.



Improved back extensor strength and ability to perform back extension and push up on Swiss ball.



Improved trunk strength and ability to stand independently and walk inside the parallel bars with KAFO.

Case Report - 46

Diagnosis : *Duchenne Muscular Dystrophy*

16 year old male, a case of DMD presented with history of frequent falls while walking. Gradually, he started developing lower limb weakness. He could walk on toes till age of 12 years and then stopped walking. Later, upper limb weakness developed with difficulty in over head activities. Gradually, he started developing scoliosis, due to faulty posture. Neurologically, he was hypotonic and hyporeflexic.

On examination, he had all his sensations intact. He had grade 1 strength in bilateral upper limb and lower limb proximally and grade 3 strength in bilateral upper limb and lower limb distally. He also had bilateral knee, hip and feet contractures and deformity with kyphoscoliosis of the spine.

Functionally, he was dependent on the caretaker for all his activities of daily living. He was wheelchair bound for mobility. He had undergone autologous stem cell transplant in 2004 at AIIMS in New Delhi and had also undergone allogenic stem cell transplant in 2005 at New Zealand. No significant improvements were noticed after both the transplants. On FIM he scored 54

On investigations, the serum creatine phosphokinase levels were raised to 40,180 IU and electromyography studies were suggestive of primary muscle disease

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Quadriceps, Peronei longus and brevis, Glutei, hamstrings, Adductors of lower limbs, Abdominals, Back extensors, Biceps, Triceps and Deltoid.

Clinical Improvements seen After Stem Cell Therapy

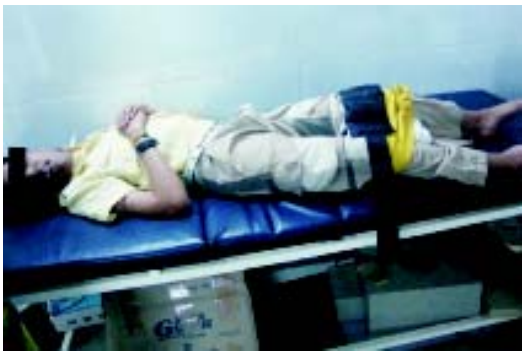
Functionally: On follow up after 3 months, he reported feeling of wellbeing and improved stamina, as effort required to perform exercises during rehabilitation was reduced significantly and he could appreciate the contraction of muscles while exercising which was not present before. His neck and shoulder girdle strength had increased with improved neck holding capacity. His trunk strength, mainly abdominals and back extensor strength had increased, with improved dynamic sitting balance. He could also perform reach outs and could lift objects from ground, while being seated on the bed. He also could perform activities of daily living like brushing independently, as his grip strength had increased, (as assessed and documented by the dynamometer objectively). He got independent in bed mobility like rolling, turning on the bed, etc which needed a lot of assistance earlier. Also his caretaker reported that, lifting and transferring him had become easier as he himself was able to assist in the act and shift his body weight partially. At the end of 6 months, he started to stand independently with bilateral push knee splints and walker, for 15 minutes at a time. His spine curvature, which was kyphoscoliotic, had also straightened up minimally, due to toning up of postural muscles. He had multiple joint contractures like bilateral hip knee flexion and

elbow flexion, but all his tightness had started to reduce with opening up of the joints, due to sustained stretching and weight bearing while standing.

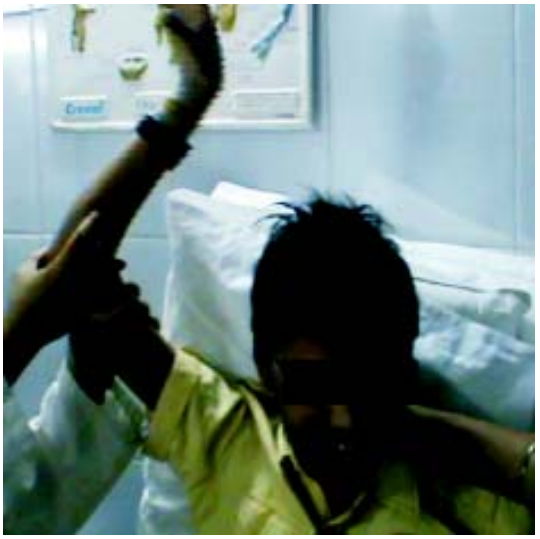
	Before stem cell therapy	After stem cell therapy
Functional Independence Measure	54	58
Creatinine Phosphokinase levels	3000 IU	700 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**Elbow**	Before therapy	After therapy
1	1++	Biceps	1	1++
1	2+	Triceps	1	2+
1	1++	Brachioradialis	1	1++
1	1++	Brachialis	1	1++
2+	3++	Opponens pollicis	2+	3++
1	2	**ABDOMINALS**		



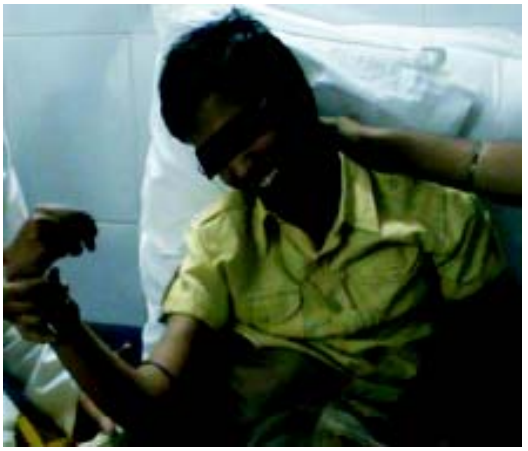
Stretching of hip and knee flexion contractures



Exercising for the triceps, to increase elbow extensor strength.

Strengthening exercise for lower abdominal muscles.

Improved back and neck extensor strength.



Improved sitting tolerance and balance.

Case Report - 47

Diagnosis : *Muscular Dystrophy*

A 16 year old, a known case of DMD with history of bilateral lower limb weakness noticed at the age of 7years with a tendency of walking on toes and frequent falls while walking. He could walk till the age of 9 years. After that the weakness progressed and he has been bedridden.

Neurologically, he was hypotonic and hyporeflexic. All his sensations were intact. He had grade 1 strength in bilateral lower limb and upper limb muscles. He was extremely overweight. Functionally, he was totally dependent on the caretaker for all his activities of daily living. He was wheelchair bound for mobility. On FIM he scored 58. On investigation the creatine phospho kinase levels were raised to 7630 IU. Electromyography studies revealed end stage myopathic disease. Muscle biopsy showed end stage muscle disease.

Clinical Improvements seen After Stem Cell Therapy

Functionally: He was grossly overweight prior to the therapy, but 3 months post therapy, he reported feeling of wellbeing and improved stamina, as effort required to perform the activities of daily living was reduced significantly. His upper limb strength had increased, with ability to raise hands and attempt to do day to day activities like eating. His trunk strength had increased with improved dynamic sitting balance. He had gross weakness and deformities like bilateral hip knee flexion contracture and bilateral Talipo Equino Varus but gradually, the contractures started loosening up as flexibility in his muscles had increased due to regular sustained stretching, during physical rehabilitation session.

Improved sitting balance and ability to push up on hand sideways to sit upright.

Improved ability to do independent wrist extension exercises.

Improved trunk strength and ability to perform sit ups, while exercising.

Case Report - 48

Diagnosis : *Muscular Dystrophy*

A 15 year old male, had a history of frequent falls and difficulty in climbing stairs since the age of 9 years. Gradually, weakness in bilateral lower limb progressed and bilateral upper extremity weakness also developed. He also complained of urgency of urination since 4 years with history of night bedwetting.

Neurologically, he was hypotonic and hyporeflexic. All his sensations were intact. He had grade 2+ strength in bilateral upper limb and lower limb proximally and grade 3++ in all four limbs distally (proximal muscle weakness was more than the distal muscles). On examination, he had bilateral pseudohypertrophy of calves, deltoid and triceps. He had bilateral TA tightness and bilateral knee flexion contracture ~ 15°. Functionally, he was independent in most of his activities of daily living, but performs them in a modified manner. He had a Lordotic and Equinnus gait and also showed Gowers' sign. On FIM he scored 70.

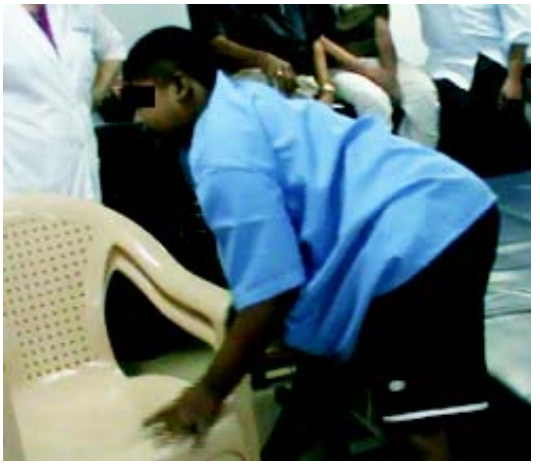
On investigations, the serum creatine phosphokinase levels were raised. Electromyography studies were suggestive of primary muscle disease. The 2 D Echo revealed Cardiomegaly and Cardiomyopathy with Ejection Fraction of 25%.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally glutei,hamstrings,quadriceps.

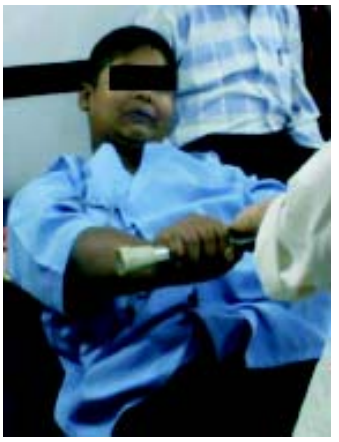
Clinical Improvements seen After Stem Cell Transplant

Functionally: At the end of 6 months, he reported feeling of wellbeing and increased stamina as effort required to perform the exercises and activities of daily living was reduced significantly. He reported increased strength in his limb and trunk muscles, with ease in all movements. His movements in bed like rolling, getting up from supine to sit position, shifting on the edge of the bed, had all become independent as opposed to earlier when, he would need assistance in doing all these activities. As strength of his upper limbs improved, he could perform overhead activities with ease like reach outs, bathing himself (mainly hair bath), etc. With regular exercises and self stretching exercises, his calf muscles had loosened up. Also, as strength of his lower limbs increased, his gait improved significantly. Earlier, he would walk with equinnus wide based gait, (due to tightness and weakness of anti gravity lower limb muscles) but 2 months post therapy, he started walking with plantigrade foot stance and narrow base of support. His abdominal and trunk muscle strength increased, along with improved urine holding capacity, as he had urinary stress incontinence earlier.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	4087 IU	107 IU



Increased Trunk and limb strength with ability to stand independently from the bed.



Increased abdominal strength and ability to perform sit ups, while exercising.

Increased upper limb strength and ability to lift weights.

Case Report - 49

Diagnosis : *Duchenne Muscular Dystrophy*

A 12 year old male, diagnosed with DMD showed a history of frequent falls and difficulty in climbing stairs since the age of 5-6 years. Gradually, weakness in bilateral lower limb progressed and bilateral upper extremity weakness also developed. He could walk till the age of 7-8 years. Neurologically, he was hypotonic and hyporeflexic. He had grade 1+ strength in bilateral upper limb and lower limb with predominantly proximal muscle weakness more than distal. He had all sensations intact. On examination, he had pseudohypertrophy of bilateral calf, deltoid, biceps and triceps muscles. He had bilateral knee flexion,elbow flexion contracture with bilateral Talipes Equino Varus.

Functionally, he was dependent on the caregiver for all his day to day activities and transfers and was wheelchair bound for mobility. On FIM he scored 48. On Broke and Vignos scale he scored 5 and 9 respectively. He had received embryonic cell transplant a year back with minimal improvements.

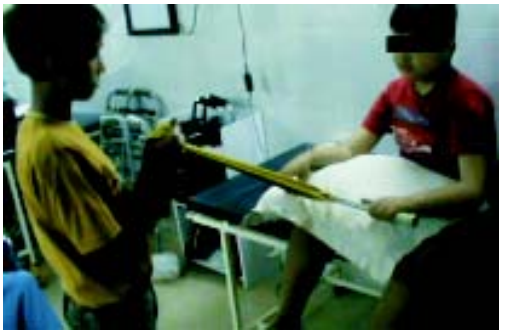
On investigation, the serum creatinephosphokinase levels were raised to 638 IU/ml and electromyography studies showed myopathic changes.

Stem cells were also injected intramuscularly at the motor points of the following muscles: Bilateral Glutei muscles.

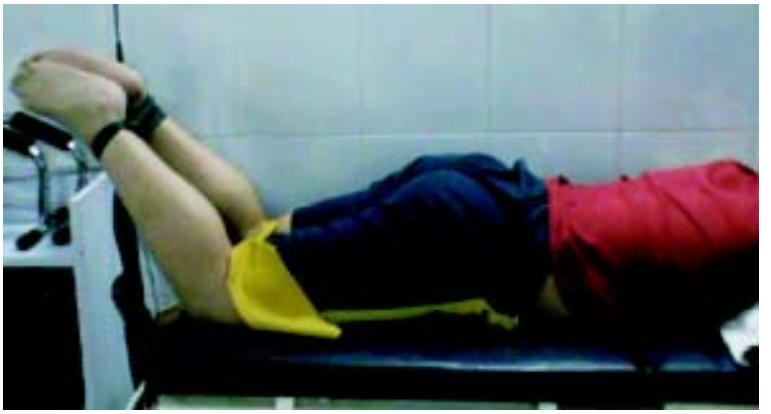
Clinical Improvements seen After Stem Cell Therapy.

Functionally: 3 months after the therapy, he performed all the exercises with less effort. His stamina had also increased. He reported that the flexibility of his calf muscles had improved, earlier they were firm and rigid but gradually they became looser and softer than before. Also the pain, in the calf muscles while stretching them had reduced significantly. He reported increased upper limb and shoulder girdle strength, with improved ability to hold the neck. While performing exercise, during physiotherapy sessions he could perform Swiss ball activities easily; his dynamic sitting balance had improved.

Improved dynamic sitting balance and ability to do Swiss Ball exercises.



Improved Upper limb strength and ability to perform resisted upper limb strengthening exercises with the theraband.



Improved Calf Muscle flexibility and patient compliance to sustained stretching during the therapy, as calf pain and stiffness had reduced.

Case Report - 50

Diagnosis : *Duchenne Muscular Dystrophy*

A 10 year old male, diagnosed with DMD showed history of difficulty in walking and getting up from the floor, at the age of 3. He could walk till the age of 7, but gradually, weakness in bilateral lower limb progressed and he stopped walking. Later, bilateral upper extremity weakness also began with difficulty in performing overhead activities.

Neurologically, he was hypotonic and hyporeflexic. All his sensations were intact. He had grade 2 strength in bilateral lower limb and upper limb proximally and grade 3+ strength distally, in all the four limbs. On examination, he showed predominantly proximal muscle weakness more than the distal muscles. He had bilateral hip and knee flexion contracture of ~ 40º and bilateral Talipe Equino Varus. He had bilateral elbow hyperextension of ~ 25º with excessive carrying angle.

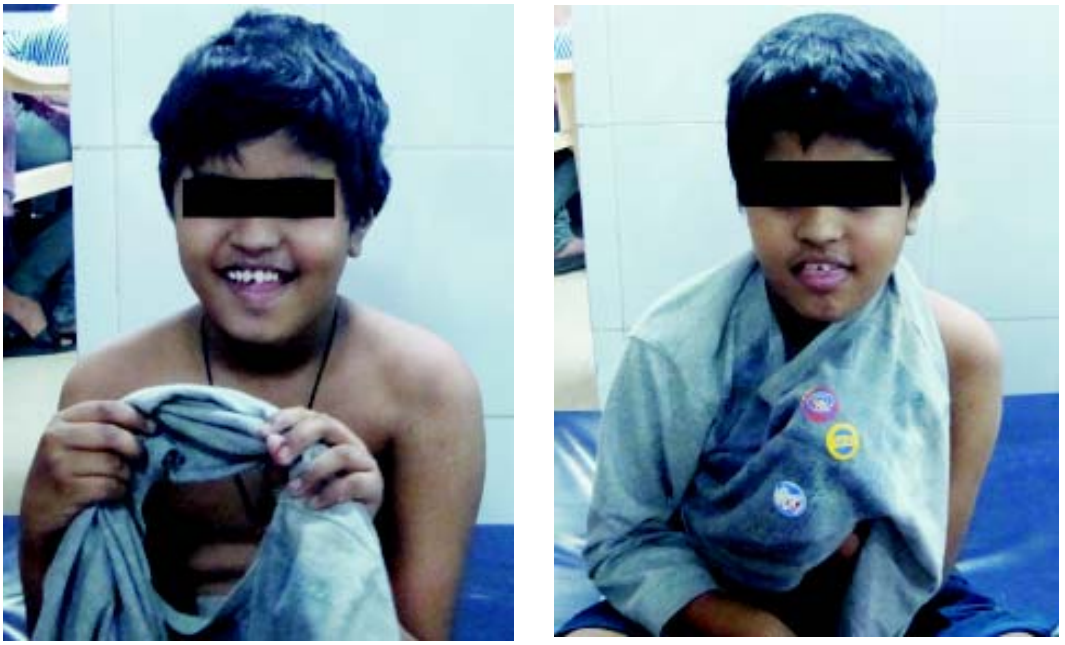
Functionally, he was dependent for most of his activities of daily living and transfers and was wheelchair bound for mobility. He had stopped schooling since 2-3 months, due to gross motor weakness. On FIM he scored 88.

On investigation, his serum creatine phosphokinase levels were raised to 12870 IU. Electromyography studies and muscle biopsy confirmed diagnosis of muscular dystrophy.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Bilateral glutei, deltoid (anterior middle and posterior fibres, quadriceps (vastus medialis, vastus lateralis and rectus femoris) and abdominals (rectus abdominus).

Clinical Improvements seen After Stem Cell Transplant:

Functionally: At the end of 6 months, he reported feeling of wellbeing and improved stamina, as effort required to perform exercises was reduced significantly. His upper limb strength had increased, with ability to raise the upper extremities overhead and perform upper body dressing independently. His grip strength had also increased and could hold and grasp things better than before. His lower limb strength had also increased. He was made to stand on the tilt table thereby leading to improved bone density and toning of muscles.



Improved upper limb strength and ability to perform independently upper body dressing.

Case Report - 51

Diagnosis : *Muscular Dystrophy*

A 13 year old, male had history of delayed motor milestones and difficulty in getting up from the floor at the age of 6-7 years (with Gowers' maneuver), also complained of frequent falls and difficulty in climbing stairs. Progression of weakness had been rapid. Since the past 2 years, he was unable to stand and walk.

Neurologically, he was hypotonic and hyperreflexic with all sensations intact. He had grade 1 strength in bilateral lower limb muscles and grade 2 in bilateral upper limb muscles. On examination, he had pseudohypertrophy of bilateral calf muscles. He had bilateral genu valgum deformity and equinovarus deformity of the foot. Over a period, he had developed right sided scoliosis. Functionally, he was able to do activities using his hands like eating, combing, dressing, etc., but totally dependent on the caregiver for mobility and transfers. He was wheel chair bound for mobility. On FIM he scored 75.

On investigation, the serum creatine phosphokinase levels were raised to 2550 IU and electromyography studies revealed myopathic disease.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei muscles.

Clinical Improvements seen After Stem Cell Therapy

Functionally: Prior to the therapy he had very weak musculature, with all muscles around grade 1 strength. At the end of 3 months post therapy, he reported feeling of wellbeing and improved stamina. His trunk strength had improved with ability to sit up erect from his spine and roll independently on mat; previously, he would sit in a sloughed posture. He also reported ease and independence in performing day to day activities like dressing his lower body, for which he needed lot of manual assistance earlier. He gradually felt increase in upper limb strength as well with ease in feeding himself independently.

Manual Muscle testing : Following muscles showed improved strength

RIGHT		MUSCLES	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
0	1	Adductors	0	1
		KNEE		
0	1+	Extensors	0	1+
		ANKLE		
0	1+	Peronei	1+	0

Ability to perform independent rolling on mat due to improved trunk stability.

Improved grip strength and ability to perform gripping exercises with the gripper.

Improved lower limb strength and ability to perform hip flexor strengthening exercises (suspension therapy).

Improved lower limb strength and ability to perform knee flexor strengthening exercise in suspension.

Case Report - 52

Diagnosis : *Duchenne Muscular Dystrophy*

A 10 year old male with complaints of bilateral lower limb weakness and frequent falls while walking since the age of 3 years. He gradually developed difficulty in climbing stairs and getting up from the floor (Gowers' sign positive). He had upper extremity weakness with difficulty in overhead activities

Neurologically, he was hypotonic and hyporeflexic. All his sensations were intact. He had grade 3- strength in bilateral lower limb and grade 2+ strength in bilateral upper limb with proximal muscle weakness more than the distal muscles. On examination, he had pseudohypertrophy of bilateral calf and deltoid muscles. There was a family history of similar affliction in his elder brother and maternal cousin. Functionally, he was dependent on his mother for assistance in all his activities of daily living. He walked with Lordotic Gait and wide base of support. On FIM he scored 60.

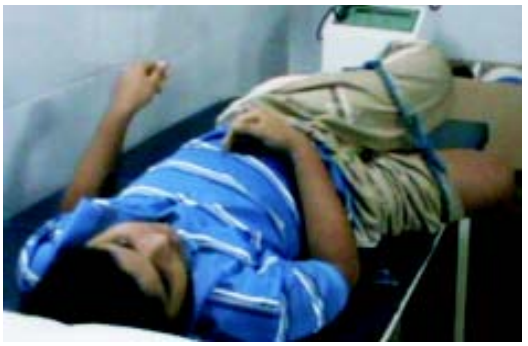
On investigations, the serum creatine phosphokinase levels were 3344 UL. Electromyography studies were suggestive of primary muscle disease and genetic analysis for limited exon deletion in the dystrophin gene did not reveal any mutations.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Deltoid,glutei,quadriceps,abdominals.

Clinical Improvements seen After Stem Cell Therapy.

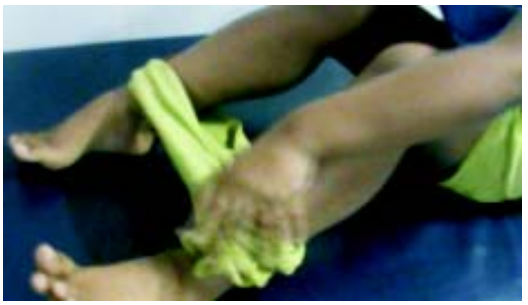
Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina, as effort required to perform all exercises was reduced significantly. He got independent in most of his activities of daily living like feeding, bathing, dressing, for which he would need assistance by the mother earlier.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	3344 IU	2016 IU



Improved lower abdomen strength and ability to perform oblique abdominal strengthening exercises independently.

Improved back and hip extensor strength with ability to come up on all fours position .



Ability to perform lower body dressing independently .

Case Report - 53

Diagnosis : *Muscular Dystrophy*

Clinical Presentation: A 40 year old female having complaints of difficulty in getting up from floor and climbing stairs since 1996, progressed to gradual wasting and weakness of both thigh muscles. Since past 2 years, upper extremity weakness had also begun with difficulty in overhead activities.

Neurologically, she was hypotonic and hyporeflexic with intact sensations. She had grade 2++ strength in bilateral lower limb muscles and grade 3 in bilateral upper limb muscles with proximal muscle weakness >> distal (distal musculature strength - grade 4 in all 4 limbs). On examination, she had hypertrophy of bilateral calf muscles. Functionally, she needed assistance in her ADL. She could walk, but for short distances and had easy fatiguability. On FIM she scored 111.

On investigations,the serum creatine phosphokinase levels were raised(4850 IU). Electromyography studies were suggestive of primary muscle disease, while the muscle biopsy confirmed the diagnosis of muscular dystrophy.

MRI of the upper and lower limbs before the stem cell therapy revealed marked fatty infiltration of the pelvic girdle, thigh (with mild volume loss) and leg muscles bilaterally.Upper limbs were relatively spared with only mild fatty infiltration seen in few arm muscles (such as triceps and brachioradialis).

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally Glutei, Quadriceps, Abdominals, Hamstrings and Deltoid

Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, she reported feeling of wellbeing and improved stamina, as effort required to perform the activities of daily living was reduced significantly .She could sustain exercises for almost 60 minutes, without complaints of fatigue. Her lower limb and trunk muscle strength increased with improved stability and ease in walking .She could walk for longer distances with improved balance and confidence .She could also stand from lower surfaces like sofa, without any aid which was not possible before the therapy. Her upper limb strength also increased with ability to perform overhead reach outs.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	4850 IU	1780 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		MUSCLES	LEFT	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
2	2++	Extensors	2	2++
2	2++	Flexors	2	2++
2	2++	Abductors	2	2++
2	2++	Adductors	2	2++
		KNEE		
1	2	Flexors	1	2
		SHOULDER		
3-	3+	Extensors	3-	3+
3-	3+	Flexors	3-	3+
3	4	Abductors	3	4
2+	3	Adductors	2+	3

Improved trunk strength and ability to perform bridging.

Improved lower abdominal strength

Improved trunk strength and ability to come to quadruped position

Case Report - 54

Diagnosis : *Muscular Dystrophy*

A 45 year old female gave history of bilateral lower limb muscle weakness with difficulty in walking, climbing stairs and getting up from floor since 1990. She could still manage to walk till 2006. Later, about 10 years back, weakness progressed to the upper extremities also.

Neurologically, she was hypotonic and hyporeflexic with all sensations intact. She had grade 1+ strength in bilateral lower limbs and grade 2++ in bilateral upper limbs with proximal weakness >> distal. On examination, she was overweight and had orthopnoea (with difficulty in breathing on lying supine). She had tight tendoachellis bilaterally. Functionally, she needed assistance in few ADL. She could do ground level activities using her upper extremities. On FIM she scored 82. She was wheelchair bound for mobility. On investigations, the serum creatine phosphokinase levels were raised. Electromyography studies were suggestive of primary muscle disease. MRI of the upper and lower limbs before the stem cell therapy revealed severe fatty infiltration in most of the muscles.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Quadriceps, Tibialis Anterior, Peronei, Abdominals, Deltoid, Biceps, Long flexors.

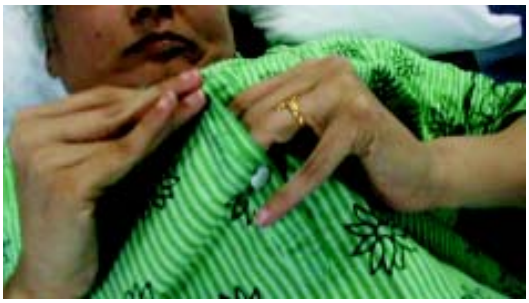
Clinical Improvements seen After Stem Cell Therapy

Functionally: On follow up, at the end of 6 months, she reported feeling of wellbeing and improved stamina. She also reported no fatigue or exhaustion in doing daily activities. Prior to the therapy, she had symptoms of breathlessness on lying supine, but post therapy, her respiratory muscle strength improved with increased lung capacity and she was relieved of her breathlessness by almost 70 %. Her trunk muscle strength increased significantly, with complete independence in bed mobility , like getting up from lying position , sitting to stand and transferring at same level, all of which needed assistance by the caretaker prior to the therapy. Her upper limb and grip strength increased with ability to perform activities of daily living like dressing, feeding, bathing, toilet activities, independently .She was also able to cut vegetables and perform cooking for the family all by herself.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	1206 IU	739 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
1+	2	Extensors	1+	2
1+	2+	Flexors	1+	2+
1+	2+	Abductors	1+	2+
1+	2-	Adductors	1+	2-
		KNEE		
0	1++	Flexors	0	1++
0	1++	Extensors	0	1++
		FOOT		
0	1+	Dorsiflexors	0	1+
		SHOULDER		
2	2++	Flexors	2	2++
1+	2+	Abductors	1+	2+
2+	3	Adductors	2+	3
1	3+	External Rotators	1	3+
0	2	Opponens Pollicis	0	2
2	2+	**ABDOMINALS**	2	2+



Improved fine motor activity and ability to perform buttoning, independently.

Improved trunk strength and ability to pick up objects from floor , by bending trunk.

Improved ability to shift on the edge of the bed independently.

Case Report - 55

Diagnosis : *Congenital Muscular Dystrophy*

A case of a 9 year old female, case of Congenital Muscular Dystrophy with history of left Erb's palsy at birth. She had history of aspiration on 12th day of birth following which her milestones were delayed. She has a family history of similar affliction in her younger brother too. She has family history of mental retardation in paternal aunt and inversion in Y chromosome of father.

Neurologically, she was hypotonic and hyporeflexic. All her sensations were intact. She had gross weakness of all 4 limbs. Her muscle power was grade 1 in all the limbs proximally and grade 3 distally. On examination, she had bilateral genu valgum with inversion contracture of foot bilaterally and left side pronator contracture.

Functionally, she was totally dependent on the caregiver for all her ADL. She was cognitively preserved and attended school, but wheelchair bound for mobility. On FIM she scored 66.

On investigations, the serum creatine phosphokinase levels was raised. Electromyography studies were suggestive of a myogenic lesion.

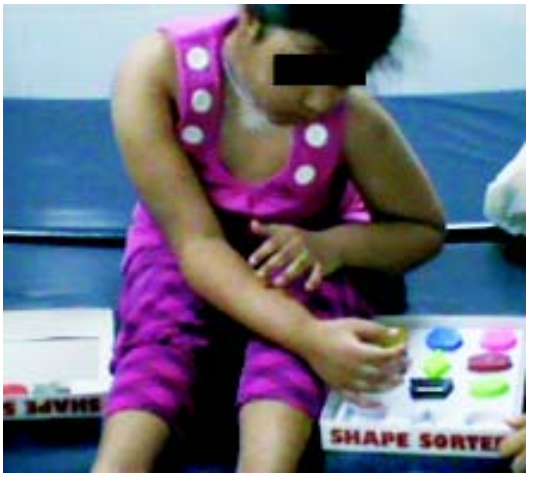
MRI of the upper and lower limbs before the stem cell therapy revealed: Marked fatty infiltration of the pelvic girdle and leg muscles with relative sparing of the thigh muscles.Partial fatty infiltration of the arm and forearm muscles also seen.

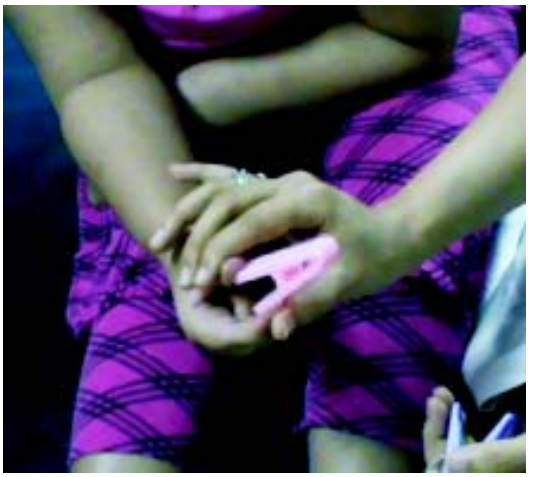
Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally Peronei, Tibialis Anterior, Quadriceps, Biceps, Triceps, Abdominals and Glutei.

Clinical Improvements seen After Stem Cell Therapy

Functionally: On follow up at the end of 3 months, parents reported that her stamina to perform exercises had increased after the therapy. Her trunk strength had increased with ability to sit erect and upright without back rest, which was not possible prior to therapy. Her upper limb and grip strength had increased with improved ability and speed to write. She also got independent in feeding. She was made to stand with bilateral push knee splints in standing frame, leading to improved bone density and toning of muscles. Gradually she started to sustain it for 30 minutes, thereby showing improved standing tolerance. Parents even reported that she began to initiate lower limb movements which were not present prior to the therapy.

	Before stem cell therapy	After stem cell therapy
Creatinine Phosphokinase levels	186 IU	170 IU





Improved sitting balance and ability to perform gripping activities.

Standing with bilateral push knee splints on standing board

Case Report - 56

Diagnosis : *Muscular Dystrophy*

A 10 year old male, known case of muscular dystrophy since the age of 5 gave history of bilateral lower limb weakness, with difficulty in climbing stairs and getting up from floor. He later started walking on his toes. Neurologically, he was hypotonic and hyporeflexic with intact sensations. He had grade 3+ strength in all four limbs proximally and grade 4 distally. On examination, he had bilateral pseudohypertrophy of calf muscles. He had no family history. Functionally, he was independent in most of his ADL. He had a lordotic equinnus gait with a wide base of support. On FIM he scored 105. On Brooke and Vignos scale, he scored 2 and 3 respectively.

On investigations, the serum creatine phosphokinase levels were raised , and EMG showed primary muscle disease .Genetic testing for limited exon deletions of the dystrophin gene, did not reveal any mutations.MRI of musculoskeletal system reveals fatty infiltration of the legs of the upper and lower limbs.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Quadriceps, Glutei, Tibialis Anterior, Abdominals, and Triceps.

Clinical Improvements seen After Stem Cell Therapy.

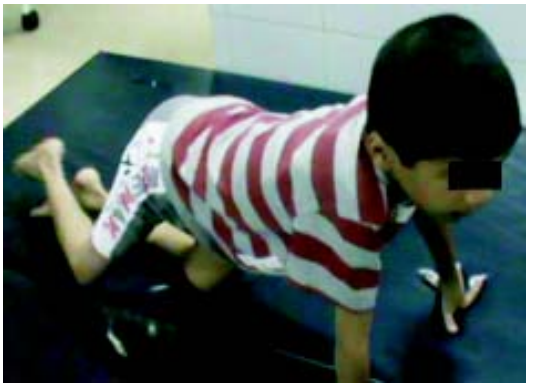
Functionally: On follow up, at the end of 3 months, he reported that the effort required to perform the exercises was reduced significantly. Earlier he would fatigue out, during the day, but post therapy he was energetic and enthusiastic the entire day. His lower extremity and trunk strength increased gradually. According to his parents, they observed that the frequency of his falls while walking had reduced significantly. He could climb stairs with less assistance as compared to prior therapy. Also while performing exercises, as his trunk strength had increased, he was able come to quadruped position independently, and perform exercises like crawling in that position, which was not at all possible before therapy. His upper limb strength increased, with ability to perform overhead activities with weights. He started exercising with half a kilogram weight and gradually progressed to 1 kg over 4 months.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	8463 IU	4407 IU

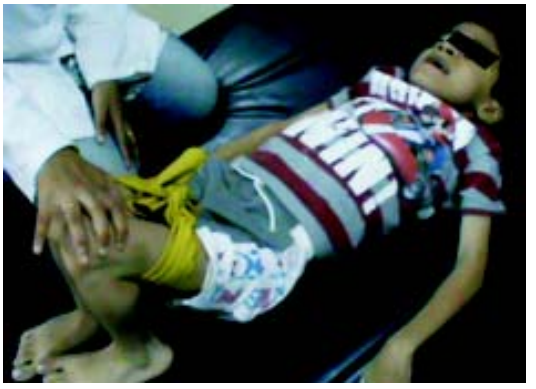
Manual Muscle testing : Following muscles showed improved strength .

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**KNEE**	Before therapy	After therapy
2+	3	Extensors	2+	3

Improved Lower limb and trunk strength with ability to climb stairs with minimum assistance.



Improved trunk strength and ability to perform exercises in quadruped position independently.



Improved trunk control and ability to perform bridging independently.

Improved upper limb strength and ability to do overhead activity with 1 kg weight cuffs on.

Case Report - 57

Diagnosis : *Duchene's Muscular Dystrophy*

A 16 year old male, known case of DMD since the age of 4, wherein parents started noticing that he had difficulty in squatting and also frequently lost balance while walking. Gradually weakness progressed, leading to involvement of the upper extremities as well. He could walk till 2000(about 10 years back).

Neurologically, he was hypotonic and hyporeflexic. All his sensations were intact. On examination, he had grade 1 power in all 4 limbs proximally and grade 2+ distally. He developed severe right Kyphoscoliosis along with Bilateral TEV (Talipe Equino Varus) and bilateral knee flexion contracture. He was cachexic with gross wasting and weakness of all muscles. Functionally, he was totally dependent for all ADL on caregiver and was wheelchair bound for mobility. On Brooke and Vignos scale, he scored 5 and 9 respectively.

On investigation, the serum creatine phosphokinase levels were raised, the Electrophysiological studies showed a generalized intrinsic muscle disease with an excess of "Myopathic" potentials at all sites of examination and DNA testing revealed deletions in exons 8 to 11 of the dystrophin gene, confirming diagnosis of DMD.

MRI of the lower limbs showed marked atrophy & fatty replacement of the muscles of the lower limbs including the calf muscles is also noted.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Quadriceps, Glutei, Peronei, Tibialis Anterior, Deltoid, Triceps.

Clinical Improvements seen After Stem Cell Therapy.

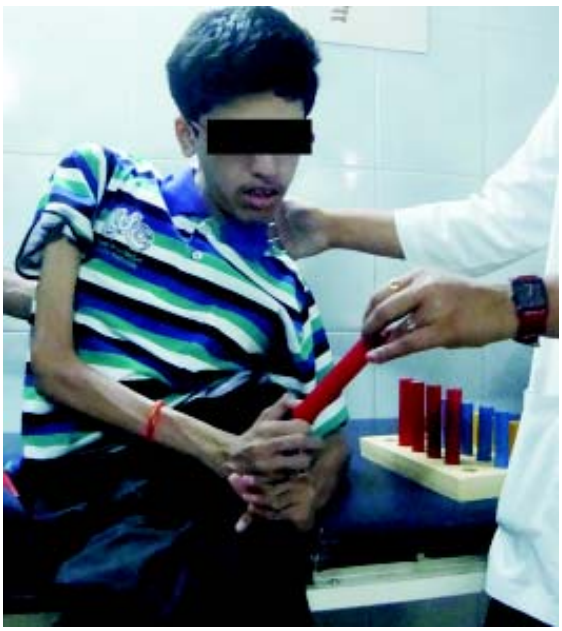
Functionally: On follow up, at the end of 3 months, he reported that the effort required to perform the exercises was reduced significantly. Earlier he would feel fatigued out and lethargic the entire day, but post therapy he felt fresh and energetic throughout. Mother reports that she feels toning and improved consistency of calf muscles as compared to earlier when they were hard and firm on palpation. His upper limb and grip strength had also improved mainly grasp, opposition and pinch .His static sitting balance has also improved tremenduously.

	Before stem cell therapy	After stem cell therapy
Creatinine Phosphokinase levels	2259 IU	853 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		MUSCLES	LEFT	
Before therapy	After therapy	**SHOULDER**	Before therapy	After therapy
1	2	Abductors	1	2
2	3-	Triceps	2	3-
		WRIST		
2	3	Flexors	2	3
0	1	Extensors	0	1
		ANKLE		
0	1	Evertors	0	1

Improved static sitting balance, and ability to sit independently on the edge of the cot.



Improved Pinch strength and ability to hold peg board.

Case Report - 58

Diagnosis : *Muscular Dystrophy*

A case of a 27 year old male with history of back pain in 2003-04 , along with progressive lower extremities weakness and foot drop (left more than right), complained of limping while walking. MRI spine revealed scoliosis at L2-L3 level, so was considered for corrective surgery. However, during preoperative investigation, an incidental increased CPK finding led to suspicion of muscular dystrophy, which was confirmed by EMG later.

Neurologically, he was hypotonic and hyporeflexic with intact sensations. On examination, he had grade 1 muscle power distally and grade 3? proximally in bilateral lower extremities. Upper extremities had a power of grade 3++. He typically had proximal muscle weakness more than distal. Functionally, he was independent in all his activities of daily living; but had difficulty in climbing stairs, getting up from low level and driving. On FIM he scored 123.

On investigations, the serum creatine phosphokinase level was raised to 1392 IU, EMG findings were suggestive of generalized primary muscle disease and MRI of upper and lower limbs revealed fatty infiltration in pelvic girdle, leg and bilateral thighs muscle with loss of muscle volume.

Stem cells were also injected intramuscularly at the motor points of the following muscles: Glutei, Tibialis Anterior, Tibialis Posterior, Hamstrings, Extensor Hallucis Longus, Peronei.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: 3 months post therapy, he could sustain exercise sessions for longer hours without complaints of fatigue, as opposed to earlier when he would tire out and feel lethargic most part of the day. He required less effort to perform his daily activities. He reported a remarkable halt in the progression of the physical weakness. In fact, he reported increased limb and trunk strength with improved stability in standing and ability to stand erect, upright with more confidence. His gait had improved with less waddling and better grip on floor while walking. Also, now he could walk independently without any manual assistance, which he always needed previously. He also reported ease in standing up from lower surfaces.

	Before stem cell therapy	After stem cell therapy
Creatinine Phosphokinase levels	1392 IU	512 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**KNEE**	Before therapy	After therapy
1	2+	Flexors	1	2+
		ANKLE		
1	2	Dorsiflexors	1	2
0	1+	EHL	0	1+
2	3+	**ABDOMINALS**		

Improved lower limb and trunk strength with ability to perform all fours with unilateral hip extension

Improved upper limb and back strength and ability to perform push ups.

Improved upper limb strength and ability to perform overhead activity with weights.

Improved balance, with ability to perform exercises on balance board and unilateral stance .

Case Report - 59

Diagnosis : Muscular Dystrophy

A 29 year old male, known case of MD since the age of 15 years gave history of bilateral lower extremities weakness and complained of frequent falls while walking and difficulty in climbing stairs. Gradually, weakness progressed leading to difficulty in getting up from floor. He also started noticing weakness of upper extremities with difficulty in overhead activities since last 6 years.

Neurologically, he was hypotonic and hyporeflexic with intact sensations. On examination, he had grade 2++ muscle power in bilateral lower extremities and grade 3+ in bilateral lower extremities with proximal muscle weakness more than distal muscle. He had a family history of muscular dystrophy with elder sister being affected. Functionally, he needed assistance in few of the activities of daily living and transfers. He walked with wide base of support and waddling gait. On FIM he scored 110.

On investigations, the serum creatine phosphokinase levels were raised to 370 IU. Electromyography studies were suggestive of primary muscle disease, while the muscle biopsy confirmed the diagnosis of muscular dystrophy.

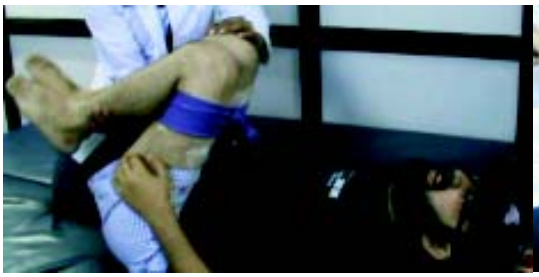
MRI of the upper and lower limbs before the stem cell therapy revealed extensive fatty infiltration in pelvic girdle muscles, bilateral thigh muscles and leg muscles with mild fatty infiltration of the arm and forearm muscles.

Stem cells were also injected intramuscularly at the motor points of the following muscles:Deltoid, Triceps, Biceps, Glutei, Hamstrings, Quadriceps, Back Extensors and Abdominals.

Clinical Improvements seen After Stem Cell Therapy

Functionally: 3 months after the therapy, He reported that he felt energetic most part of the day, as opposed to earlier when he would feel lethargic and tired. His stamina had improved and effort required to perform exercises was reduced significantly. He started standing with bilateral push knee splints and could walk in the parallel bars, thereby leading to improved bone density and toning of muscles, without fear of fall due to buckling of knees.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	370 IU	210 IU



Improved lower abdominal strength and ability to perform lower body crunches.

Improved upper abdominal strength and ability to perform crunches.

Improved trunk control and upper limb strength and ability to get up from bed.

Walking with bilateral push knee splints and walker or parallel bars with minimum assistance.

Case Report - 60

Diagnosis : *Muscular Dystrophy*

A case of a 52 year old male patient with history of bilateral lower extremities weakness with frequent falls while walking and difficulty in climbing stairs since 17 years. Gradually he noticed difficulty in performing overhead activities due to upper extremities weakness.

Neurologically, he was hypotonic and hyporeflexic with intact sensations. On examination, he had muscle strength of grade 2++ in bilateral lower extremities proximally with bilateral foot drop. He had grade 2+ muscle power in bilateral upper extremities proximally and weak intrinsic (smaller muscles) of the hand. He had wasting of proximal muscles of bilateral upper extremities. He had a family history with his elder brother affected with the same condition and he expired at age of 42. Functionally, he needed assistance for all ADL and mobility. On FIM he scored 66.

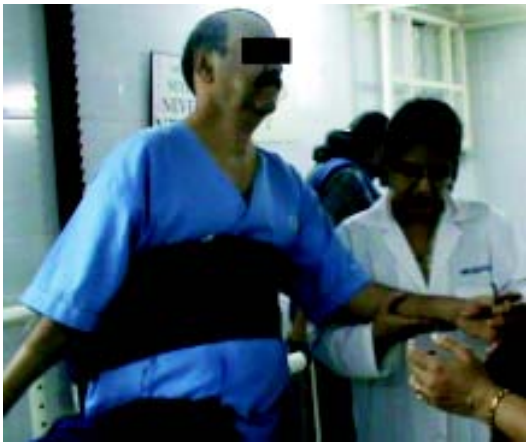
On investigations, the serum creatine phosphokinase levels were raised. Electromyography studies showed of low amplitude motor evoked responses from lower limb more than upper limb, which were suggestive of primary muscle disease

MRI of the upper and lower limbs before the stem cell therapy revealed diffuse symmetrical atrophy with fatty replacement of the muscles of the upper as well as lower limbs.

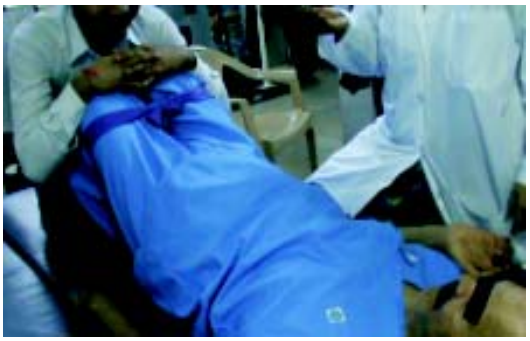
Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Deltoid, Biceps, Triceps, Glutei, Hamstrings, Tibialis Anterior, Gastrosoleus and Abdominals.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: On follow up, at the end of 3 months, he reported feeling of wellbeing and improved stamina. He reported increased ability to sustain exercises for longer hours which was not at all possible before therapy. He reported increased trunk and lower limb strength, thereby leading to increased ability to stand on the standing board.



Exercises to strengthen upper extremity while standing on standing board with bilateral push knee splints.



Ability to perform bridging in lying position , because of increased trunk muscle strength.

Suspension exercises in lying position

Exercises to strengthen upper extremity with weights.

Case Report - 61

Diagnosis : *Duchenne Muscular Dystrophy*

A 13 year old had gradually increasing weakness in bilateral lower limbs began, with difficulty in getting up from floor and climbing stairs since the age of 3 years. Weakness of limbs was progressive and he was wheelchair bound by the age of 8 years. A gradual decrease in the muscle strength of both the upper limbs was also noticed.

Neurologically, he was hypotonic and hyporeflexic. He had all sensations intact. On examination, he had grade 0 muscle power in all 4 limbs proximally and grade 2+ distally in all 4 limbs proximally and grade 2+ distally in all 4 limbs. He had multiple deformities, such as bilateral knee, hip, elbow and wrist contractures, along with severe scoliosis and TEV. Functionally, he was totally dependent for all his activities of daily living. On FIM he scored 48. On Brooke and Vignos scale, he scored 5 and 9 respectively.

On investigation, the serum creatine phosphokinase levels were raised to 208 IU. The electromyography studies showed evidence of primary muscle disease affecting proximal muscles maximally. The compound muscle action potential was low from the muscles sampled. DNA testing revealed deletions in exons 46 to 51 of the dystrophin gene, confirming diagnosis of DMD.

MRI of the upper and lower limbs before the stem cell therapy revealed partial fatty infiltration of the thigh muscle, gastrocnemius and flexor muscles of the arm with significant muscle volume. Extensor compartment muscles in the arm spared.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Deltoid, Triceps, Abdominals, Glutei, Quadriceps.

Clinical Improvements seen After Stem Cell Therapy.

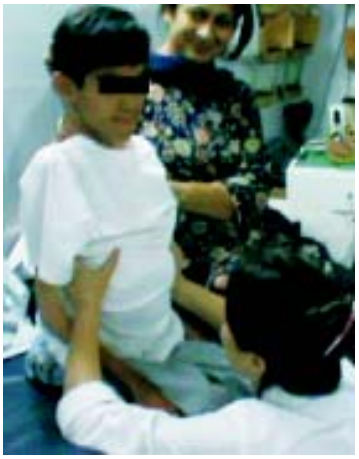
Functionally: On follow up at the end of 2 months, he reported feeling of wellbeing and improved stamina. He could sustain exercises for longer .His trunk strength improved with ability to sit upright for long hours , with erect posture and without any assistance , which was not possible earlier. Gradually with regular rehabilitation and sustain stretching, all his contractures and tight musculature started loosening up, especially bilateral hip knee flexor and elbow flexor tightness. His range of motion at all joints increased by 15 - 20 ° (as documented by the goniometer).

At the end of 6 months, his neck musculature increased in strength, with ability to perform active neck movements, as opposed to earlier when he had a neck drop, due to weak neck muscles. Also while performing exercises for strengthening of all muscles, he could initiate movements himself as opposed to earlier, when all exercises were passive. So initiation and flicker in the muscles had begun, thereby giving him a feeling of contraction of all muscles. His grip strength also increased , leading to improved hand functions. His bed mobility activities like rolling and bridging also got independent

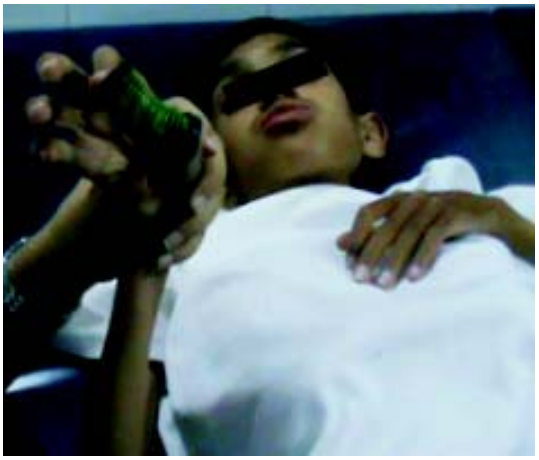
	Before stem cell therapy	After stem cell therapy
Creatinine Phosphokinase levels	208 IU	186 IU

Manual Muscle testing : Following muscles showed improved strength

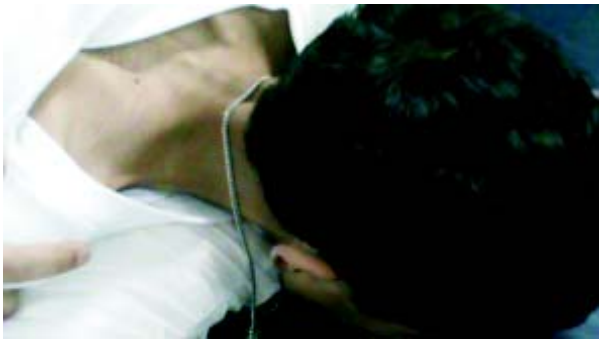
RIGHT		MUSCLES	LEFT	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
1	2	Abductors	1	2
1	2	Adductors	1	2+
		ANKLE		
0	1	EHL	0	1
		SHOULDER		
2	2++	Abductor Pollicis	2	2++
1	2+	Internal Rotators	1	2+

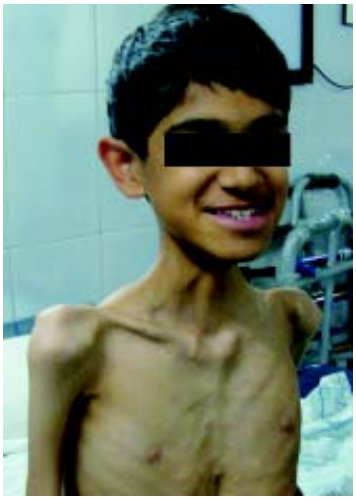


Improved trunk control dynamic sitting exercises.



Improved grip strength and ability to do pinching activities.





Improved neck extensor strength and ability to do active neck extension exercise.

Case Report - 62

Diagnosis : *Duchenne Muscular Dystrophy*

Parents of a 4 and a half year old male child gave history of delayed motor milestones. He complained of difficulty in walking and frequent falls on attempting to walk, which was noticed since the age of 2 years. He was diagnosed with DMD at the age of 3 years. He was mobile, but had difficulty in jumping, climbing stairs and getting up from floor.

Neurologically, he was hypotonic and hyporeflexic with intact sensations. On examination, he had grade 3+ strength in all 4 limbs with weakness predominantly in the proximal muscles. He had pseudohypertrophy of bilateral calf and deltoid muscles. He showed positive Gowers' sign. Functionally, he was dependent on his mother for most activities of daily living. On FIM he scored 76. On Brooke and Vignos scale, he scored 2 and 9 respectively.

On investigation, serum creatine phosphokinase were raised to 20,000 IU. Electromyography studies showed an excess myopathic potential in right deltoid, vastus medialis and tibialis anterior. MRI revealed fatty infiltration of the muscles of the pelvic girdle, thighs, calves, shoulder girdle (predominantly parascapular regions) and erector spinae. The fatty infiltration was maximum and severe in the gluteal muscles and medial compartment of the thigh. Deletion analysis of dystrophin gene showed deletion involving multiple exons 49-52 confirming the diagnosis.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Quadriceps, Glutei, Abdominals, Deltoid.

Clinical Improvements seen After Stem Cell Therapy

Functionally: At the end of 3 months, he reported that the effort required to perform the exercises was reduced significantly. Earlier, he had complains of breathlessness on activity because of weak respiratory muscles, but at the end of 3 months, his respiratory muscle endurance improved with ease in performing incentive spirometry exercises .Earlier he would choke up while having fluids but his swallowing capacity improved significantly. His grip strength also increased as assessed by the dynamometer.

	Before stem cell therapy	After stem cell therapy
Creatinine Phosphokinase levels	20,000 IU	16350 IU

Improved upper limb strength and ability to perform catching of ball.

Improved grip strength and ability to perform peg activities independently.

Improved upper abdominal strength and ability to perform abdominal crunches / sit ups.

Case Report - 63

Diagnosis : *Limb Girdle Muscular Dystrophy*

Clinical presentation:A 20 year old college going boy gave history of difficulty in running since last 4 years. Later lower limb weakness progressed, such that he started having difficulty in getting up from floor, climbing stairs and frequent falls while walking. He also noticed difficulty in overhead activities and lifting weights with hands.

Neurologically, he was hypotonic and hyporeflexic. His sensations were intact. He had grade 3+ strength in all 4 limbs proximally and grade 4 power distally with predominantly proximal /antigravity muscle weakness. On examination, he had pseudohypertrophy of bilateral calf muscles. Functionally, he was independent in most ADL. He walked with bilateral lordotic Trendelenberg's lurch. On FIM he scored 123.

On investigations, the serum creatine phosphokinase levels were 2242 IU. Electromyography studies were suggestive of primary muscle disease.

MRI of the upper and lower limbs before the stem cell therapy revealed partial infiltration of the thigh muscles, a few leg muscles and biceps (arm muscles) with sparing of most muscles of the Upper limbs.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally Quadriceps, Hip extensor, Abdominals, Back extensors and Deltoid, Triceps, Biceps.

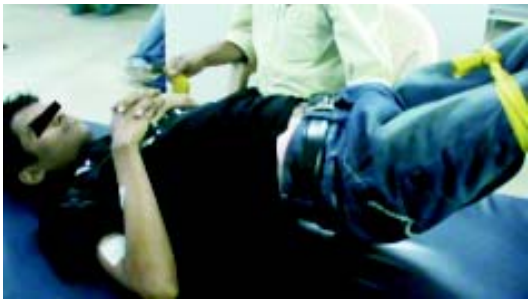
Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina. His trunk and lower limb strength had increased and he was able to get up from squatting position with ease which was not possible for him earlier. He had hyperlordotic wide based equinnus gait , but post therapy his gait stability improved with plantigrade feet. His frequency of falls had reduced significantly, Earlier he would fall 5 -6 times a day, but post therapy his frequency reduced to once a week, thereby showing improved stability in standing. His upper limb strength had increased with ability to do over head activities with weights in hands, which was not possible before.

	Before stem cell therapy	After stem cell therapy
Creatinine Phosphokinase levels	2242 IU	930 IU

Increased upper limb abductor strength and ability to abduct over head with weights.

Increased lower limb abductor strength and ability to do abduction against gravity.



Increased trunk strength and ability to do bridging .

Improved trunk strength and ability to perform kneeling.

Improved trunk strength and ability to get up from lying to sitting position

Case Report - 64

Diagnosis : *Duchenne's Muscular Dystrophy*

An 8 and a half year old male, diagnosed with DMD at the age of 3½ years. It started in the form of delayed walking at the age of 1 ½ year and hypertrophy of calf muscles. By the age of 7 years, he had started complaining of bilateral lower limb weakness leading to difficulty in running, getting up from floor and climbing stairs. He also had difficulty in lifting objects from ground and early fatigue. He had been on continuous rehabilitation since the age of 3.

Neurologically, he was hypotonic and hyporeflexic with intact sensations. On examination, he had grade 3+ strength in bilateral lower limb muscles and grade 3++ in bilateral upper limb with predominantly proximal muscle weakness. Functionally, he needed assistance for most ADL. He had a waddling gait and required wheel chair for longer distance, due to early fatigue. On FIM he scored 115. On Brooke and Vignos scale, he scored 2 and 2 respectively.

On investigation, the serum creatine phosphokinase levels were raised,to 2000 IU Electromyography studies showed a generalized primary muscle disease affecting the upper and lower limbs. DNA testing revealed deletions in exons 46 and 47 of the dystrophin gene, confirming diagnosis of DMD.

MRI of the upper and lower limbs before the stem cell therapy revealed partial fatty infiltration of predominantly the pelvic girdle muscles and the leg muscles with relative sparing of the shoulder girdle and arm muscles with no fatty infiltration or alteration in muscle volume.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Quadriceps, Glutei, Abdominals, Back Extensors, Deltoid, Biceps.

Clinical Improvements seen After Stem Cell Therapy

Functionally: On follow up, at the end of 3 months, his mother reported that he had improved in his endurance, as he could sustain playing and was more active than before. His trunk and lower limb strength had increased with ability to climb stairs and get up from squatting position with ease. He could also perform activities like bending and picking up items from the floor easily, which were very difficult for him earlier. His Brooke Scale for Upper extremity strength and ability , improved from 1 to 2. His grip and pinch strength had also increased as assessed and documented by a dynamometer.

Manual Muscle testing : Following muscles showed improved strength

RIGHT		MUSCLES	LEFT	
Before therapy	After therapy	HIP	Before therapy	After therapy
3-	3+	External Rotators	2	3+
3	3+	Abductors	3	3+

Improved upper limb strength and ability to perform overhead activity with weights.

Improved trunk strength and ability to bend and pick up objects from the ground.

Improved ability to get up from sitting to standing position. (half kneeling)

Improved lower limb strength and ability to perform (SLR) straight leg raising.

Case Report - 65

Diagnosis : *Walker Warberg Syndrome (Congenital Muscular Dystrophy)*

A 3 year old toddler came with a history of absence of neck holding and inability to crawl. He was investigated and diagnosed clinically to be suffering from a congenital muscular dystrophy (possible Fukuyama Syndrome). However, genetic test results ruled out the same. Hence, a working/probable diagnosis of Walker-Warberg Syndrome was considered.

Neurologically, he was hypotonic and hyporeflexic. He could sit without support (once made to do so by bearing weight on hands). He had partial/poor neck holding (probably due to large head), could do rolling independently, could reach out for toys, but could not crawl. In supine lying, he could kick with his legs and lift his hands over his head. Vision and hearing appeared normal. Speech was delayed, could utter only monosyllables. He had not achieved voluntary control of his bladder/bowel activities. Cognitively, he appeared preserved, could follow commands and recognize parents. He had history of convulsions (Generalized Tonic Clonic) at 1 year of age and had been on anticonvulsants since then. He had a family history of similar affliction in his elder sister, who also suffered from congenital MD with severe motor delay and hypotonia. She expired in February 2008, at the age of 7½ years due to breathing difficulty. He had been on continuous rehabilitation since 6 months of age. He could stand at the balance board with bilateral AFO. Functionally, he was dependent on his mother for all ADL. On FIM he scored 18.

On investigations, the serum creatine phosphokinase levels were found to be 488 IU. Electromyography study revealed brief low amplitude polyphastic myopathic units interspersed with normal units more in the T.A. as compared to the Gluteus suggesting of primary muscle disease.

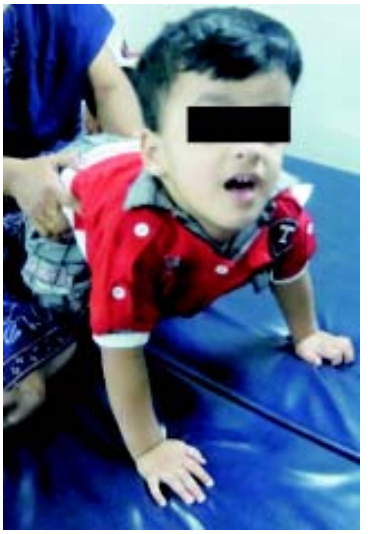
MRI Brain before the stem cell therapy revealed, T2 hyperintensity were throughout cerebral white matter, cerebellum and brain stem, polymicrogyria seen in anterior fronto temporal regions along with extensive cortical abnormality with cortical dysplasia. It also showed hypoplastic pons with fused midbrain colliculi. 2 D- Echo cardiography: LVEF-60% .

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally Neck extensors, Abdominals, Back Extensors.

Clinical Improvements seen After Stem Cell Therapy

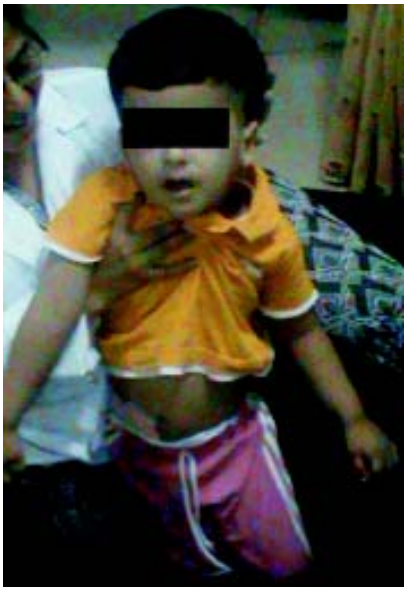
Functionally: On follow up at the end of 6 months, mother reported that his activities and stamina, while performing exercises had increased significantly .His trunk and neck muscle strength had increased significantly. He was able to perform bed

mobility exercises like rolling, coming on all fours, kneeling, in prone position, active neck extension activities. His speech has also improved significantly, with increased babbling, and ability to say words like "dada", "baba", "amba" His upper limb strength has also increased with ability to reach out and grasp objects with ease. Also while performing exercsise, when he was made to stand on standing board, he could hold his neck upright, with ease.



Improved neck and trunk muscle with ability to come on Quadruped position and perform active neck extension

Standing on the standing board.



Ability to perform assisted kneeling activity in during therapy sessions.

Case Report - 66

Diagnosis : *Duchenne Muscular Dystrophy*

An 11 year old boy, diagnosed with DMD since the age of 2 ½ years, showed history of bilateral lower extremity weakness with difficulty in climbing stairs, getting up from floor and frequent falls while walking. Gradually, the upper extremity weakness developed with difficulty in overhead activities. He had stopped walking completely since a year.

Neurologically, he was hypotonic and hyporeflexic with all sensations intact. On examination, he had grade 2 muscle power in bilateral lower extremity and grade 3- in bilateral upper extremity with proximal muscle weakness more than distal. He had bilateral hip and knee contractures with mild postural scoliosis. He was wheel chair bound and dependent on his parents for all the activities of daily living. On Brooke and Vignos scale, he scored 4 and 9 respectively and on FIM scale he scored 60. On investigation, the serum creatine phosphokinase levels were raised to 1828 IU. Electromyography study showed evidence of generalized myopathic process. DNA test revealed deletions in exons 45 to 50 of the dystrophin gene (indicating out of frame mutations), confirming diagnosis of DMD.

MRI of the upper and lower limbs before the stem cell therapy revealed marked fatty infiltration of predominantly pelvic girdle muscles involving glutei, posterior thigh muscles, adductors and vasti with relative sparing of sartorius, gracilis, semitendinosis and adductor brevis and marked fatty infiltration of soleus, peroneus muscles and anterior compartment muscles with relative sparing of flexor compartment muscles including tibialis posterior muscles. 2 D Echo Cardiography LVEF 60% .

Stem cells were also injected intramuscularly at the motor points of the following muscles: Deltoid, Glutei, Quadriceps Tibialis Anterior, Peronei, Back extensors, Abdominals and Adductors of hip.

Clinical Improvements seen After Stem Cell Therapy.

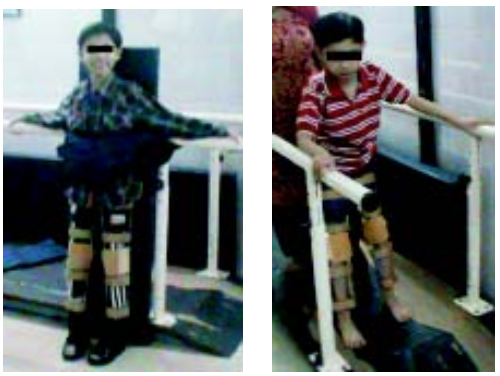
Functionally: At the end of 3 months, he reported ease in performing exercises with efforts required reducing significantly. His stamina had improved; he could sustain exercises for longer durations without complaining of fatigue. He could independently perform the day to day activities like feeding, bathing and dressing himself. Earlier, he would depend on his mother to do all of them. He reported improved upper limb strength and ease in performing overhead activity which was not possible for him before. Also, his grip and pinch strength had increased significantly, with ease in doing activities with the hand gripper and writing skills in school. He had bilateral knee flexor tightness and occasionally walked with equinnus wide based gait and by dragging both his feet. Post therapy, he was given bilateral push knee splints and could walk with them by hiking his pelvis. His bilateral tendoachilles muscle loosened up and he could dorsiflex upto neutral position voluntarily.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	1828 IU	1120 IU

Improved pinch strength and ability to clip.

Improved trunk strength and ability to perform all fours position.

Improved lower limb and trunk strength and ability to perform kneeling .



Standing progression from bilateral push knee splints and standing board to independent standing in the parallel bars.

Case Report - 67

Diagnosis : *Muscular Dystrophy*

An 18 year old case of Muscular Dystrophy, presented with symptoms of bilateral lower extremity weakness and complaints of difficulty in getting up from squatting since the age of 5 (1997). Gradually weakness progressed, leading to frequent falls and he finally stopped walking since 2000 (age of 8). He also had upper extremity weakness with inability to perform overhead activities or use upper extremity for any ADL. He had a family history of muscular dystrophy with maternal cousins similarly afflicted.

Neurologically, he was hypotonic and hyporeflexic with intact sensations. On examination, he had bilateral calf, deltoid and tongue muscle hypertrophy. He also had the multiple deformities bilaterally such as elbow flexion , knee flexion contracture with bilateral TEV , Genu Valgum with wrist extensor and supinator contracture and severe right sided scoliosis. He had grade 0 muscle power in all 4 limbs proximally and grade 1 in bilateral upper extremity distally (at wrist). Functionally, he was totally dependent for all ADL and wheelchair bound for mobility. On FIM he scored 18.

On investigations, the serum creatine phosphokinase levels were raised to 2056 IU. Electromyography studies were suggestive of primary muscle disease. MRI of the upper and lower limbs before the stem cell therapy revealed complete fatty infiltration of the pelvic girdle, thigh, leg, arm and forearm muscles.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Quadriceps, Peronei, Tibialis Anterior, Abdominals, Deltoid and Triceps.

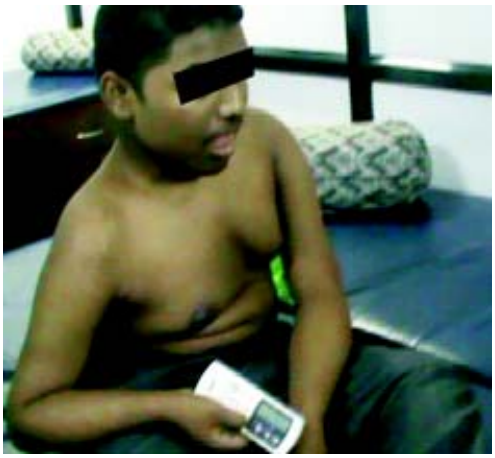
Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina. He also reported reduced fatigue or exhaustion in doing activities. He had also lost weight, and thus it was easier for the caretaker to lift and transfer him. His trunk muscles had strengthened, with improved dynamic sitting balance, and ability to sit independently on the edge of the cot (without support) for 15 minutes, which was not at all possible before therapy. Flexibility of his muscles had increased due to regular sustained stretching exercises, and he could move all his joints in full range of motion, eg: knee, fingers, etc. Earlier his joints were quite stiff and were having restricted mobility. His upper extremity strength also increased with increased grip strength and ability to operate remote control and hold mobile in his hands. As he had tongue hypertrophy, his speech had increased in pitch and nasality. But gradually with speech therapists suggestions, his voice quality became age appropriate and normal in pitch. He had multiple joint contractures in lower limbs like bilateral knee flexor contracture with bilateral talipes equino varus deformities, so he was made to stand on tilt table during therapy sessions, with bilateral push knee splints and stretched tendoachilles thereby leading to improved bone density and toning of muscles.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	2056 IU	477 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**WRIST**	Before therapy	After therapy
0	1	Flexors	0	1
0	1	Extensor Pollicis Longus	0	3



Improved grip strength and ability to operate remote independently, with sitting without support .

Standing with bilateral push knee splints and high boots , on standing board, gradually post 6 months, standing with calipers , and showing weight loss.

Improved Dynamic sitting balance and ability to sit without support.

Case Report - 68

Diagnosis : *Muscular Dystrophy*

An 10 year old male, known case of muscular dystrophy, since the age of 5 which started with bilateral lower limb weakness and difficulty in getting up from floor. Gradually weakness progressed and he had stopped walking since 2 years. Off late, even upper extremity weakness had set in since a year with difficulty in overhead activities. Neurologically, he was hypotonic and hyporeflexic. He had all sensations intact. He had grade 2 strength in bilateral upper extremity and lower extremity proximally and grade 3+ distally in all 4 limbs. On examination, he had pseudohypertrophy of bilateral calf muscles and bilateral knee flexion and TA tightness which was stretchable. Functionally, he needed assistance for all ADL. He was wheelchair bound for mobility. On FIM he scored 81. On Brooke and Vignos scale, he scored 2 and 9 respectively.

On investigation, the serum creatine phosphokinase levels were raised, the electrophysiological studies revealed generalized myopathic process. MRI of the upper and lower limbs before the stem cell therapy revealed extensive fatty infiltration in the muscles of the pelvic girdle, thigh and leg muscles.Upper limb muscles show moderate fatty infiltration with moth eaten appearance of arm and forearm muscles.

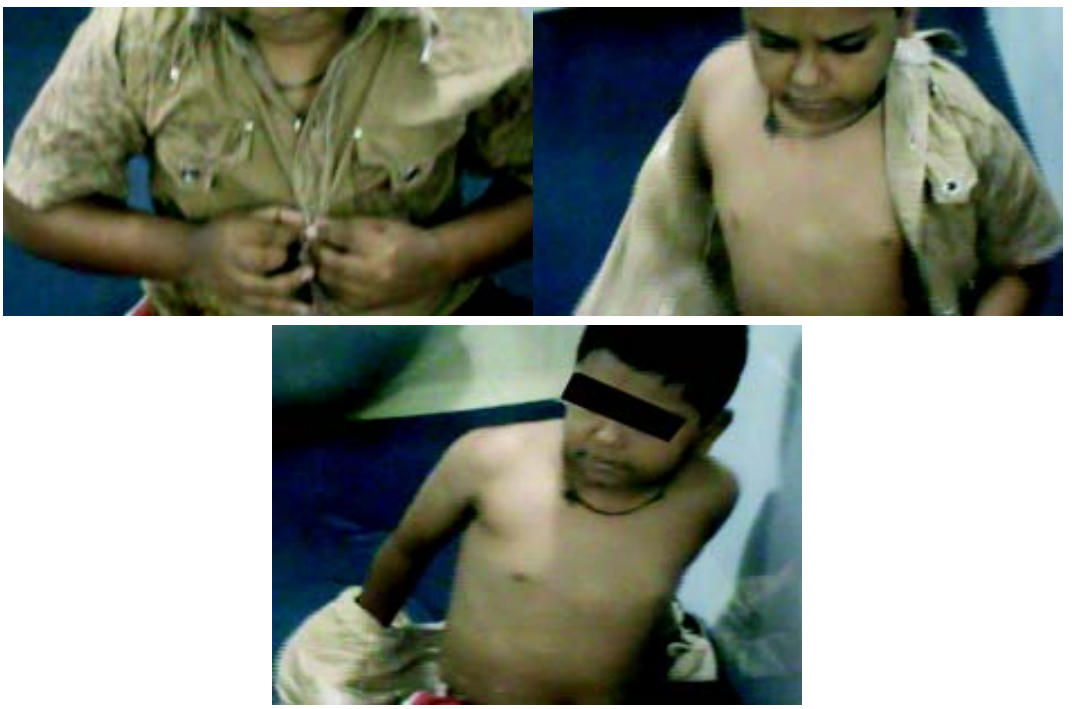
Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Quadriceps, Deltoid, and Abdominals.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: On follow up, at the end of 3 months, he reported feeling of wellbeing and improved stamina. He also reported no fatigue or exhaustion in doing activities. His trunk strength had increased with ability to come and maintain quadruped position independently .his mat exercises had also improved like rolling, getting up and sitting on the edge of the cot independently.His upper limb strength had also increased with ability to perform overhead activities independently, which was not possible prior to the therapy.

	Before stem cell therapy	After stem cell therapy
Functional Independence Measure	81	82
Creatinine Phosphokinase levels	4274 IU	1724 IU

Ability to perform activities in quadruped position.



Ability to perform upper body undressing independently.

Case Report - 69

Diagnosis : *Muscular Dystrophy*

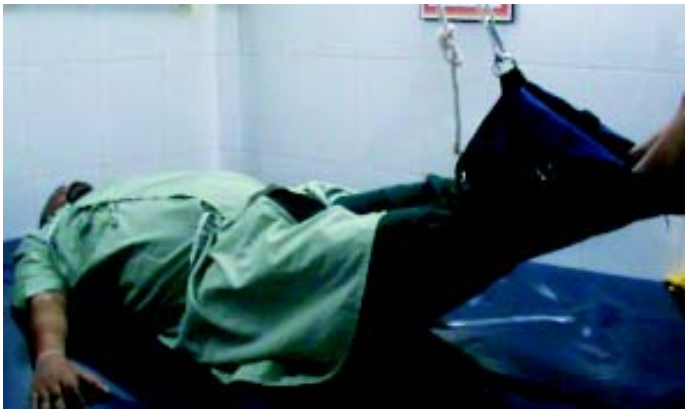
A case of a 42 year old male with a history of progressive bilateral foot muscle weakness since last 20 years, which developed into bilateral foot drop. Eventually, upper extremity weakness began, starting with the left upper limb. Gradually, weakness progressed to all 4 limbs. Till about six years back, he could walk with support with gradual progress in his disability. He was wheelchair bound for mobility. He had family history of MD with elder sister affected similarly.

Neurologically, he was hypotonic and hyporeflexic with all sensations intact. He had grade 2+ muscle power in bilateral upper extremity and grade 2? in bilateral lower extremity with proximal muscle more affected than distal. Functionally, he was totally dependent on caregiver for all ADL and wheelchair bound for mobility. On FIM he scored 48. On investigation: EMG reveals primary muscle disease.

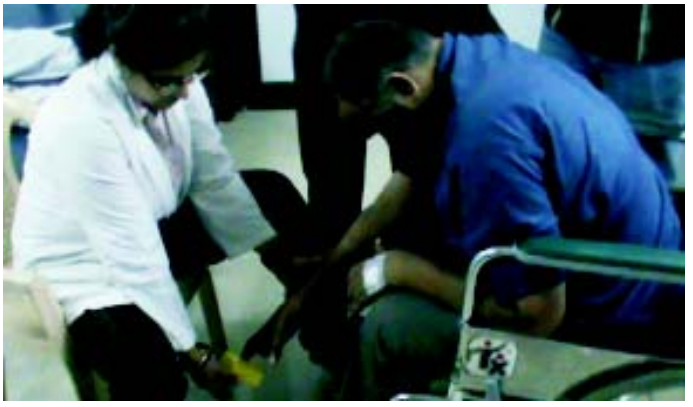
Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Deltoid, Biceps, Glutei, Abdominals, Quadriceps, Hamstrings, Peronei, Tibialis Anterior, Sternocleidomastoid, Gastro Soleus.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: On follow up, at the end of 3 months, he reported feeling of wellbeing and improved stamina. He experienced an overall increase in his muscle strength. He had severe muscle tightness and contractures, but with regular sustained stretching, gradually flexibility of his muscles increased with improved range of motion at all joints, mainly hip, knee, ankle and elbow joints. His trunk strength had increased with improved dynamic sitting balance. Also his wife reported that she could transfer him with ease, as he had begun to take his body weight and assist in the act of transferring, which was not possible before.



Exercises to strengthen the quadratus muscle



Improved trunk strength and ability to bend and pick up objects.

Exercises to strengthen pinches and grips.

Case Report - 70

Diagnosis : *Myotonic Muscular Dystrophy*

A case of a 54 year male afflicted with muscular dystrophy since the last 20 years, reported of weakness in bilateral upper extremities (right more than left) He also gave history of inflammation in both the eyes as well as cataract for which he got operated in 2003. Gradually lower extremities weakness had also begun, but he managed to walk with assistance.

Neurologically, he was hypotonic and hyporeflexic with intact sensations. He had grade 2 muscle power in bilateral upper extremities and grade 4 in bilateral lower extremities. He also had facial muscle weakness along with difficulty in swallowing leading to choking as well as slurred speech, due to oromotor muscle weakness. Functionally, he needed assistance in most ADL, but was mobile indoors. He had a high steppage gait with imbalance. On FIM he scored 100.

On investigations, the serum creatine phosphokinase levels were raised. Electromyography studies showed myopathic pattern with myotonic discharges.

MRI of the upper and lower limbs before the stem cell therapy revealed: Mild to moderate fatty infiltration of the pelvic girdle,thigh, leg muscles with minimal fatty infiltration in arm and forearm muscles.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Deltoid, Biceps, Triceps, Extensor Digitorum, Brachioradialis, Extensor Pollicis Longus, Flexor Pollicis Longus, Orbicularis Oris, Orbicularis Oculi, Rhizorius

Clinical Improvements seen After Stem Cell Therapy.

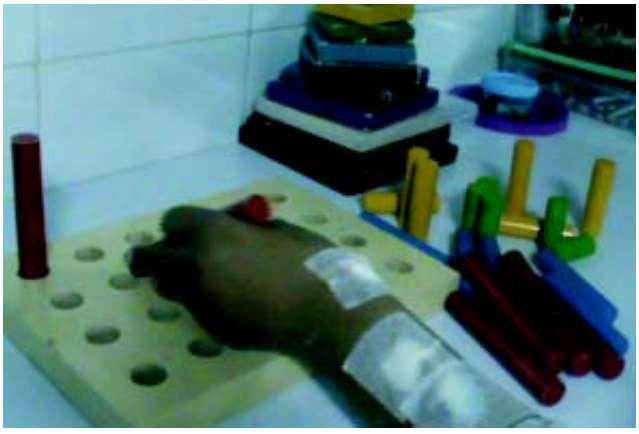
Functionally: At the end of 3 months, he reported that the effort required to perform the exercises was reduced significantly. His lower limb and trunk strength increased, with ease in doing bed mobility exercises. He got completely independent in getting up from bed, sitting to stand and walking, all of these activities needed assistance by the wife, prior to the therapy. His gait also improved with increased stability and steadiness. His upper extremity strength increased with ability to perform over head activities which was not at all possible before the therapy .He got independent in activities of daily living like dressing, feeding, combing …etc. His facial muscles were weak with poor facial expressions. Post therapy his facial muscles increased in strength, and his oromotor control improved, with ability to purse lips and close his mouth completely. Also due to increased oromotor muscle strength , improvements in his speech were noticed with reduction in nasality. His problem of drooling resolved completely.

	Before stem cell therapy	After stem cell therapy
Functional Independence Measure	100	104
Creatinine Phosphokinase levels	226 IU	120 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**SHOULDER**	Before therapy	After therapy
2-	2+	Flexors	2-	2+
2+	3-	Abductors	2+	3-
3	3+	Biceps	3	3+
3	3+	Triceps	3	3+
3	3+	Brachioradialis	3	3+
		WRIST		
2-	3	Flexors	2-	3
3-	3	Extensors	3-	3
2	3	Flexor Pollicis Brevis	2	3

Facial muscle exercises and ability to purse lips and recovery of facial expressions .



Improved Grip strength and ability to perform peg activities.

Improved lower limb and trunk strength, with ability to perform kneel walking

Case Report - 71

Diagnosis : *Duchenne's Muscular Dystrophy*

A 9 year old male, known case of DMD since the age of 4 years gave history of bilateral lower extremities weakness leading to difficulty in climbing stairs and frequent falls while walking. Gradually progressive weakness resulted first, in difficulty in getting up from floor (Gowers sign positive), then in an altered walking pattern (an Equinnus Gait) and easy fatiguability. Later hampering of performing overhead activities was subsequently noted.

Neurologically, he was hypotonic and hyporeflexic with intact sensations. On examination,he had pseudohypertrophy of bilateral calf muscles. He had grade 2+ muscle power in bilateral lower extremities and grade 3+ in bilateral upper extremities with proximal muscle weakness more than distal. Functionally, he was independent in most ADL and had difficulty in climbing stairs and squatting. On FIM he scored 87. On Brooke and Vignos scale, he scored 2 and 9 respectively.

On investigation, the serum creatine phosphokinase levels were raised to 10,300 IU, the electrophysiological studies showed a generalized myopathic process. DNA testing revealed a deletion in the dystrophin gene involving multiple exons (46-51), confirming diagnosis of DMD.

MRI of the upper and lower limbs before the stem cell therapy revealed evidence of diffuse fatty infiltration in all the muscle groups with volume loss.

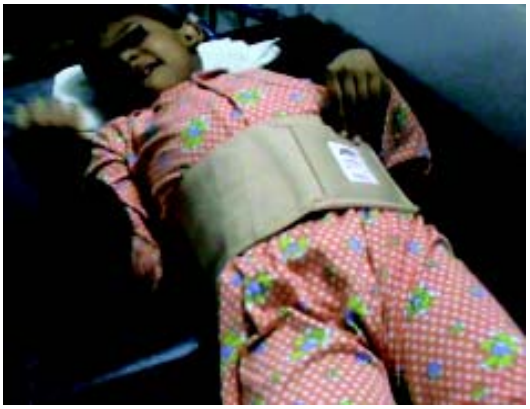
Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Deltoid, Triceps, Glutei, Quadriceps, Tibialis Anterior, Peronei and Abdominals.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported that the effort required to perform exercises was reduced significantly. His stamina and endurance had improved significantly, as opposed to earlier when he would feel fatigued out and lethargic the entire day. His trunk strength had improved, with ability to perform bridging and back extension exercises on bed, which was not possible before. His lower limb strength had also increased and he was able to climb stairs with the aid of the railing. According to his father, his ability to climb stairs and gait had got near normal post therapy.

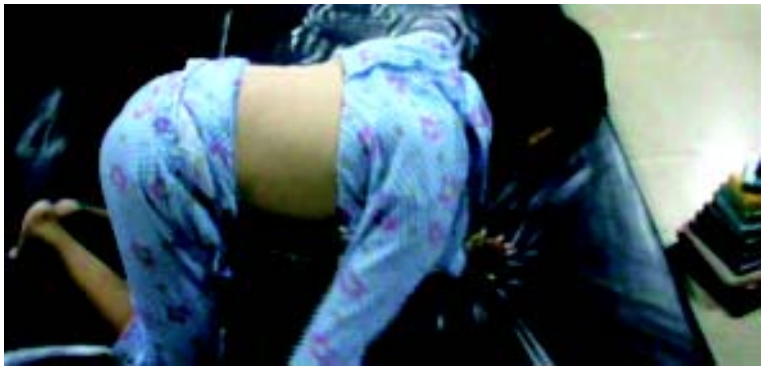
	Before stem cell therapy	After stem cell therapy
Functional Independence Measure	87	97
Creatinine Phosphokinase levels	10300 IU	4918 IU

Improved trunk muscle strength and ability to perform bridging exercises.



Improved upper limb strength and ability to perform strengthening exercises with weights.

Improved lower limb strength and ability to perform kicking, thereby maintaining unilateral stance without support.



Improved trunk strength and ability to come to quadruped position and perform crawling.

Case Report - 72

Diagnosis : *Duchenne's Muscular Dystrophy*

A 11 year old male patient, who had gradually progressive weakness, starting with the lower limbs since 5 years of age, gave history of difficulty in climbing stairs, frequent falls while walking. The problems increased such that he had stopped walking completely since last 2 years. Upper extremities weakness had also been noticed since the past year and a half with inability to do overhead activities. He had no family history of such condition.

Neurologically, he was hypotonic and hyporeflexic. On examination: he had all sensations intact. He had grade 1+ muscle power in bilateral lower extremities muscle and upper extremities muscle proximally and grade 3 distally in all 4 limbs. He had pseudohypertrophy of bilateral calf muscles. He developed contractures over a period.

Functionally, he needed assistance in all ADL and was wheelchair bound for mobility. On FIM he scored 54. He had already undertaken Mesenchymal Stem Cell Transplant twice (March and May '10).

On investigation: Genetic Analysis: showed deletion in exons from 49-52 and increased creatine phosphokinase levels to 2938 IU and Electrophysiological studies was suggestive of small polyphasic narrow complex with full interference pattern suggestive of myopathy. MRI (musculoskeletal system) showed extensive fatty infiltration in girdle muscles and extensively raised extramyocellular and intramyocellular lipids/creatinine ratio.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Deltoid, Biceps, Triceps, Brachioradialis, Quadriceps, Glutei, Tibialis Anterior, Peronei, Abdominals and Back Extensors.

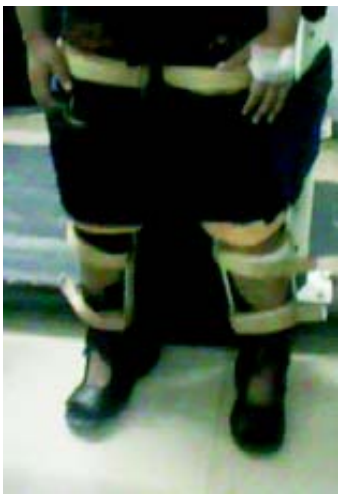
Clinical Improvements seen After Stem Cell Therapy.

Functionally: On follow up, at the end of 3 months, he reported feeling of wellbeing and improved stamina. His trunk strength increased and he was able to sit on the edge of the bed, with no support, thereby showing improved static sitting balance. His posture became erect and upright .His upper limb and grip strength increased with ability to perform activities of daily living like feeding, combing independently. With regular sustained stretching, flexibility of her joints mainly knee, improved with increased range of motion. He was recommended bilateral push knee splints and was made to stand on the standing board in order to improve the bone mineral density and bring about toning of muscles. He was able to sustain standing for 40 minutes at a stretch.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	2938 IU	1062 IU

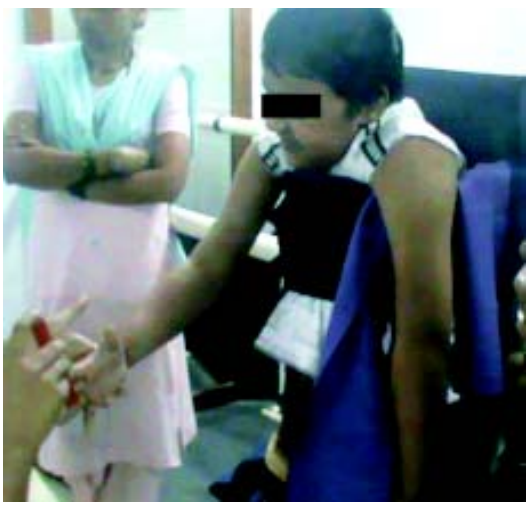
Manual Muscle testing : Following muscles showed improved strength

RIGHT		MUSCLES	LEFT	
Before therapy	After therapy	HIP	Before therapy	After therapy
0	1	Adductors	0	1
0	1	Rotators	0	1



Standing on standing board with bilateral push knee splints to improve bone mineral density and bring about toning of muscles.

Ability to stand on standing board and perform reach outs for pegs.



Improved grip strength and ability to perform gripper exercises.

Case Report - 73

Diagnosis: Muscular Dystrophy

An 11 year old male, known case of muscular dystrophy since 2004. It started with symptoms of bilateral lower extremities weakness with difficulty in squatting and getting up from floor. There was gradual progression of weakness, leading to frequent falls while walking. He even started developing upper extremities weakness with difficulty in overhead activities. He stopped walking since last 2 years.

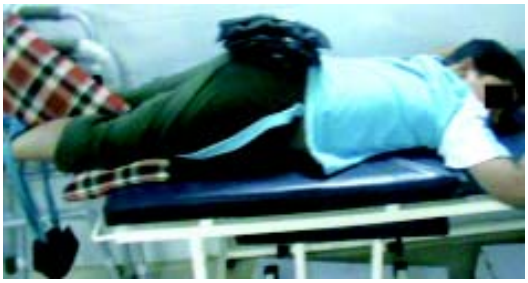
Neurologically, he was hypotonic and hyporeflexic. He had all sensations intact. On examination: he had hypertrophy of bilateral calf muscles. He had grade 1+ muscle power in bilateral lower extremities proximally and grade 3 distally. He has grade 2+ muscle power in bilateral upper extremities proximally and grade 3+ distally. He had tightness of bilateral knee flexors and attitude of TEV (right more than left feet). He had no family history.

On investigations: There were raised creatine phosphokinase levels of 4387.50 IU. Muscle Biopsy confirmed muscular Dystrophy. The 2 D Echo showed a LVEF -62%.The electrophysiological studies revealed a primary muscle disorder.MRI - Upper & Lower limbs with Spectroscopy showed moderate to extensive fatty infiltration of the pelvic girdle & bilateral Thigh muscles. There was moderate fatty infiltration of the bilateral arm & forearm.

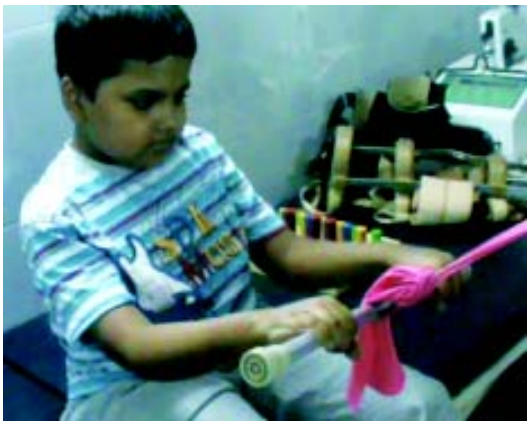
Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Quadriceps, Tibialis Anterior, Peronei, Deltoid, Biceps, Triceps, Brachioradialis, Back Extensors and Abdominals.

Clinical Improvements seen After Stem Cell Therapy.

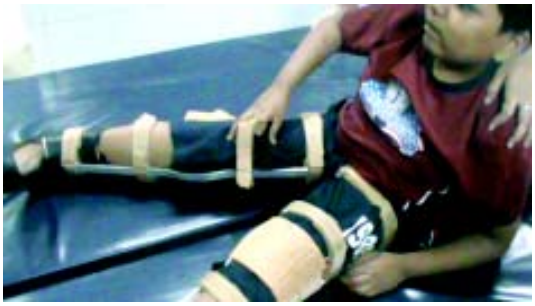
Functionally: On follow up, at the end of 3 months, he reported that the effort required to perform the exercises was reduced significantly. After the therapy his immunity for respiratory tract infection had improved, as prior to therapy he would suffer from severe respiratory infection once in every 3 months, but post therapy with regular breathing exercises, his respiratory muscles increased in strength with no episode of infection for almost a year. With regular sustained stretching, flexibility of his muscles increased with improved range of motion of all joints. His knee flexor muscle flexibility increased with ability to straighten the knees completely. According to the mother his trunk strength improved with ability to sit upright erect on the edge of the cot, which was not possible prior to the therapy. His grip strength had increased, with ability to perform activities like picking up fine objects like marbles or beads independently. He was recommended bilateral push knee splints and made to stand on the standing board, with that aim of improving bone density due to weight bearing and bring about toning of muscles. He was able to sustain standing for almost 35 minutes.



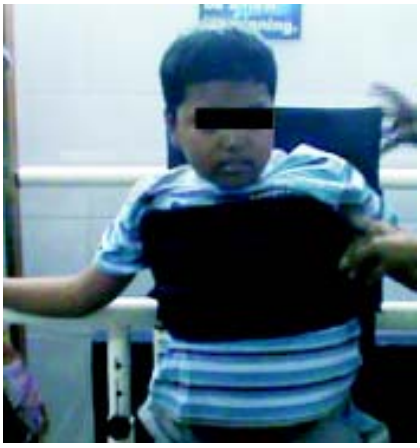
Stretching of tight hip and knee flexor muscles, thereby improving joint range of motion and flexibility.

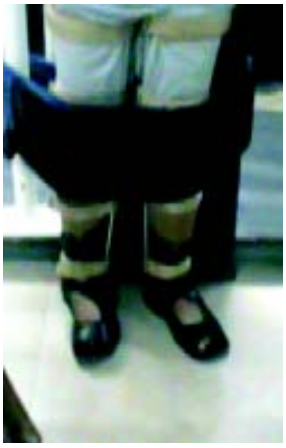


Increased trunk and upper limb strength leading to improved dynamic sitting balance and ability to perform resisted upper extremity strengthening exercise with the aid of the theraband.



Improved grip strength and ability to remove splints independently.





Standing on standing board with bilateral push knee splints and high boots with posterior steel shank to stretch muscles and improve bone mineral density.

Case Report - 74

Diagnosis : *Muscular Dystrophy*

A 46 year old house wife gave history of gradually progressive generalized muscle weakness since 12 years. It started with bilateral lower extremities weakness leading to difficulty in walking. She gradually developed ptosis and nasality in speech as well. She complained of early fatigue on any activity. She also developed upper extremities weakness with difficulty in overhead activities.

Neurologically, she was hypotonic, hyporeflexic with intact sensations. On examination, she had grade 2++ muscle power in bilateral lower extremities and grade 3++ in bilateral upper extremities. She also had facial muscle weakness along with bilateral ptosis. She had hypertrophy of bilateral calf muscles. She had a family history of a elder sister having Myasthenia Gravis and a brother being diagnosed with SMA type III. Functionally, she was independent in most ADL and needed assistance in getting up from floor and climbing stairs. She walked with wide base of support and assistance. On FIM she scored 100.

On investigations, the serum creatine phosphokinase levels was raised. Electromyography studies were suggestive of generalized primary muscle disease, while the muscle biopsy showed features of end stage muscle disease.

MRI of the upper and lower limbs before the stem cell therapy revealed: Fatty infiltration of most proximal lower limb muscles, such as adductors and hamstrings with sparing of Sartorius. Upper limb muscles also show fatty infiltration, though to a lesser extent.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Quadriceps, Hamstrings, Tibialis Anterior, Plantar flexors, Abdominals, Back Extensors, Orbicularis oculi, Rhizorius, Orbicularis oculi.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, she reported feeling of wellbeing and improved stamina, with ability to perfrom exercises without any complaints of fatigue. Her facial muscles were very weak, but post therapy, with regular exercises, her frontalis and nasalis muscle increased in strength, with improved expressions. Her trunk and lower limb muscle strength increased with ability to get up from floor easily. She was able to walk independently for 200 meters without any aid, which was not at possible before therapy.

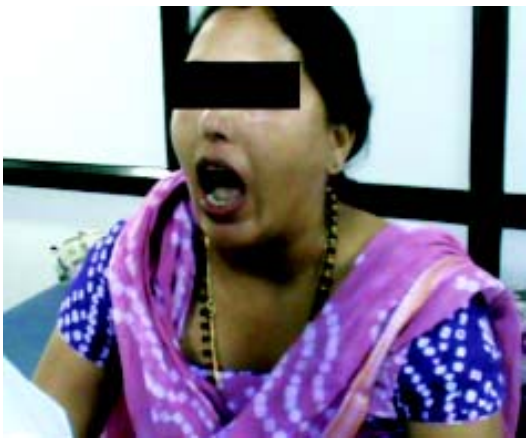
	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	880 IU	299 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		MUSCLES	LEFT	
Before therapy	After therapy	HIP	Before therapy	After therapy
2+	3	Back extensors	2+	3

Improved abdominal strength .

Improved back extensor strength.



Improved facial muscle strength and ability to open mouth

Improved trunk and upper limb strength with ability to lift up objects in kneeling position.

Case Report - 75

Diagnosis : *Muscular Dystrophy (Myotonic)*

Clinical presentation: A 55 year old male gave history of generalized muscle weakness since 1988 -89. It initially started with complaints of bilateral upper extremity weakness with difficulty in lifting them and performing overhead activities. Gradually weakness progressed to bilateral lower extremities leading to difficulty in walking and climbing stairs. He also complained of early fatigue on activities. He had a strong family history of muscular dystrophy.

Neurologically, he was hypotonic and hyporeflexic with intact sensations. Muscle strength in bilateral lower extremities was grade 3++ and in upper extremities was grade 1, with proximal muscles affected more than distal. Neck musculature had a power of grade 2. He had wasting of all girdle muscles and foot drop bilaterally. Functionally, he was independent in most ADL. He needed assistance while walking and had a high steppage gait (with foot drop). On FIM he scored 105.

On investigations, the serum creatine phosphokinase levels were raised. Electromyography studies were suggestive of primary muscle disease.

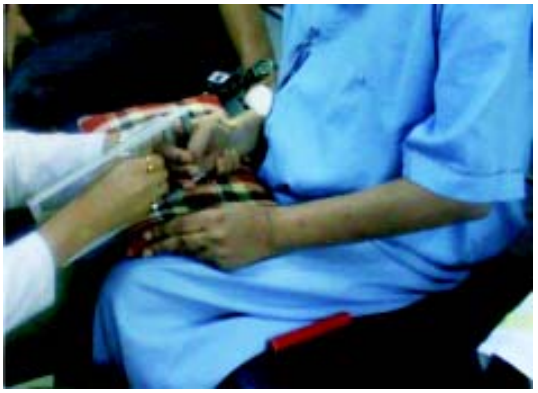
MRI of the upper and lower limbs before the stem cell therapy revealed moderate fatty infiltration of pelvic girdle, thigh, leg, arm and forearm muscles.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally bilaterally Deltoid, Biceps, Triceps, Brachioradialis, EDL, EPL, FPL, Peronei, Tibialis Anterior, Gastrosoleus.

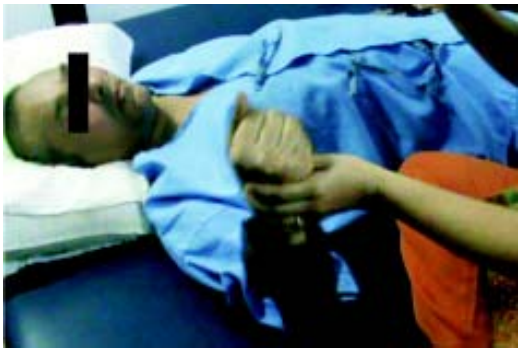
Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina along with increased exercise tolerance. His trunk and lower limb muscles improved with ability to get up from lying position, to sitting independently without any effort. During exercises all his bed mobility exercises improved significantly and he could perform all of them independently. With regular breathing exercises, his speech consistency improved with reduced nasality. He was recommended bilateral push knee splints and was given gait training. He was able to walk with assistance.

Walking with the help of bilateral push knee splints and assistance.



Exercises with gripper to strengthen grip.



Exercises to strengthen biceps with weight cuff.

Exercises to strengthen trunk muscles, by bending and picking up objects.

Case Report - 76

Diagnosis : *Congenital Muscular Dystrophy*

A 2 year old male child born to parents having consanguineous marriage was noticed to be having delayed milestones, like no neck holding till 8 months of age was diagnosed to be suffering from congenital muscular dystrophy.

Neurologically, he was hypotonic and hyporeflexic. He had grade 3+ strength in bilateral lower extremities muscles and grade 2+ in bilateral upper extremities distally and very poor neck musculature. He had tendency for bilateral knee and elbow subluxation. He had normal IQ and speech. Functionally, he had good hand grasps but poor reach outs, due to proximal muscle weakness. He was dependent on his mother for most ADL.

On investigations, the serum creatine phosphokinase level was slightly raised. Electromyography studies were suggestive of primary muscle disease, while the Muscle biopsy from left biceps showed prominent myopathic features with variation of myofibre rounding, internalized nuclei, myophagocytosis and occasional regenerating fibres.

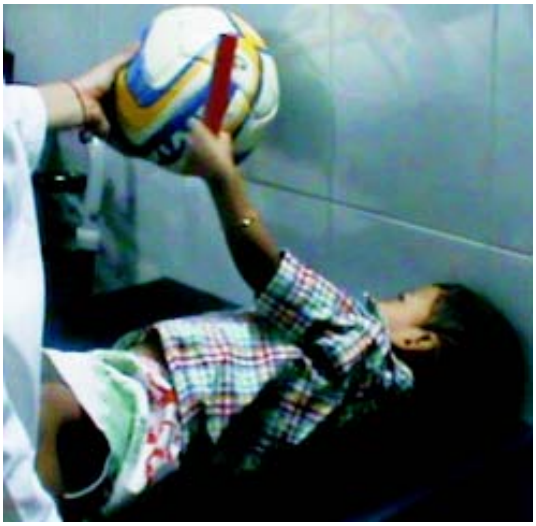
MRI Brain did not reveal any significant abnormality, while MRI of the upper and lower limbs before the stem cell therapy revealed moderate to extensive fatty infiltration of the pelvic girdle and thigh muscles (esp. hamstrings) with relative sparing of the distal leg muscles and muscles of the upper extremities.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally Peronei, Adductors, Glutei, Deltoid, Triceps, Abdominals, Back Extensors and Neck Extensors.

Clinical Improvements seen After Stem Cell Therapy

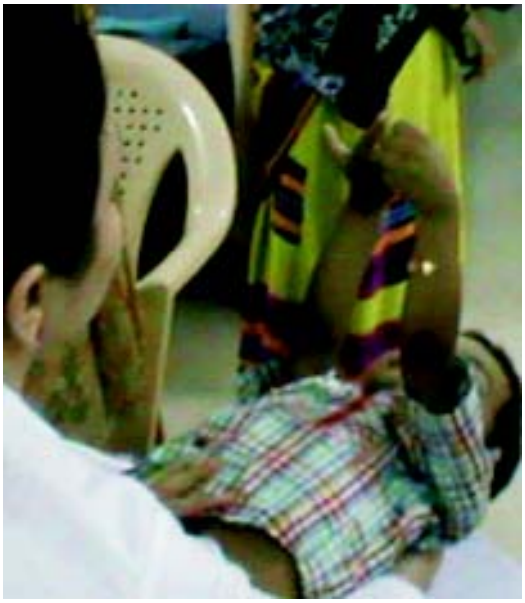
Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina. According to the mother, his limb muscles had toned up .His neck and trunk muscle strength had improved, with ability to hold the neck upright, which was not possible before therapy. While performing Swiss ball activities, he was able to perform neck extension and reach out for objects, which was not at all possible prior to therapy. His grip strength and hand functions had improved with ability to hold objects easily and better than before (fist opening, grasping objects and chest level reach out).When being made to stand on standing board with bilateral push knee splints , he was able to control his neck movements voluntarily.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	504 IU	250 IU

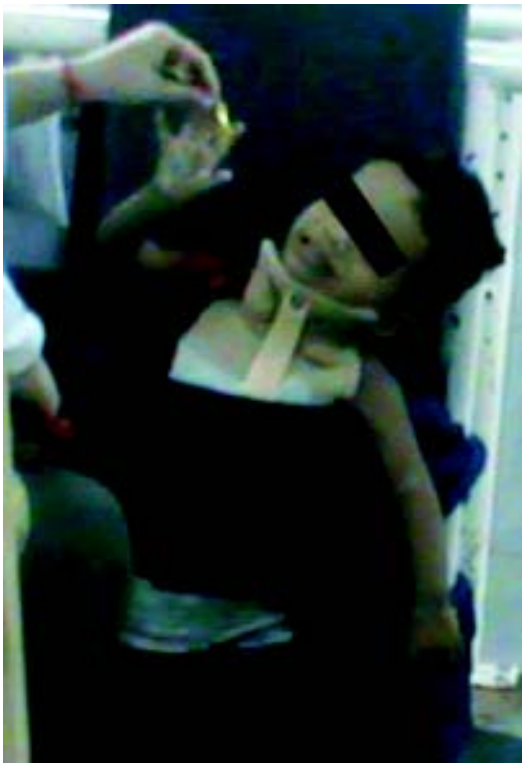


Improved Upper limb strength and reach outs .

Improved trunk control and half kneeling activity.



Improved over head reach outs on Swiss ball .



Improved reach outs in standing on the standing board.

Case Report - 77

Diagnosis : *Duchenne Muscular Dystrophy*

A 10 year old male , known case of muscular dystrophy, with history of lower extremities weakness noticed at age of 4 years with complaints of frequent falls while walking, difficulty in squatting, for which parents consulted a neurologist.Routine investigations like CPK and EMG indicated muscular dystrophy. He started having difficulty in climbing stairs with wide based gait at age of 6. He stopped walking 6 months ago and also has developed difficulty in overhead activities since last 3 months. Neurologically, he was hypotonic and hyporeflexic. On examination, he had hypertrophy of bilateral calf muscles. He had grade 2? muscle power in bilateral upper extremities and grade 1++ in bilateral lower extremities with proximal muscle weakness more than distal. He had no family history. Functionally, he needed assistance in most ADL and was wheelchair bound for mobility. On FIM he scored 62.

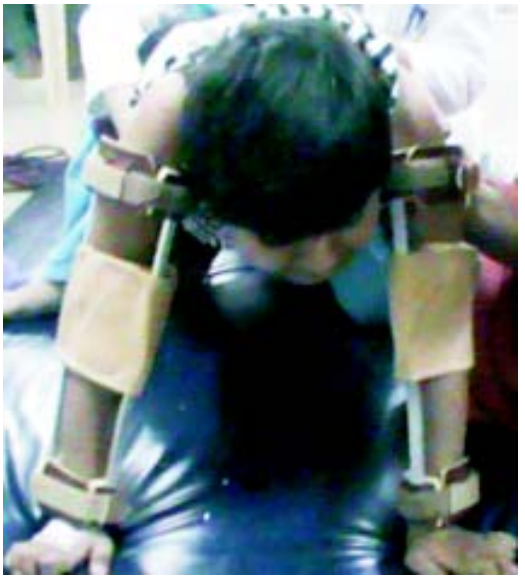
On investigation: Increased creatine phosphokinase levels of 22260 IU and Electomyography was suggestive of primary muscle disease. MRI upper extremities and lower extremities show fatty infiltration of muscles.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Deltoid, Triceps, Glutei, Adductors, Quadriceps, Tibialis Anterior, Peronei, Abdominals and Back Extensors.

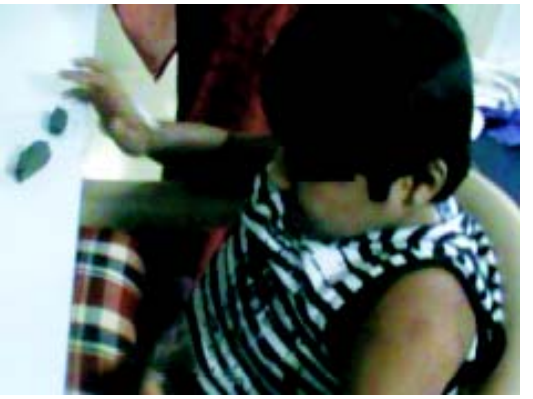
Clinical Improvements seen After Stem Cell Therapy

Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina. His trunk strength had increased and he was able to get up from supine to sitting position on the edge of the cot independently. His upper limb strength also improved with ability to perform overhead activities, which were not possible before therapy. He was made to stand with bilateral push knee splints in standing board, with the aim to improve bone density and bring about toning of muscles. Gradually his standing tolerance improved, and he could sustain standing for 60 minutes at a stretch.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	2898 IU	1376 IU

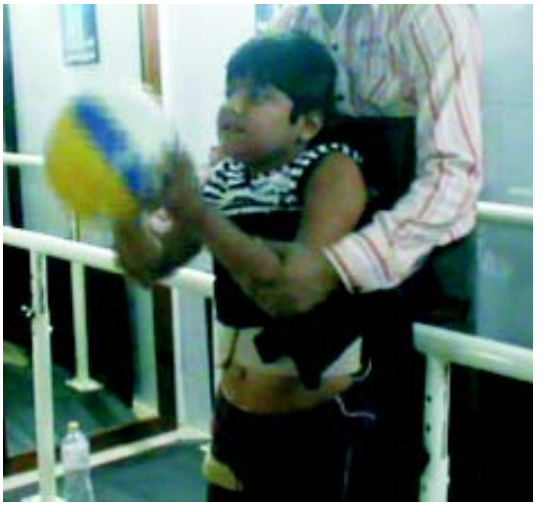


Exercises to improve trunk strength and ability to come to quadruped position.



Increased grip strength and ability to perfrom clay activities.

Ability to stand with bilateral push knee splints and assistance .



Throwing ball, in standing position on the standing board , to train for overhead activities.

Case Report - 78

Diagnosis : *Limb Girdle Muscular Dystrophy*

A young IT professional aged 23 years, presented with a history of bilateral lower extremities weakness and symptoms of frequent falls while walking due to buckling of knees since last 2 years.

Neurologically, she was hypotonic and hyporeflexic. On examination, she had grade 3++ muscle power in bilateral lower extremities and grade 4++ in bilateral upper extremities muscles with majority weakness noticed in quadriceps and glutei (antigravity muscles). Functionally, she was independent in most activities of daily living but needs assistance in climbing stairs, squatting and running. On FIM she scored 125.

On investigation, serum creatinine phosphokinase levels were raised to 3769 IU. EMG was suggestive of generalized myopathic process and muscle biopsy was suggestive of myopathy. MRI scan upper limb and lower extremities showed fatty infiltration of the muscles.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Adductors, Quadriceps.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: She reported feeling of wellbeing and improved stamina, as effort required to perform the activities of daily living was reduced significantly. She could climb stairs without any support which was not possible before. She could get up from floor with much ease, thereby showing improved trunk and hip stability.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	3769 IU	1732 IU

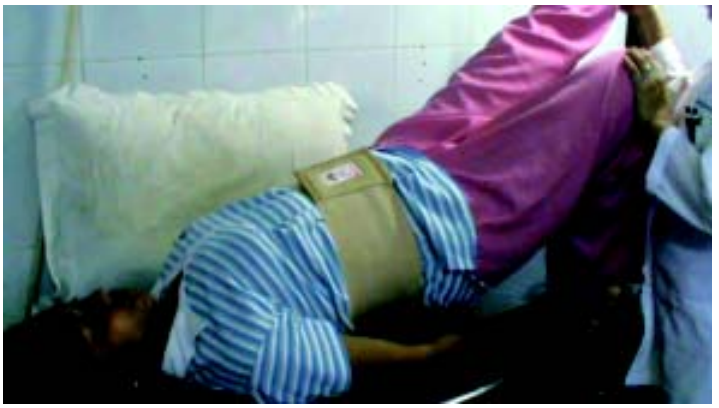


Fig 1: Improved trunk stability and ability to raise one leg while bridging.

Fig 2: Independent descending of stair case without holding the railing.

Improved trunk strength and ability to perform mini squats with minimum assistance.

Case Report - 79

Admission diagnosis : *Duchenne's Muscular Dystrophy*

A 10 year old male as diagnosed with DMD at the age of 7 years as he complained of difficulty in climbing stairs and squatting. He also presented with a history of bilateral weakness of lower limbs. Gradually, weakness in both his legs progressed leading to his walking on toes.

Neurologically, he was hypotonic and hyporeflexic. He had all sensations intact. On examination, he had pseudohypertrophy of calf with tightness of bilateral tendoachellis. He had grade 3+ muscle power in bilateral lower limb and grade 3++ in bilateral upper limb muscles. Functionally, he needed assistance in activities of daily living. He had a hyperlordotic equinnus gait with bilateral internal rotation of hip. On FIM he scored 95. On Brooke and Vignos scale, he scored 2 and 7 respectively. On investigation, the serum creatine phosphokinase levels were raised to 12770 IU. In electromyography studies, right peroneal stimulation with recording from EDB showed low amplitude, which could be due to less muscle mass. DNA testing revealed deletions in exons 49 and 50 of the dystrophin gene, confirming diagnosis of DMD.

MRI of the upper and lower limbs before the stem cell therapy revealed diffuse fatty infiltration of the muscles of the bilateral pelvis, thigh and external compartment of leg muscles. Muscles of the flexor compartment of leg and adductor muscles as well as upper limb muscles were spared.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Quadriceps, Glutei, Deltoid, Abdominals, Peronei, Triceps.

Clinical Improvements seen After Stem Cell Therapy

Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina .His trunk strength had increased and he was able to sit erect as opposed to earlier when he would sit in a slouch posture. His upper limb strength had also increased and he could perform his activities of daily living like bathing and dressing independently. Even his bed mobility had improved like rolling and sitting up on bed, which needed a lot of assistance earlier. He had bilateral tendo Achilles tightness, because of which he had equinnus gait , but gradually with sustained stretching , his gait improved and he started walking with plantigrade feet. His standing tolerance and balance had also improved, with ability to stand for 10 minutes at a stretch. He was also able to walk with the help of bilateral push knee splints and walker for about 20 minutes, which was not possible before the therapy. His Brooke Scale for Upper limb had improved from 2 to 1.

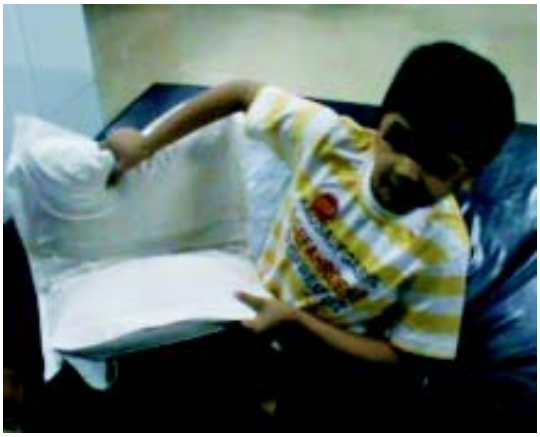
	Before stem cell therapy	After stem cell therapy
Functional Independence Measure	90	91
Creatinine Phosphokinase levels	12770 IU	6960 IU

On Follow up after 1 year : But all his improvements sustained for 9 months post therapy, after which natural course of the disease progressed and he started showing deterioration in his muscle strength. He also started requiring manual assistance while walking apart from the walker. Although the strength of upper limbs remained the same, he started requiring assistance while transferring from wheelchair to bed.

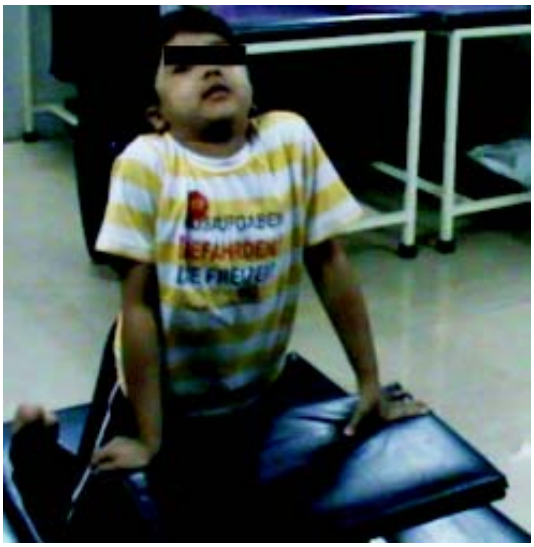
Manual Muscle testing : Following muscles showed deterioration in strength :

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	HIP	Before therapy	After therapy
3++	3	Flexors	3++	3
3	1+	Internal Rotators	3	1+
3	1+	External Rotators	3	1+

Improved trunk control and ability to crawl independently.



Improved upper limb strength and ability to lift weights .



Improved trunk and upper limb strength and ability to come on kneeling position .

Case Report - 80

Diagnosis : *Duchenne's Muscular Dystrophy*

An 11 year old male, diagnosed with DMD at the age of 2 years, as he presented a history of difficulty in getting up from floor (a positive Gower's sign) and frequent falls while walking. Gradually, lower extremity weakness progressed and he stopped walking at the age of 9 years. Upper extremity weakness also set in gradually, with difficulty in overhead activities.

Neurologically, he was hypotonic and hyporeflexic. He had all his sensations intact. On examination, he had grade 1+ strength in bilateral lower limb and grade 2 in bilateral upper extremity with predominantly proximal muscle weakness (proximal more than distal). Functionally, he was dependent on caregiver for most activities of daily living. He was wheelchair bound for mobility. On FIM he scored 48. On Brooke and Vignos scale, he scored 5 and 8 respectively.

On investigation, the serum creatine phosphokinase levels were raised to 2275 IU Electromyography study showed evidence of a myopathic lesion with reinnervation superimposed on the myopathic changes. Low amplitude, short duration polyphastic motor unit potentials were noted in the muscles sampled. Muscle biopsy showed Xp 21 myopathy. DNA testing revealed deletions in exons 48 to 50 of the dystrophin gene, confirming diagnosis of DMD.

MRI of the upper and lower limbs before the stem cell therapy revealed, moderate degree of muscular atrophy diffusely involving both upper and lower limbs with marked adiposity in the intramuscular, intermuscular and subcutaneous fat planes.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: : Deltoid, Biceps, Triceps, Brachioradialis, Extensor Digitorum, Abdominals, Quadriceps, Tibialis Anterior, Peronei, Glutei, Back Extensors, Rhombhoids, Trapezius.

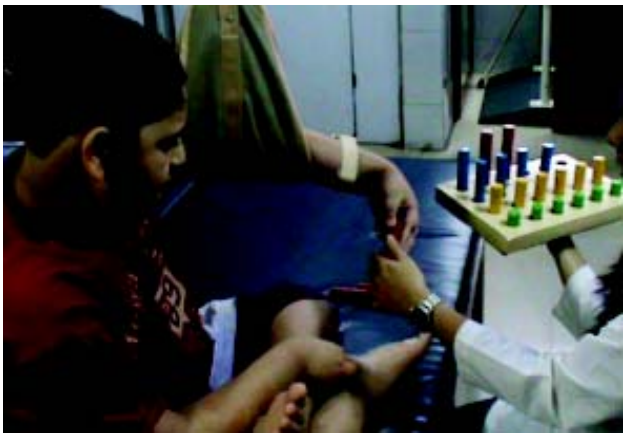
Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported that the effort required to perform the exercises was reduced significantly. Earlier he would feel fatigued out and lethargic the entire day. But post therapy, he was able to sustain exercise sessions for longer. His hand grip strength had increased (as assessed by dynamometer) with improved ability to hold the pen and write, as opposed to earlier when he was unable to write because of poor grip. Also as his grip improved, he was able to pick up pouch, operate a remote and open a zipper independently. His upper limb strength also increased and he could sustain overhead activities which were very difficult earlier, with ease and independence in eating. He had bilateral knee flexor tightness, but with gradual sustained stretching and wearing of bilateral push knee splints ,his knee flexors increased in length.

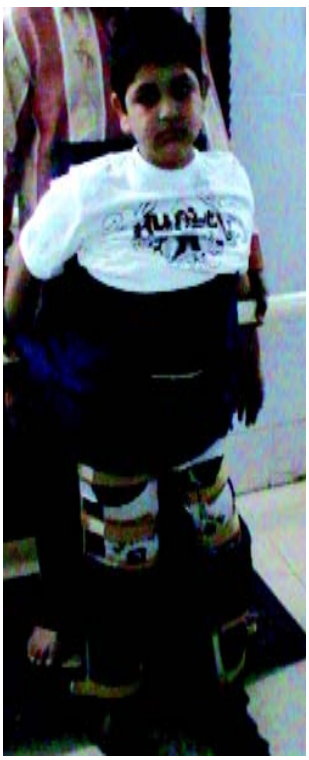
	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	2275 IU	1640 IU

Manual Muscle testing : Following muscles showed improved strength

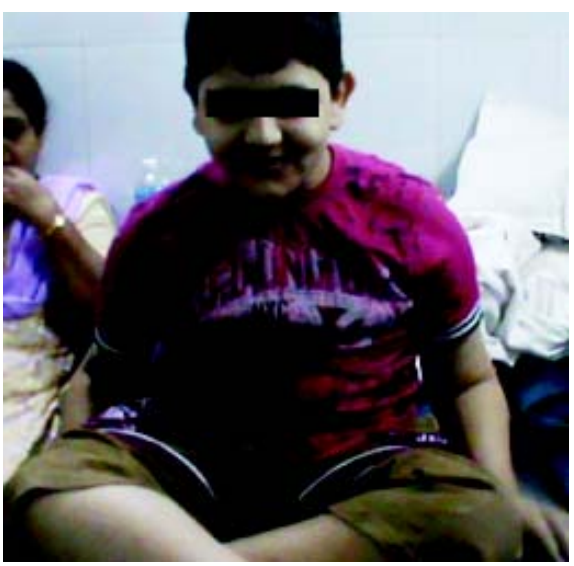
RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	HIP	Before therapy	After therapy
1	2+	Extensors	1	2+
1	2+	Flexors	1	2+
1	2+	Abductors	1	2+
1	2+	Adductors	1	2+
0	1	Internal Rotators	0	1
0	1+	External Rotators	0	1+



Improved upper limb and grip strength and ability to perform peg board activity with ease.



Improved trunk control and sitting balance.



During therapy sessions, standing with bilateral push knee splints, high boots and standing board, to stretch open the lower limb contractures and improve the bone mineral density.

Case Report - 81

Diagnosis : *Muscular Dystrophy*

An 19 year old, known case muscular dystrophy, which started with bilateral lower limb weakness leading to difficulty in walking and climbing stairs since the age of 9. The weakness was progressive with affection of the upper extremity also around the age of 12. He could walk till the age of 9 years. Neurologically, he was hypotonic and hyporeflexic with intact bladder & bowel sensations. On examination, he was obese and had bilateral knee hyperextension. He had grade 0(zero) power in bilateral upper and lower extremities proximally and grade 3+ distally in upper extremity. Functionally, he was totally dependent for all his ADL and transfers. He was wheelchair bound for mobility. On FIM he scored 56. On Brooke and Vignos scale, he scored 2 and 9 respectively.

On investigation, the serum creatine phosphokinase levels were mildly raised.Electrophysiological studies showed evidence of generalized myopathic process in all the muscles examined.

MRI of the upper and lower limbs before the stem cell therapy revealed marked fatty infiltration of the pelvic girdle muscles involving the glutei, posterior thigh muscles, adductors and Vasti. Partial fatty infiltration of the neck muscles noted. There is marked fatty infiltration of all the arm muscles (flexor & extensor comp.) There was marked fatty infiltration of all the forearm muscles with minimal sparing of the flexor digitorum profundus. No osseous abnormality detected.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Deltoid, Triceps, Biceps, Abdominals, Adductors, Quadriceps, Tibialis Anterior, Peronei.

Clinical Improvements seen After Stem Cell Therapy.

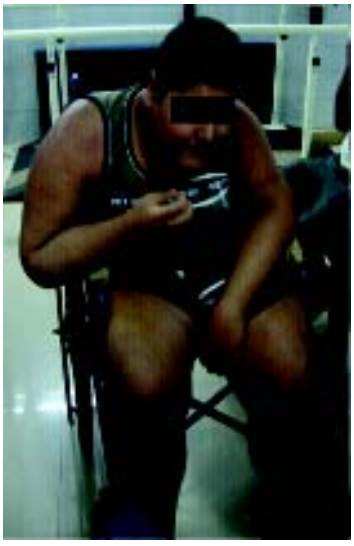
Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina. He was very obese and lethargic, but post therapy, following aggressive rehabilitation he had lost 10 kilograms of weight, and his waist size reduced from 42 to 35 inches .His alertness and spontaneity of movements had improved, and he was feeling more active than before. His grip strength increased with independence in eating, combing and brushing, which was not possible before. He could also hold objects like mobile phone, remote control and could play videogames independently, which were all assisted activities earlier. His trunk strength increased with improved dynamic sitting balance. Earlier he would complain of pain in all his joints, which post therapy because of exercises, had reduced significantly. He also got independent in his bed mobility like rolling and side lying. His lower limb strength had increased, earlier he had no movements, but post therapy he showed flicker of movements in all lower limb muscles.

Manual Muscle testing: Following muscles showed improved strength

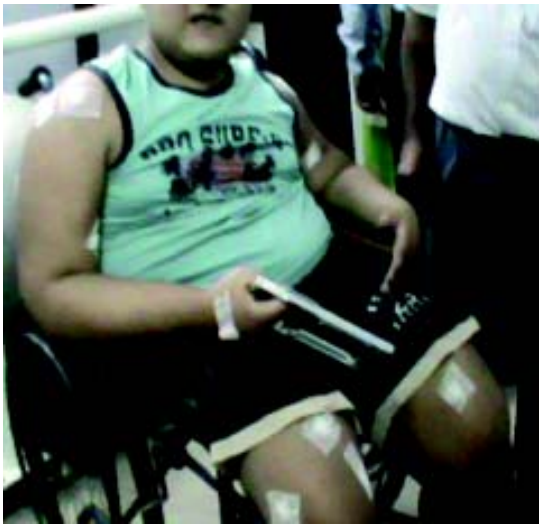
RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	HIP	Before therapy	After therapy
0	1	Extensors	0	1
0	1+	External Rotators	0	1+
0	1+	Adductors	0	1+
		KNEE		
2	2++	Flexors	2	2++
		FOOT		
3	3+	Tibialis Posterior	3	3+
0	1	EHL	0	1
		SHOULDER		
1	1++	Extensors	1	1++
1	1++	Abductors	1	1++
1	1++	Triceps	1	1++
0	1++	Internal Rotators	0	1++
1	1+	Biceps	1	1+
1	1++	Triceps	1	1++

Increased trunk strength and improved bed mobility like rolling and side lying .

Improved trunk control and ability to sit independently on the edge of the bed.



Improved Upper Limb strength and ability to eat independently.



Improved grip strength and ability to perform gripper exercises.

Case Report - 82

Diagnosis : *Muscular Dystrophy*

Clinical Presentation: A 38 year old housewife gave history of symptoms of left lower limb weakness, especially proximal muscles, leading to difficulty in climbing stairs and getting up from floor, since 7 years. Her weakness had been progressive. She had a waddling gait. She also had difficulty in overhead activities.

Neurologically, she was hypotonic and hyporeflexic with all sensations intact. She had grade 2+ strength in bilateral lower extremities proximally with bilateral foot drop and grade 3+ in bilateral upper extremity. Functionally, she was independent in most ADL with difficulty in climbing stairs, squatting, etc. On FIM she scored 109.

On investigations, the serum creatine phosphokinase levels were slightly raised. Electromyography studies were suggestive of primary muscle disease, though the muscle biopsy did not show any abnormality (probably due to sampling of unaffected muscle).

MRI of the upper and lower limbs before the stem cell therapy revealed partial fatty infiltration in the proximal muscles of all four limbs(glutei, deltoid) and marked fatty infiltration in the leg muscles and flexor compartments of the forearm.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally Glutei, Abdominals, Adductors of the hip, Hamstrings, Tibialis Anterior, Peronei, Triceps.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: On follow up, at the end of 3 months, she reported feeling of wellbeing and improved stamina. Her trunk and upper limb strength had increased with ability to perform bed mobility activities independently, like rolling, getting up from lying to sitting position, transfers from bed to chair, getting up from commode , bathing , etc. Earlier she needed assistance in all these activities. Her lower limb strength also increased with improved stability in walking, and ability to climb stairs which she could not do before the therapy.

	Before stem cell therapy	After stem cell therapy
Functional Independence Measure	109	111

Improved lower limb and trunk strength and ability to perform knee extension with weights.

Learning to get up independently , from lying to sitting position on the cot

Improved trunk strength and ability to perform bridging and all fours independently.

Improved upper limb strength and ability to perform overhead activity independently.

Case Report - 83

Diagnosis : *Limb Girdle Muscular Dystrophy*

Clinical Presentation: A case of a 37 year old male patient with history of bilateral lower limb weakness which was progressive in nature, since 1996.This lead to difficulty in walking, climbing stairs and getting up from floor. Since past 8 years, even upper extremity weakness had developed with difficulty in overhead activities. He could walk with the help of stick. He had a family history of muscular dystrophy, with younger sister being affected similarly.

Neurologically, he was hypotonic and hyporeflexic. He had all sensations intact. On examination, he had grade 2+ strength in bilateral lower limbs and grade 2++ in bilateral upper limbs with proximal muscle weakness more than distal. Functionally, he was dependent on the wife for most ADL. He could walk with the help of stick but required assistance for transfers. On FIM he scored 86.

On investigations, the serum creatine phosphokinase levels were raised to 3730 IU. Electromyography studies were suggestive of primary muscle disease. MRI of the upper and lower limbs before the stem cell therapy revealed marked fatty infiltration of predominantly the pelvic girdle muscles, thigh muscles and arm muscles with relative sparing of the glutei, rectus femoris, Sartorius,deltoid,and forearm muscles.

Stem cells were also injected intramuscularly at the motor points of the following muscles: Deltoid, Abdominals, Glutei, Quadriceps, LL Adductors and Hamstrings.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: On follow up, at the end of 3 months, he reported feeling of wellbeing and improved stamina. His trunk and lower limb strength had increased, with ability to walk independently indoors, with the aid of a stick .Earlier he would need his wife's support along with a walker to walker indoors. He improved in his bed mobility as well like, getting up from lying to sitting position on the edge of the cot, and getting up from cot to standing. Earlier he would strain his neck and back while sitting upright but post therapy with exercises, his trunk strain resolved completely with no complaints of pain.

Improved lower limb and trunk strength with ability to walk with a stick.

Improved trunk strength and ability to shift on the edge of the cot independently.

Case Report - 84

Diagnosis : *Limb Girdle Muscular Dystrophy*

A 36 year old female patient, with a family history of muscular dystrophy(in elder brother) gave history of experiencing bilateral lower extremity weakness with complaints of difficulty in climbing stairs, getting up from floor since the age of 12-13 years. Gradually weakness progressed leading to difficulty in walking as well as ability to perform overhead activities. She had completely stopped walking since 2007.

Neurologically, she was hypotonic and hyporeflexic with intact sensations . On examination,she had grade 1+ muscle power in bilateral lower extremities and grade 2++ power in bilateral upper extremities with proximal muscle weakness more than distal. She had hypertrophy of bilateral calf muscles. Functionally, she was dependent for most ADL and wheelchair bound for mobility. On FIM she scored 59.

On investigations,the serum creatine phosphokinase levels was raised. Electromyography studies were suggestive of primary muscle disease, while the muscle biopsy confirmed the diagnosis of muscular dystrophy.

MRI of the upper and lower limbs before the stem cell therapy revealed severe atrophy of the muscles of the appendicular and axial skeleton with extensive fatty infiltration.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Deltoid, Adductors of shoulder, Biceps, Glutei, Quadriceps, Hamstrings, Adductors of hip, Abdominals, Back Extensors.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: On follow up, at the end of 3 months, she reported feeling of wellbeing and improved stamina. She could perform all exercises with ease and better. Her trunk strength and dynamic sitting balance had improved, with ability to sit on the edge of the cot and pick up objects from the ground by bending from trunk .With sustained regular stretching, flexibility of all her joints mainly hip, knee and elbow improved. She was able to flex her elbows independently and use them for functional activities like eating , bathing , combing, Also the caretaker reported that it was easier to shift her from bed to wheelchair and vice versa , as she was assisting in transferring herself , because of increased trunk strength.

	Before stem cell therapy	After stem cell therapy
Creatinine Phosphokinase levels	3028 IU	1152 IU

Improved lower abdominal strength and ability to perform strengthening exercis

Ability to perform upper limb resisted exercise with the help of theraband.

Improved upper limb strength and ability to perform active elbow extension with half kg weights on.

Case Report - 85

Diagnosis : *Muscular Dystrophy*

Clinical Presentation: A 29 year old male presented with complains of difficulty in climbing stairs and getting up from floor since 2 years. He also had upper extremity weakness, which had started recently, about a year ago, with difficulty in overhead activities. He also complained of easy fatiguability. He walked with a Lordotic Trendelenberg's gait.

Neurologically, he was hypotonic and hyporeflexic, He had all sensations intact. He had grade 3++ strength in bilateral upper limb and lower limb proximally and grade 4+ distally. Functionally, he was totally independent in all ADL. He walked with a bilateral Trendelenberg's Gait. On FIM he scored 124.

On investigations,the serum creatine phosphokinase levels was raised. Electromyography studies were suggestive of a myogenic cause.

MRI of the upper and lower limbs before the stem cell therapy revealed symmetrical areas of atrophy and fatty replacement of the gluteal and thigh muscles with sparing of the leg,inter-costal arm and forearm muscles.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei and Quadriceps.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: On follow up, at the end of 3 months, he reported feeling of wellbeing and improved stamina. His lower limb and trunk strength increased with improved stability while walking .Earlier he would have the fear of buckling from knees, while walking, but post therapy with regular strengthening exercises, his episodes of buckling almost reduced to nil. He was also able to climb stairs, with no aid of the railing .He could climb almost 15 steps comfortably as opposed to earlier when he would fatigue out and lose balance very easily while climbing. During exercise sessions he improved in his mat exercises like kneeling, kneel walking and quadruped position.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	2410 IU	804 IU

Manual Muscle testing : Following muscles showed improved strength

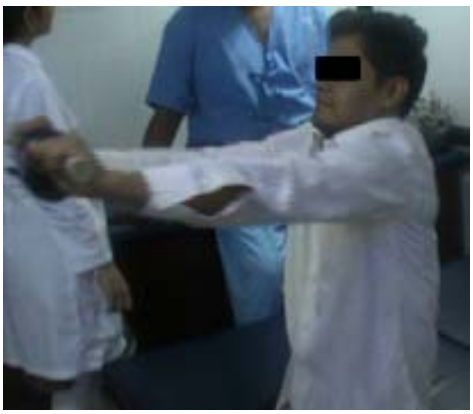
RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
2	2++	Extensors	2	2++

Improved trunk strength and ability to bend and pick up objects from floor.

Improved trunk strength and ability to perform kneeling exercises with weights in hands.

Improved back extensor strength and ability to perform active dorsolumbar extension

Independent stair case climbing .



Increased upper limb strength and ability to perform upper extremity strengthening exercises with weights.

Case Report - 86

Diagnosis : *Duchenne Muscular Dystrophy*

A 13 year old boy was diagnosed with DMD at the age of 3years when his parents noticed hypertrophy of his bilateral calf muscles. Gradually, weakness in both lower extremities began which led to difficulty in getting up from the floor with Gowers' maneuver and climbing stairs with frequent falls while walking. He stopped walking 4 years back. He also developed upper extremity weakness with difficulty in overhead activities.

Neurologically, he was hypotonic and hyporeflexic with all sensations intact. On examination, he had the bilateral knee and elbow flexion deformity with Tallipoequinovarus. He had grade 1 power in his bilateral upper extremity, proximally and grade 3 distally. Functionally, he was dependent for most activities of daily living and wheelchair bound for mobility. On FIM he scored 48. On Brooke and Vignos scale, he scored 4 and 9 respectively.

On investigation, the serum creatine phosphokinase levels were raised to 2004 IU. Electromyographic study of both deltoid, biceps, vastalis lateralis and soleus suggested a myopathic pattern. It revealed reduced insertional activity, polyphagic reduced amplitude with complete interference pattern. DNA testing revealed deletion in dystrophin gene of exon 53, confirming the diagnosis. Muscle biopsy section showed featured suggestive of muscular dystrophy.

MRI of the upper and lower limbs before the stem cell therapy revealed, marked fatty infiltration of predominantly the pelvic girdle muscles, leg muscles with relative sparing of the tibialis posterior, flexor hallucis longus and flexor digitorum longus muscles. There is partial fatty infiltration of the muscles of the arm and forearm (mainly flexor compartment).

Stem cells were also injected intramuscularly at the motor points of the following muscles: Glutei, Quadriceps, Peronei, Abdominals, Triceps, Biceps and Deltoid.

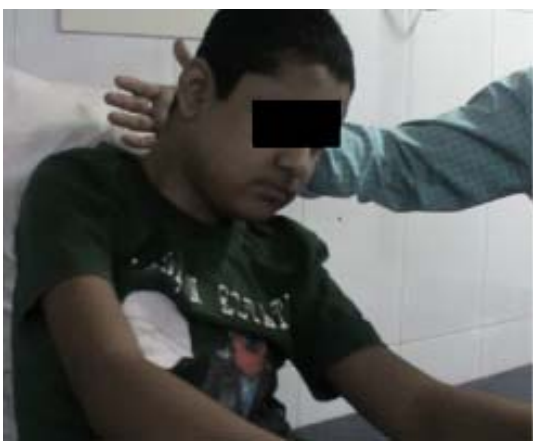
Clinical Improvements seen After Stem Cell Therapy.

Functionally: On follow up at 6 months, he reported feeling of wellbeing and improved stamina, as effort required to perform the exercises was reduced significantly. Earlier, he would feel fatigued out and lethargic the entire day. Flexibility in his muscles had increased, as he had severe tightness of knee flexors, but gradually, due to compliance to sustained stretching and splintage, he began to straighten his knees. Earlier, he was non cooperative for exercise sessions but gradually he got compliant and would perform exercises with ease. Also, his other joints like ankles and elbow bilaterally had started opening up, as he had severe flexion contractures in them. His neck muscle strength increased with improved neck holding. During physiotherapy sessions, he was made to stand on the standing board thereby leading to improved bone density and toning of muscles.

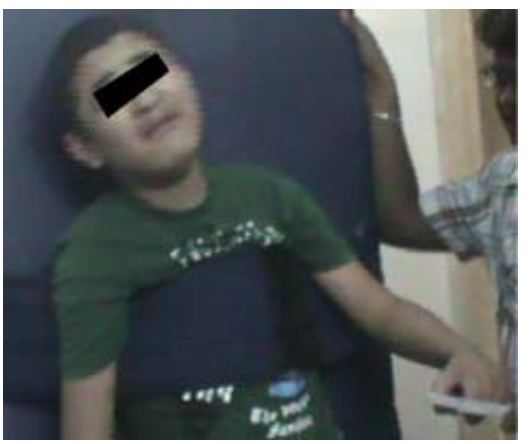
	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	2004 IU	1927 IU

Improved sitting balance and trunk control, with ability to sit without support on the edge of the cot.

Upper limb strengthening and gripping activities during the therapy sessions.



Improved trunk control and ability to bend and reach out, without loosing balance.



Standing on the standing board and performing gripping activity.

Case Report - 87

Diagnosis : *Duchenne Muscular Dystrophy*

A 9 year old boy, suffering with DMD since the age of 6 complained of bilateral lower extremity weakness leading to frequent falls while walking. Gradually, the weakness progressed with difficulty in climbing stairs, getting up from squatting position and performing overhead activities (indicating progression to affection of upper limbs too).

Neurologically, he was hypotonic and hyporeflexic with intact sensations. Manual muscle charting indicated grade 2+ strength in bilateral lower limbs and grade 3 in bilateral upper limbs, with proximal muscle weakness more than distal. On examination, he had pseudohypertrophy of bilateral calf muscles. Functionally, he needed assistance in few activities of daily living. He had a lordotic Trendelenberg's gait. On FIM he scored 122. On Brooke and Vignos scale, he scored 2 and 3 respectively.

On investigation, the serum creatine phosphokinase levels were raised to 2470 IU. Electromyography/nerve conduction studies showed evidence of generalized myopathic process in all the muscles examined. Muscle biopsy showed severe fascicles where some fibre size variation was noted along with distinct rounding, some ragged fibres, occasional hyalinization, some miniaturized fibre, mild perimyscial fibrosis and prominent vessels. Genetic test revealed deletion in exons 49-50 of the dystrophin gene confirming the diagnosis of DMD.

MRI of the upper and lower limbs before the stem cell therapy revealed, partial fatty infiltration of predominantly the pelvic girdle, posterior thigh and vasti muscles with relative sparing of other thigh muscles. Partial fatty infiltration of the upper limbs muscles: triceps and pronator tere, supinator, flexor carpi ulnaris and extensor pollicis longus muscles with sparing of rest of the muscles was also noted. 2 D echo Cardiography: LVEF- 65%

ECG: abnormal ECG probably suspecting acute MI (anterior), Ventricular hypertrophy and short PR interval RSR pattern .

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Abdominals, Quadriceps, Adductors of Hip, Deltoid, Biceps.

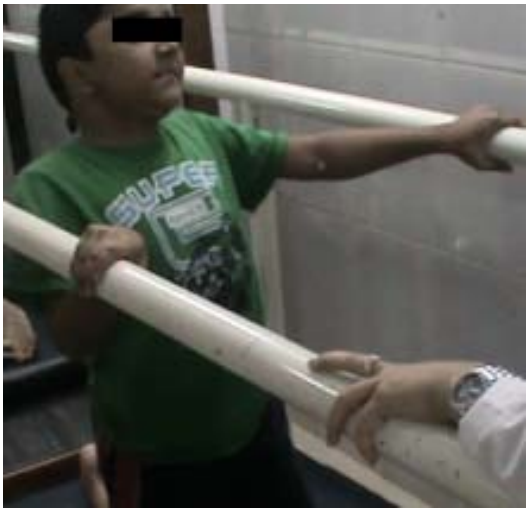
Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina. His lower limb and trunk strength had increased, with significant reduction in frequency of falls. Earlier, he had hyper lordotic waddling gait, but after the therapy as strength of his girdle muscles improved he was able to walk with erect posture and narrow base of support, his swaying while walking was much less and he was more stable. He also reported ease in getting up from lower level surfaces without

any manual assistance. Also, while descending on the chair, he could perform controlled sitting, as opposed to earlier when he would just collapse, because of gravity and weak muscles giving way to it. He could climb stairs comfortably and with less effort.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	2470 IU	1910 IU

Improved upper limb and trunk strength with ability to lift weights and rotate the trunk



Improved lower limb and trunk strength with ability to perform kneeling.

Improved trunk strength and ability to get up independently from bed.

Ability to walk independently with erect posture and narrow base of support with no waddling

Case Report - 88

Diagnosis : *Limb Girdle Muscular Dystrophy*

A 41 year old male patient, a clinically diagnosed case of LGMD, since 1991, gave history of bilateral lower extremity weakness with difficulty in squatting and climbing stairs. Gradually weakness progressed such that he was wheelchair bound since 5 years. He also had upper extremity weakness with difficulty in overhead activities.

Neurologically, he was hypotonic and hyporeflexic with intact sensations. On examination he had grade 2 muscle power in bilateral lower extremity proximally, bilateral foot drop and grade 2 in bilateral upper extremity. He had following multiple contractures , such as, left elbow flexion and pronator contracture and right wrist extension and radial deviation limitation. Functionally, he was dependent on caregiver for most ADL and wheelchair bound for mobility. On FIM he scored 53.

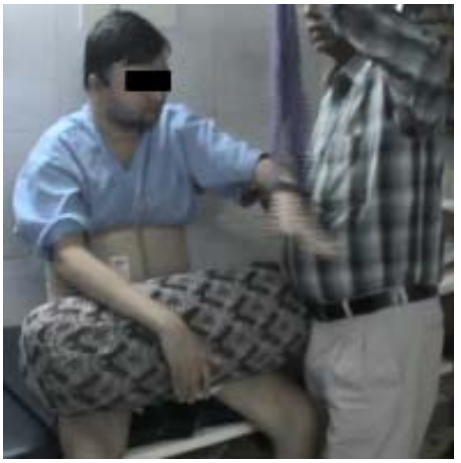
On investigations, the serum creatine phosphokinase levels were raised. Electromyography studies were suggestive of end stage muscle disease.

MRI of the upper and lower limbs before the stem cell therapy revealed extensive fatty replacement and atrophy involving the muscles of upper and lower limbs.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally Deltoid, Biceps, Triceps, Opponens, Quadriceps, Tibialis Anterior, Peronei, Abdominals

Clinical Improvements seen After Stem Cell Therapy

Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina. His complaint of fatigue or exhaustion in doing activities got completely resolved. His trunk strength had increased with improved dynamic sitting balance on the edge of the cot .Earlier he would need assistance by the caretaker or backrest to support him, but post therapy he was able to do that independently. With regular sustain stretching; his lower limb hip and knee flexion contractures had also opened up, thereby leading to increased flexibility of his muscles.



Suspension exercises to improve upper limb muscles.

Exercises to improve abdominal muscles

Improved trunk strength and sitting balance on the edge of the cot.

Case Report - 89

Diagnosis : *Muscular Dystrophy (LGMD)*

Clinical Presentation: A 48 year old patient with a history of gradually progressive bilateral lower extremity weakness since 20 years, which manifested as difficulty in climbing stairs and getting up from the floor. Gradually weakness increased and she had stopped walking since 7-8 years. She also reported upper extremity weakness since 5 years with difficulty in overhead activities.

Neurologically, she was hypotonic and hyporeflexic with intact sensations. She had grade zero muscle power in bilateral lower extremities and grade 1 power in bilateral upper extremity muscles proximally and grade 3++ distally. On investigation, she had hypertrophy of bilateral calf muscles. She had bilateral TA tightness. Functionally, she needed assistance for most ADL and was wheelchair bound for mobility. On FIM she scored 72.

On investigation, though serum creatine phosphokinase levels were within normal limits, EMG revealed generalized active primary muscle disease affecting distal more than proximal lower extremity and distal and proximal upper extremity muscles.

MRI of the upper limbs and lower limbs showed marked fatty infiltration of the pelvic girdle,thigh,legs, arms and forearm muscles.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Deltoid, Triceps, Biceps, Trapezius, Palmar Interossei, Opponens Pollicis, Dorsal Interossei, Abdominals, Back Extensors, Glutei, Quadriceps, Tibialis Anterior, Peronei and Hamstrings.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: On follow up, at the end of 6 months, she reported feeling of wellbeing and improved stamina. Her trunk strength increased with improved bed mobility. She got independent in rolling , shifting on the edge of cot and getting up from lying to sitting position. Earlier she would need assistance in all these activities. Her upper extremity and grip strength increased with independence in activities like eating and combing , all of which needed assistance prior to therapy. During therapy she was recommended to stand on standing board using bilateral push knee splints, in order to bring about toning of muscles and improve the bone mineral density due to weight bearing. She could sustain standing for almost 60 minutes at a stretch, which she performed almost after 5 years of immobility.

Manual Muscle testing : Following muscles showed improved strength

RIGHT		MUSCLES	LEFT	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
0	2-	Extensors	0	2-
0	1+	Flexors	0	1+
0	1+	Abductors	0	1+
0	1+	Adductors	0	1+
		KNEE		
0	2-	Flexors	0	2-
1	2+	Extensors	1	2+
		SHOULDER		
1	2+	Flexors	1	2+
1	2+	Abductors	1	2+
1	2+	Adductors	1	2+
0	1++	**ABDOMINALS**		


Improved grip and pinch strength and ability to perform gripping exercises with gripper.

Suspension exercises to strengthen hip girdle musculature.

Standing with bilateral push knee splints on standing board , to bring about toning of muscles and improve bone mineral density due to weight bearing.

Case Report - 90

Diagnosis : *Limb Girdle Muscular Dystrophy*

A young IT professional, aged 29 years, gave history of bilateral lower limb weakness since 10 years with increasing difficulty in climbing stairs and getting up from floor. Gradually weakness progressed to the upper extremities, over the last 3 years with difficulty in overhead activities. He also had history of epilepsy, with seizure frequency of once a year till November 09 and hence is on antiepileptic medications.

Neurologically, he was hypotonic and hyporeflexic with intact sensations. He had grade 2+ strength in bilateral lower limbs and grade 2+ in bilateral upper limbs with proximal muscle weakness more than distal. Functionally, he needed assistance for most ADL. He walked with a stick with lordotic gait and predominant abdominal muscle weakness. On FIM he scored 63.

On investigations, the serum creatine phosphokinase level were (2902 IU) raised. Electromyography studies were suggestive of primary generalized muscle disease, while the muscle biopsy confirmed the diagnosis of muscular dystrophy and immunohistochemical profile was that of Dysferlinopathy.

MRI of the upper and lower limbs before the stem cell therapy revealed moderate fatty infiltration in all four limbs.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally:Quadriceps, Tibialis Anterior, Peronei, Glutei, Abdominals, Deltoid and Biceps.

Clinical Improvements seen After Stem Cell Therapy

Functionally: On follow up, at the end of 3 months, he reported feeling of wellbeing and improved stamina. He could perform all exercises with ease .His trunk strength had increased with ease in performing all mat exercises. He got independent in getting up from lying to sitting position and also from sitting to standing , all of which needed aid from the caretaker. His upper limb strength had increased with ability to push up on bed and prop himself up on bed independently. He also got independent in his activities of daily living like bathing, dressing , feeding.

	Before stem cell therapy	After stem cell therapy
Functional Independence Measure	63	65
Creatinine Phosphokinase levels	2902 IU	1967 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
2	2+	Extensors	2	2+
2	2+	Abductors	2	2+
2	2+	Adductors	2	2+
		KNEE		
0	1++	Flexors	0	1++
2	2+	Extensors	2	2+
		ANKLE		
0	1++	Dorsiflexors	0	1++
2	2++	**ABDOMINALS**	2	2++
		SHOULDER		
2	3+	Rotators	2	3+

Ability to perform dressing independently.

Increased grip and pinch strength and ability to perform gripping on pins.

Ability to lift up weights of 250 grams.

Ability to perform upper extremity strengthening exercises with weights.

Case Report - 91

Diagnosis : *Duchene's Muscular Dystrophy*

A 13 year old male was diagnosed with DMD at the age of 3 years. Parents noticed frequent falls while walking along with gradual weakness of bilateral lower limb muscles. Further, difficulty in climbing stairs and getting up from floor was noticed. He stopped walking at age of 10, which also coincided with onset of upper limb weakness leading to difficulty in overhead activities.

Neurologically, he was hypotonic and hyporeflexic. He had all his sensations intact. On examination: had grade 1 muscle power in all 4 limbs proximally and grade 3+ distally. He showed no family history of similar condition. He had been on continuous rehabilitation and walked indoors with help of calipers for about 60 steps. Functionally, he was dependent on the caregiver for most activities of daily living and was wheelchair bound for mobility. On FIM he scored 49. On Brooke and Vignos scale, he scored 2 and 9 respectively.

On investigation, creatine phosphokinase levels were raised to 3620 IU, muscle biopsy gave an impression of muscular dystrophy, electromyography studies showed evidence of myopathic pattern in all the muscles in the upper limbs and genetic test revealed deletions in exons 53-55, these deletions and clinical presentations were consistent with diagnosis of DMD.

MRI of the musculoskeletal system revealed, marked fatty infiltration of pelvic girdle muscles, anterior and peroneal compartment leg muscles, chest girdle and paraspinal muscles while partial infiltration of gastrocnemii and soleus, flexor and extensor compartment muscles of the arm and flexor muscles of the forearm.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Quadriceps, Abdominals, Biceps, Triceps and Deltoid.

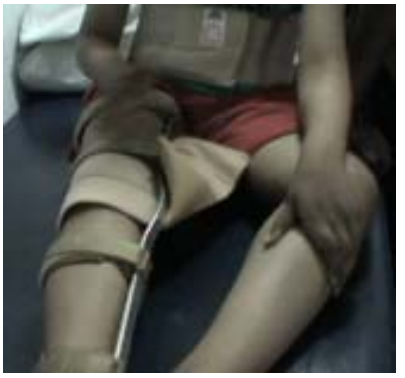
Clinical Improvements seen After Stem Cell Therapy.

Functionally: 3 months after the therapy, his endurance to sustain exercises was increased tremendously. He reported feeling of wellbeing and improved stamina. Earlier, he would feel fatigued out and lethargic the entire day. His posture had improved, and was more erect and upright unlike before when he would sit with a hump and sloughed posture. He could walk independently with the help of calipers and a walker. As strength of his limbs improved he began to raise his upper extremity for overhead activities, which was not possible prior to the therapy.

	Before stem cell therapy	After stem cell therapy
Functional Independence Measure	49	54
Creatinine Phosphokinase levels	3620 IU	1764 IU

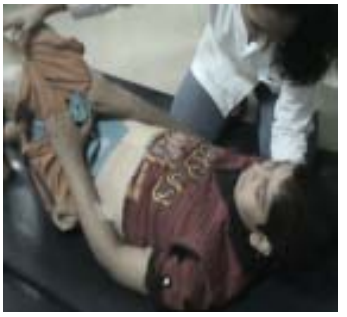
On Reevaluation Assessment Scale Improvement: He improved on Brooke Scale for Upper Extremities from Grade 3 to 2 as he was able to raise his arms above head, only by flexing the elbow or using accessory muscles as opposed to earlier when he could not raise the hands above head at all. He even improved on his Vignos Scale for Lower extremities from Grade 9 to 7 as he was wheel chair bound totally but after the therapy he was able to walk with bilateral push knee splints independently.


Mobility improved with ability to walk with walker and push knee splints and later independently, without the walker.



Improved hand function and grip strength with ability to remove the splints independently.

Improved upper limb strength and ability to do activity of daily living like combing.




Improved trunk strength, with ability to perform assisted crunches and kneeling.

Case Report - 92

Diagnosis : *Muscular Dystrophy*

A 10 year old boy with history of weakness in both lower limbs was diagnosed with DMD at the age of 3 years since his parents noticed that he had difficulty in getting up from squatting. This weakness gradually progressed such that, he started losing his balance while walking and walked with a wide based equinnus with lordotic gait and needed support of one person since the last 3 months.

Neurologically, he was hypotonic and hyporeflexic. His sensations as well as bladder and bowel functions were intact. On examination, he had pseudohypertrophy of calf muscles with tendoachilles tightness which was stretchable upto neutral (right more than left). He also had a mild kyphotic posture on sitting. Functionally, he needed maximum assistance for all his activities of daily living. On FIM he scored 68. On Brooke and Vignos scale, he scored 3 and 9 respectively.

On investigation, the serum CPK levels had raised to 4895 IU. The detection analysis of dystrophin gene for DMD/BMD (for presence of 18 exons) showed no deletions. Muscle biopsy confirmed the diagnosis of muscular dystrophy. The muscle fibres varied in shape and size and angulation of fibres was seen. Few fibres edematous and blood vessels were filled with RBCs and scattered inflammatory cells were also seen.

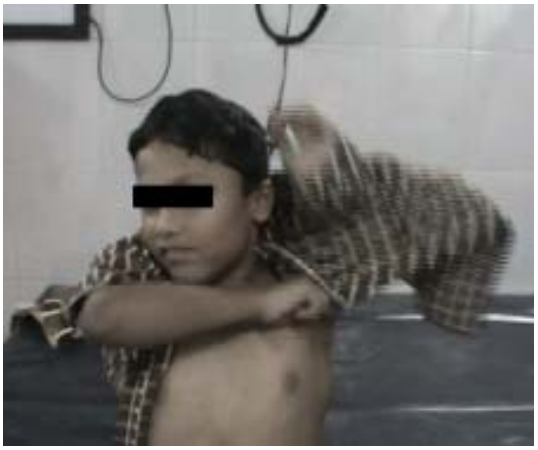
MRI of the upper and lower limbs before the stem cell therapy revealed moderate-to-extensive fatty infiltration of the pelvic girdle muscles. Mild-to-moderate fatty infiltration was noted in the muscles of the bilateral thigh. Minimal fatty infiltration of the muscles of anterior compartment of the leg with the muscle fibres showing moth-eaten appearance. In the lateral compartment peroneus brevis muscle showed moderate fatty infiltration while the muscle fibres of the peroneus longus were well-maintained. Mild-to-moderate fatty infiltration was noted in the deeply placed muscles of the posterior compartment of the leg. Mild fatty infiltration in the muscles of the arm and the forearm with moth-eaten appearance.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Quadriceps, Adductors of hip, Deltoid, Adductors of shoulder; Abdominals and Back Extensors.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: On follow up at the end of 3 months, he reported feeling of wellbeing and improved stamina, as effort required to perform the activities of daily living was reduced significantly. He could dress his lower body, and could also comb his hair independently, which would be difficult to do earlier.

	Before stem cell therapy	After stem cell therapy
Functional Independence Measure	68	69



Improved ability to perform upper body dressing.

Improved grasp and hand function.

Improved knee flexor strength and ability to bend the knee.

Improved strength of lower limb abductors and ability to perform resistive suspension therapy exercises.

Case Report - 93

Diagnosis : *Muscular Dystrophy*

A case of a 13 year old male , presenting with history of pain and cramps while walking since the age of 10.Following which he gradually started having difficulty in getting up from floor and in climbing stairs .He also reports increasing frequency of falls while walking. In the last 2-3 months, he developed weakness in his upper limbs with difficulty in overhead activities.

Neurologically, he was hypotonic,hyporeflexic with intact sensations.On examination, he had winging of scapulae bilaterally and scoliosis of spine. Muscle power was grade 2 in the proximal muscles of both upper and lower limbs . Functionally he needed minimal assistance for his activities of daily living (ADL) He is ambulatory with lordotic gait. On FIM he scored 101.

On investigations,the serum creatine phosphokinase levels was raised. Electromyography studies were suggestive of primary muscle disease, while the muscle biopsy confirmed the diagnosis of muscular dystrophy.

MRI of the upper and lower limbs before the stem cell therapy revealed generalized loss of muscle bulk with associated thinning of the pelvic girdle muscles, moderate fatty infiltration of the thigh muscles, minimal infiltration of the leg muscles and sparing of the upper limb muscles.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally Glutei, Adductors of hip, Quadriceps, Abdominals, Tibialis Anterior, Deltoid, Rhomboids, Latissmus dorsi, Pectoralis; Abdominals and Back Extensors

Clinical Improvements seen After Stem Cell Therapy.

Functionally: On follow up, at the end of 6 months, he reported feeling of wellbeing and improved stamina. His trunk and lower limb strength had increased with improved stability in walking. His gait which was equinnus wide based hyper lordotic, gradually got near normal with plantigrade feet along with increased walking tolerance and speed . His stance stability improved with ability to perform unilateral stance while exercising, which was not possible before the therapy. His lower limb antigravity muscle strength increased and he was able to perform squatting independently .He could also use an Indian toilet and get up to stand easily, which was very difficult before therapy. Earlier he would fall 4-5 times a day, but post therapy his frequency of falls almost reduced to 2 times in six months. He was also able to climb stairs independently, where in earlier he would need the aid of the railing. His upper limb strength had increased with ability to lift weights and perform overhead activities, which he could not do before.

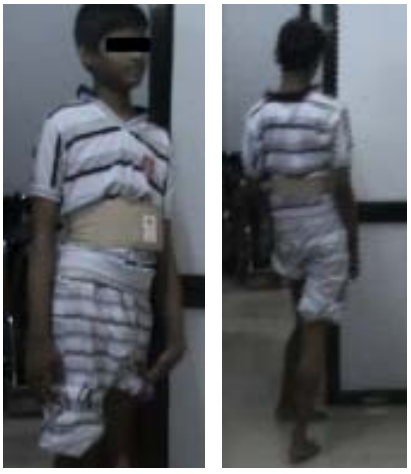
	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	8880 IU	5966 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
2	2+	Extensors	2	2+
2	2++	Abductors	2	2++
2	2++	Adductors	2	2++

Increased trunk strength and ability to perform cat camel exercises in quadruped position.

Ability to shift on the edge of the bed independently.



Improved gait, with narrow base of support and plantigrade feet placement.

Improved lower abdominal strength and ability to perfrom lower abdominal exercises.

Improved trunk strength and ability to get up independently from lying to sitting position on the edge of the bed independently.

Case Report - 94

Diagnosis : *Muscular Dystrophy*

A 35 years old male gave history of difficulty in activities such as running, climbing stairs and squatting since the age of 5 years. Subsequently, he started to walk on his toes at the age of 9 years. At the age of 20 years, his weakness had progressed to the upper limbs with involvement of his respiratory muscles since the last 3 ½ years. He had been on the BiPAP since then due to breathlessness, especially in lying position. He could not lie down supine and was comfortable only in sidelying position.

Neurologically, he was hypotonic and hyporeflexic. All his sensations were intact. On examination, he had pseudohypertrophy of deltoid muscles with the hip,elbow and knee contractures bilaterally along with a kyphoscoliosis of the spine. Wasting of thenar and hypothenar muscles were also seen bilaterally. He had muscle power of grade 1 in proximal muscles of both the upper and lower limbs. Functionally, he needed maximum assistance in all his activities of daily living and was wheelchair bound for mobility. On FIM, he scored 69.

On investigations, the serum creatine phosphokinase levels were raised to 1800 IU. Electromyography study suggested of primary muscle disease affecting the proximal muscles maximally. The muscle biopsy showed rounded fibres of varying size, presence of foci of muscle fibre necrosis with large mononuclear cell and polymorphonuclear reaction and very slight increase of connective tissue, suggesting inflammatory myopathy with sub acute polymyositis. Genetic testing of dystrophin gene did not reveal any deletions.

MRI of the upper and lower limbs revealed extensive fatty infiltration of the pelvic girdle muscles and bilateral thigh muscles. Mild to moderate fatty infiltration of the leg muscles was noted. Moderate to extensive fatty infiltration was noted in the bilateral arm and forearm muscles with extensive fatty infiltration of the biceps femoris, extensor carpi radialis longus and coracobrachialis.Pulmonary function test showed severe restriction 2-D Echo cardiography: LVEF 60% with moderate pericardial effusion and signs of pulmonary hypertension.

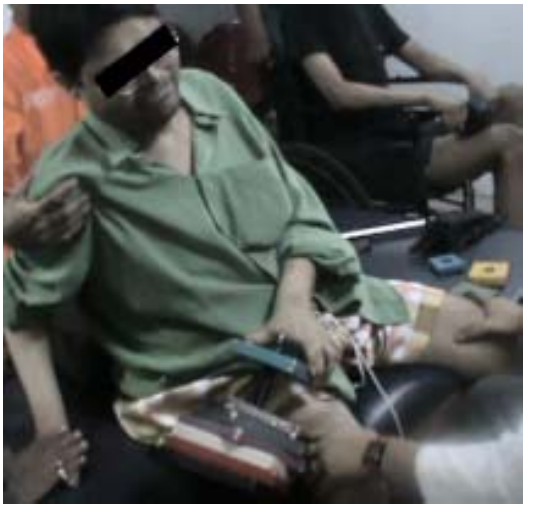
Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally Glutei, Quadriceps,Tibialis Anterior, Peronei, Biceps, Deltoid, Triceps, Trapezius, Abdominals.

Clinical Improvements seen After Stem Cell Therapy

Functionally: He reported feeling of wellbeing and activeness, as earlier he used to feel very drowsy and sleepy most of the time. He could also perform exercises with ease. His respiratory functions also improved as he would not get breathless on speaking, which was his common complaint earlier. Also he required less CPAP with oxygen and could manage to sleep in the night comfortably without it, almost after 7

months of dependency on CPAP. His posture was erect and his sitting balance had improved significantly. He could stand on the standing board with bilateral push knee splints, thereby leading to improved bone density and toning of muscles.

Improved dynamic sitting balance.



Improved hand function in sitting.

Improved upper limb strength and ability to perform resistive exercises with help of theraband.

Standing on standing board and performing neck exercises.

Case Report - 95

Diagnosis : *Muscular Dystrophy*

13 year old male presented a history of walking on toes and difficulty in climbing stair since the age of 11 years. Gradually, he reported increase in frequency of falls while walking and inability to perform squatting activities. He walked with lordotic gait but could not maintain his balance since the past 8 months. Over the last year and a half, he also complained of weakness in upper limbs with difficulty in overhead activities.

Neurologically, he was hypotonic and hyporeflexic with intact sensations. On examination, he had kyphosis, scapular muscle, thenar and hypothenar wasting. Muscle power was grade 1 in the proximal muscles of both upper and lower limbs. Functionally, he was totally dependent for all his activities of daily living. On FIM, he scored 67.

On investigation, the serum creatine phosphokinase levels were raised to 1935 IU. Needle Electromyography study suggested of a generalized myopathic process. Muscle Biopsy showed neurogenic atrophy. In DNA analysis no deletion was detected in chromosome 4 q35 .

MRI of the upper and lower limbs before the stem cell therapy revealed that there was extensive fatty infiltration of all pelvic girdle, deltoid, medial and long head of the triceps muscle. Muscles of the anterior, posterior and medial compartment of the thighs showed mild fatty infiltration along with extensor digitorum and extensor hallucis longus muscle of the legs. Minimal fatty infiltration was noted in the biceps brachii.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally glutei, quadriceps, hamstrings, deltoid, triceps, biceps, back extensors, abdominals.

Clinical Improvements seen After Stem Cell Transplant:

Functionally: At the end of 6 months, he reported feeling of wellbeing, as effort required to perform the Activities of daily living was reduced significantly. Even the caretaker reported that he required less effort in transferring him as he would attempt to transfer by himself only. All mat activities while exercising had improved like rolling on bed ,sitting on the edge of the bed and shifting , thus showing improved trunk balance.He had started kneeling with minimum assistance and could do bridging on mat while exercising. He had started walking with minimum manual assistance and with the help of bilateral push knee splints and high boots with posterior steel shank.

	Before stem cell therapy	**After stem cell therapy**
Creatinine Phosphokinase levels	1935 IU	1060 IU

Improved ability to get up from lying position to sitting upright on the edge of the bed.

Improved trunk strength, thus showing ability to kneel with minimum assistance.

Ability to perform bridging thus showing improved trunk strength.

Patient started walking with bilateral push knee splints and high boots with posterior steel shank, with minimum manual assistance.

Case Report - 96

Diagnosis : *Muscular Dystrophy*

A 7 year old boy, presented with a history of early onset of symptoms of bilateral lower extremities weakness leading to difficulty in walking and climbing stairs since the age of 5½ years. Gradually, weakness in lower extremities progressed to difficulty in squatting. He had also started developing weakness in upper extremities with difficulty in performing over head activities.

Neurologically, he was hypotonic and hyporeflexic. On examination, he had pseudohypertrophy of the bilateral calf muscles. He had grade 2++ muscle power in bilateral lower extremities muscle and grade 3+ in bilateral upper extremities with proximal muscle weakness more than distal. He walked with a waddling gait. He had difficulty in climbing stairs and in his ability to squat. On FIM he scored 77. On Brooke and Vignos scale, he scored 2 and 4 respectively. Functionally, he needed assistance in most activities of daily living.

On investigation, the serum creatine phosphokinase levels were raised to 15548 IU. Electromyography study was carried out in right deltoid, right vastus medialis and right tibialis anterior. It showed predominantly myopathic motor units in all of them while normal sensory nerve conduction findings were recorded from both sural nerves. Compound muscle action potential amplitudes were mildly attenuated in the peroneal and right tibialis nerves but motor conduction velocities and F- wave latencies were normal. Genetic testing of the dystrophin gene did not reveal exon deletion or duplication in any of the 79 exons analyzed.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Glutei, Quadriceps, Adductors of hip, Peronei, Tibialis Anterior, Deltoid, Biceps, Triceps, Trapezius, Rhomboids, Abdominals and Back Extensors.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: 3 months after the therapy, he showed increased limb and trunk strength, especially in the muscles that were injected with stem cells, primarily all antigravity muscles. Parents reported that his frequency of falls had reduced significantly. Earlier, he would fall four to five times a day, but had stopped falling completely since last 2 months. As his proximal girdle muscle stability improved, it led to improved stability during stance phase. His gait also improved.Earlier he would walk with equinnus gait, but later he started walking with heels touching the ground. His appetite had increased with improved stamina, and parents reported that he was alert and hyperactive the entire day, as opposed to earlier when he would be lethargic and would not play around with other kids.

	Before stem cell therapy	After stem cell therapy
Creatinine Phosphokinase levels	7710 IU	3240 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		MUSCLES	LEFT	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
1+	2++	Extensors	1+	2++
3	3+	Flexors	3	3+
2	2++	Abductors	2	2++
		KNEE		
3	3++	Extensors	3	3++
		ANKLE		
3	3++	Dorsiflexors	3	3++
0	3	Peronei Tertius	0	3
2	3+	**ABDOMINALS**		

Improved stance phase, with both heels touching the ground while walking.

Improved trunk strength and ability to perform crawling independently.

Improved hip girdle muscle strength to maintain kneeling and perform overhead reachouts.

Improved knee extensor strength and ability to perform dynamic knee extension activity.

Case Report - 97

Diagnosis : *Facioscapulohumeral Muscular Dystrophy*

A young boy of 16 years with a recent history of inability to do overhead activities since 6-7 months, clinically diagnosed as Fascioscapulohumeral dystrophy revealed winging of scapula bilaterally with wasting of rhomboid muscle. He had muscle power around grade 4 with minimal weakness on right side as compared to left in the upper limbs, while the muscle power in both the lower limbs was normal. He also had a family history of similar affliction on the maternal side. Functionally, he was totally independent in all his activities of daily living. On FIM, he scored 125.

On investigation, the serum creatine phosphokinase levels were raised to 1051 IU. EMG revealed intrinsic muscle disease with myogenic changes seen in the right shoulder girdle and early myogenic changes in the right thigh. MRI of the upper and lower limbs revealed minimal fatty infiltration in the gluteus maximus muscle. Mild fatty infiltration of semitendinosus, biceps femoris and semimembranosus muscle was noted with the biceps femoris muscle being most affected. The muscles of the anterior, lateral, posterior compartment appeared normal with no significant fatty infiltration. The muscles of the arm including the triceps, biceps brachii, coracobrachialis and brachioradialis appeared to be normal.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally Levator Scapulae, Supraspinatus, Infraspinatus, Rhomboids, Deltoid, Pectoralis.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: He reported feeling of wellbeing and improved stamina, as effort required to perform the activities of daily living was reduced significantly. Earlier he had difficulty in grooming activities like combing hair and wearing his turban, which he could do with ease after the stem cell therapy. Strength in his upper limbs improved and so he could move his upper limbs with ease while exercising. He reported improved trunk control and thus, ease in performing mat exercises and crawling activities.

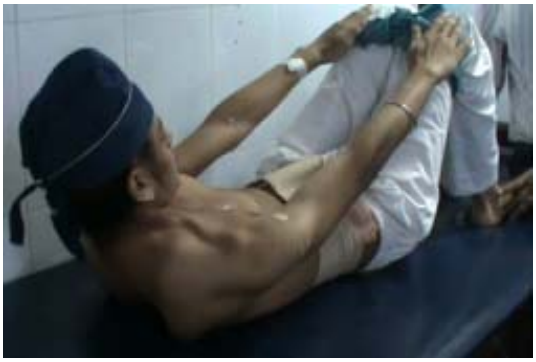
	Before stem cell therapy	After stem cell therapy
Creatinine Phosphokinase levels	1051 IU	485 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	SHOULDER	Before therapy	After therapy
3++	4+	Extensors	4	4+
3++	4+	External rotators	3++	4
4	4+	Internal rotators	4	4++
		ELBOW		
4	4+	Biceps	3++	4+
4-	4	Brachialis	3++	4+
		Brachioradialis	3+	4+
4	4+	Triceps	3+	4+

Improved Upper limb strength and ability to raise both shoulders.

Improved trunk control, thus patient is been able to lift up alternate hand and leg and balance in all fours position.



Improved abdominal strength and ability to perform upper abdominal strengthening exercises.

Improved upper limb strength and ability to raise shoulders overhead.

Case Report - 98

Diagnosis : *Duchenne's Muscular Dystrophy*

A 11 year old male presented with history of weakness in bilateral lower extremities and difficulty in squatting and climbing stairs since the age of 4years. He also reported frequent falls while walking. Gradually weakness in upper extremities also progressed leading to difficulty in overhead activities. He stopped walking since last 8 months.

Neurologically, he was hypotonic and hyporeflexic. On examination,he had grade 1+ muscle power in lower extremities and grade 2+ in bilateral upper extremities with proximal muscle weakness more than distal. Functionally, he needed assistance in most ADL and was wheelchair bound for mobility. On FIM he scored 57. On Brooke and Vignos scale, he scored 5 and 9 respectively. He had the multiple contractures, such as bilateral hip, knee flexion, pronator, elbow flexion contractures and Talipo Equinovarus deformity.

On investigation, the serum creatine phosphokinase levels were raised to 1036 IU, electrophysiological studies revealed myopathy while genetic test revealed no deletions in the tested common most 32 exons. Further, MLPA analysis for deletion/ duplication of all 79 exons was suggested.

MRI of upper and lower limbs revealed fatty infiltration in muscles.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: : Deltoid, Biceps, Triceps, Brachioradialis, Rhomboids, Trapezius, Adductor of shoulder, Glutei, Quadriceps, Tibialis Anterior, Peronei, Adductor of hip and Back Extensors and Abdominals.

Clinical Improvements seen After Stem Cell Therapy

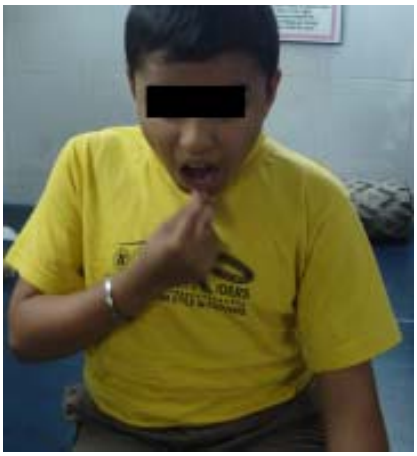
Functionally: At the end of 6 months, he reported that the effort required to perform the exercises was reduced significantly. Earlier he would fatigue very easily , without doing any activity , but post therapy he was able to sustain exercises for 6 hours a day , thereby showing improved stamina and endurance. His trunk strength increased with ability to sit erect and independently on the edge of the cot without any support. His upper limb strength also increased with ability to perform upper body dressing independently, which was not possible before. He got independent in eating and overhead activities like combing , drinking , etc. His grip strength increased with ability to do gripping exercises with springs (showing increased intrinsic muscle strength) and performing exercises with weights etc. His lower limb muscles had tightness in hip and knee flexors with equinnus foot deformity, but post therapy with sustained stretching his muscles showed improved flexibility. He was able to stand with bilateral push knee splints and AFO's initially on the standing board, but after 2 months, he developed trunk and limb strength and started assisted walking with the aid of the harness, inside the parallel bars, approximately 50 feet distance at a time. He was given

serial casting for his foot deformity, and his feet gradually came to plantigrade position. His Vignos Score for lower limb strength increased from 6 to 7

	Before stem cell therapy	After stem cell therapy
Functional Independence Measure	40 IU	61 IU
Creatinine Phosphokinase levels	1036 IU	501 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
1	2++	Extensors	1	2++
1	1++	Flexors	1	1++
1	2	Abductors	1	2
1	2	Adductors	1	2
		FOOT		
1	2++	Dorsiflexors	1	2++
3-	3+	Evertors	3-	3+
		SHOULDER		
1	2+	Rhomboids	1	2+
1+	2-	Triceps	1+	2-
		WRIST		
3+	4	Extensors	3+	4
1+	3	Interrosei	1+	3



Increased Upper limb strength and ability to eat independently.

Increased Grip strength as documented on Dynamometer.

Independent upper body dressing.

Doffing of calipers.

Standing on standing board and performing upper extremity reach outs with peg boards.

Case Report - 99

Diagnosis : *Muscular Dystrophy*

A 14 year old male, known case of muscular dystrophy, since the age of 8 years. It started with complaints of frequent falls while running. After 1 year, he got his CPK done where the levels were raised and diagnosis was confirmed as Muscular Dystrophy. Gradually weakness progressed with difficulty in climbing stairs and getting up from floor. He was able to walk till November '09. Later with increased frequency of falls, he started using wheelchair for his mobility.

Neurologically, he was hypotonic and hyporeflexic. He had all sensations intact. On examination, he had muscle power of grade 2 in proximal muscles of bilateral upper limb and lower limb muscles.

On investigation, his Creatine phosphokinase levels were raised to 9400 IU, Electromyograpy studies showed generalized primary muscle disease affecting the proximal muscle and semi distal muscles. MRI of the upper limb showed mild to moderate fatty infiltration and lower limb showed extensive fatty infiltration in the muscles of the pelvic girdle. Functionally, he is totally dependent for all his ADLs. On FIM he scored 70. On Brooke and Vignos scale, he scored 3 and 8 respectively.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally: Adductors of hip, Adductors of shoulder, Biceps, Brachioradialis, Triceps, Deltoid, Tibialis Anterior, Glutei, Quadriceps, Abdominals and Back Extensors.

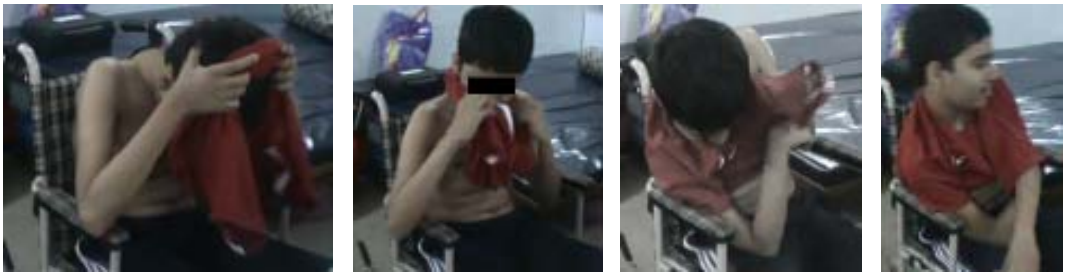
Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina. His trunk strength had increased , with independence in bed mobility activities like rolling ,getting up from side lying to sitting position .In sitting , his dynamic balance and tolerance on the edge of the cot had improved , with ability to sit without any backrest and maintain it for 15 minutes at a stretch. He could also perform shifting on the edge of the cot, which was not possible prior to the therapy. His upper limb and grip strength had also increased with independence in activities of daily living like bathing, dressing, feeding, etc. During therapy sessions, he was made to stand with bilateral push knee splints on standing board in order to stretch tight lower limb musculature and bring about toning of muscles and improve bone density. Gradually he could sustain standing for one hour a day, thereby showing improved standing tolerance. His Brooke scale improved from 3 to 2 and Vignos improved from 9 to 8.

	Before stem cell therapy	After stem cell therapy
Functional Independence Measure	70	81
Creatinine Phosphokinase levels	2067 IU	1736 IU

Manual Muscle testing : Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**HIP**	Before therapy	After therapy
1	1++	Extensors	1	1++
2	2++	Flexors	2	2++
2	2++	Abductors	2	2++
1	2+	Adductors	1	2+
		KNEE		
2	3+	Flexors	2	3+
1	2	Extensors	1	2
		SHOULDER		
2	2+	Flexors	2	2+
2	3+	Extensors	2	3+
2+	3-	Abductors	2+	3-
1	2	Adductors	1	2
2	3	External Rotators	2	3
2+	3+	Internal Rotators	2+	3+
1+	2	**ABDOMINALS**		



Ability to perform upper body dressing

Improved standing tolerance with bilateral push knee splints, on standing board.

Improved bed mobility, with ability to roll on bed independently .

Improved Grip strength

Improved trunk strength and ability to bend on wheel chair and pick up objects.

Case Report - 100

Diagnosis : *Beckers Muscular Dystrophy*

A 39 year old dentist gave a history of easy fatigue ability on activity since childhood and increased frequency of falls on running. At the age of 12, he started noticing difficulty in climbing stairs with lower extremities weakness. Later upper extremities weakness also started with inability to do overhead activity. Gradually, weakness progressed leading to difficulty in mobility and performing activities of daily living. He had stopped walking since 4-5 years.

Neurologically, he was hypotonic and hyporeflexic. On examination, had muscle weakness, proximal muscles were more weak than the distal muscles, with grade 1++ muscle power in bilateral lower extremities muscles and grade 3 muscle power in bilateral upper extremities. Functionally, he needed assistance in most activities of daily living, dependent on wheelchair for mobility and on others for bed mobility. On FIM he scored 93.

On investigation, the serum creatine phosphokinase levels were raised mildly to 322 IU. Genetic studies revealed deletions of exons 45, 46 and 47 of the dystrophin gene. These deletions indicated in-frame mutations. Electrophysiological studies showed evidence of a myogenic lesion. MRI of both lower limbs showed generalized atrophy in the flexor, extensor and adductor group of muscles on both sides. There was atrophy of soleus and gastrocnemius muscles on both sides with fatty replacement of these muscles. MRI of both the upper limbs showed atrophied musculature in flexor group of muscles in the forearm with fatty replacement of extensor group of muscles on both sides. Atrophy of biceps and triceps were also reported on both sides.

Stem cells were also injected intramuscularly at the motor points of the following muscles bilaterally:Biceps, Triceps, Hamstrings, Quadriceps, Glutei, Back Extensors and Abdominals.

Clinical Improvements seen After Stem Cell Therapy.

Functionally: At the end of 3 months, he reported feeling of wellbeing and improved stamina, with an ease in performing exercises. He could sustain exercises for longer periods without fatigue. He also reported reduction in muscular pain. His hip and proximal muscle stability had improved. He could walk independently for the first time after 7 years with calipers. He could also perform lower body dressing independently. His respiratory muscles had improved with better functioning and excursion of inter coastal muscles, with increased spirometer readings. He became independent in transferring from bed to wheel chair and also from chair to commode seat.

Manual Muscle testing: Following muscles showed improved strength

RIGHT		**MUSCLES**	**LEFT**	
Before therapy	After therapy	**ELBOW**	Before therapy	After therapy
0	1	Biceps	0	1
0	1	Brachioradialis	0	1
0	1	Triceps	0	1
		HIP		
0	1	Quadriceps	0	1

Improved hip stability and ability to perform quadrates lumborum muscle activity of swinging both Lower limbs

Hip flexor strengthening exercise.

Improved upper limb and abdominal strength, thus showing ability to lift up lower limbs with the help of upper limbs.

Improved upper limb strength, mainly gripping pinching activity, with sitting on edge of the cot.

Standing on the standing board and performing overhead activities, thus showing improved upper limb strength.

Walking with bilateral push knee splints and walker with help of minimal assistance.

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Sharan Bhudrani, Dubai:
"After the stem cell therapy, I feel more positive and independent than before."

Ankur, Mumbai:
"I was 23 years old and I knew I had no hope but my intentions of getting better was strong and then Dr. Alok Sharma along with his stem cell treatment walked in my life to make a difference. The way I was hopeless and now the way I am confident is because I have seen a progressive difference in me and my actions to some extent but definitely 100% difference in arresting degeneration of my muscles. I am looking forward to be a normal human being very shortly."

Suhail Zaveri, USA:
After stem cell therapy, the biggest achievement for me was going from standing to walking and soon I was walking for ½ an hour at a stretch. My message for children like me is that "You should never give up doing exercises..even though it is painful, you still got to keep trying."

Shreyas Karalkar, Mumbai:
"Stem Cell Therapy is a Freedom from Disability & The Path To an Independent Life. For me stem cells means S-strength, T-therapy, E-energetic, M-muscles, C-courage, E-efforts, L-love, L-life."

About NeuroGen Brain and Spine Institute

The Neurogen Brain and Spine Institute has been set up to help patients, with incurable neurological disorders, get relief from their symptoms and physical disabilities using the safest and most effective available treatments and technologies from the field of Neurosciences and Regenerative medicine in a professional and scientific as well as holistic and caring manner.

We have introduced a novel concept of NeuroRegenerative Rehabilitation Therapy (NRRT), wherein, our strategy is to promote the recovery of neural function with a close integration of stem cells and physical, occupational and speech therapies. We recognize, even small functional gains may have a significant effect on the quality of life of our patients. In addition to the medical treatment there is a significant emphasis on both clinical as well basic research, so that the best therapeutic strategies can be evolved and practiced at the same time.

NG NeuroGen Brain and Spine Institute
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