Patient and Parent Guidebook on Muscular Dystrophy

2nd Edition

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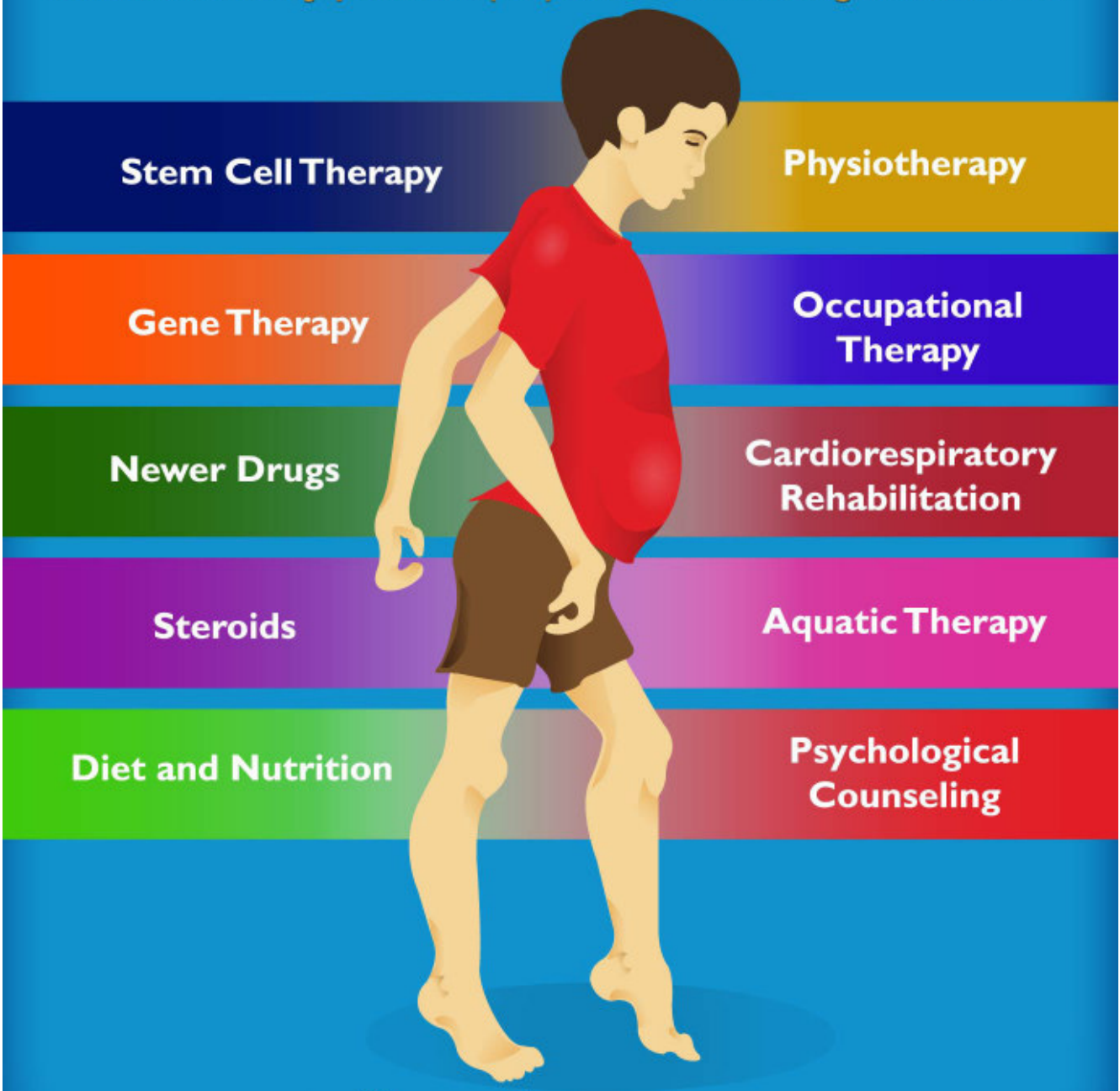

A NeuroGen Publication

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Patient and Parent Guidebook on Muscular Dystrophy

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Contents

This book is dedicated to
the courageous families of
patients
with muscular dystrophy

Until one is committed, there is hesitancy, the chance to draw back, always ineffectiveness. Concerning all acts of initiative (and creation), there is one elementary truth, the ignorance of which, kills countless ideas and splendid plans-that the moment one definitely commits oneself, then providence moves too.

All sorts of things occur to help one that would never otherwise have occurred. A whole stream of events issues from the decision raising in one's favour, all manner of unforeseen incidents and meetings and material assistance which no man could have dreamed would have come his way.

The Scottish Himalayan Expedition
By W. H. Murray

Whatever you can do or dream you can, begin it. Boldness has genius, power and magic in it. Begin it now.

GOETHE

Preface to The First Edition

Muscular dystrophy is a disease that progressively weakens not just the patient, but affects the entire family too in their day to day living. Muscular dystrophy patients are very special indeed. Despite the physical limitations due to weakening muscles, they have an extremely positive attitude towards life. They have an acceptance of reality that we all should learn from. They have the ability and courage to go through extreme physical pain and difficulty in attempting to improve their conditions through the prolonged rehabilitation process.

Whereas, as doctors our focus is and should be on the patient, what many of us don't realize is that the parents and families go through a lot of emotional and physical hardship as well. To have to manage just the routine activities of life of the patients is a very tiring and exhausting process. Having to support the medical treatments, investigations, rehabilitation, etc. takes enormous time and energy. Since muscular dystrophy patients are completely dependent, the families have a very important role to play in their daily lives as well as their medical treatments. This takes courage, caring and commitment along with determination and dedication.

Looking after these patients involves hard physical strenuous work, lots of time, a very positive attitude and a spiritual acceptance of this difficult reality. On top of all this, their having to hear from multiple doctors that there was nothing that could be done to treat the patients was frustrating and hurting. What can be worse than having to watch a family member slowly wither away and at the same time have to repeatedly hear that nothing can be done for them. (Of course, now with the availability of stem cell therapy, that is no longer true!).

The parents and the families often cannot even express their own emotional, mental and physical pains and suffering to anyone. Most parents have to give up many of their own work commitments and leisure activities just to look after the children. We therefore wrote this book for those courageous families that have to work 24X7 for several years trying to make the patients comfortable, pain free and as mobile and independent as possible.

Whilst writing this book we tried to think from the point of view of a patients parent or the patient themselves. What are the questions that they have in their minds that need to be answered, what are the areas where there is confusion in their minds, what information do they need to help them make informed decisions about future course of action. So this book has 4 sections. The first one is about the disease itself, the second is about various treatments that are already available , the third about

recent advances and the fourth about some other supportive aspects of the problem. In the second section

About the treatment there are various multidisciplinary aspects covered that include the use of steroids, other medications, orthopedic management, respiratory care and psychological management. A interesting part of this book is the importance of yoga and diet in the overall management of muscular dystrophy. These two aspects along with the chapter on exercises and stretches and assistive devices is something parents can easily implement at home.

A lot of parents are also unclear about what are the future developments that are likely to be useful for their children. Whereas some of the newer drugs and gene therapy are still in the future, stem cell therapy is available in the present moment. Therefore a separate section has been devoted to the recent advances. There is a in-depth discussion of the role of stem cell therapy in muscular dystrophy where our results have been discussed focusing primarily on the improvements that have been seen and the safety aspects. Stem cell therapy, which is a part of the newly expanding field of regenerative medicine, is here to stay. There is a growing body of published scientific literature that is showing both efficacy and safety of this form of treatment. We can keep arguing about whether it is a proven or unproven form of treatment but the fact is that the improvements that have been reported from the centers doing this therapy are better than any other form of treatment currently available and almost certainly seem to be altering the natural history of the disease. When dealing with a progressively worsening disease with a well defined mortality such as Duchene muscular dystrophy,its important to realize that the risks of not doing anything can be greater than trying a treatment with reasonable safety and efficacy. These are however grey areas and it is hoped that this book helps parents and patients make these decisions with a clearer mind.

Whereas, we as doctors and therapists can spend some time with the patients during their treatment processes, it is the families that are with the patients through the entire day and night. It is our belief that if the family members understood the disease process and the treatment methods better they would be able to make a much bigger difference to the patient's lives than we doctors can. They would also be able to make informed choices about the various new treatment options that are now becoming available. This book was therefore written for this purpose. Whereas we have written an earlier book titled "Stem cell therapy and other recent advances in muscular dystrophy", we realized that the book (which was meant for medical doctors and therapists to read) was too technical for families and patients to understand.

This book is therefore, written in a very simple non technical manner. It is meant to help parents, siblings, spouses and the patients themselves to understand what this disease is all about and what are the simple things that they can do to make life a little easier for the patients. We salute the muscular dystrophy families and offer them this book to educate, empower, enrich and enlighten them on what best they can do together for these very special children and adults with muscular dystrophy.

Preface to The Second Edition

It's been 3 years since we wrote and published our first edition of this book. Whilst a lot has happened since then both in our own clinical experience (specially with reference to stem cell therapy for muscular dystrophy) as well as in the research happening worldwide, simultaneously overall the worldwide scenario and the overall prognosis for the individual patient has remained unchanged. Muscular dystrophy is still considered an incurable disease and except for physical and occupational therapy and in some cases steroids not much more is being offered to the patients in general.

But there definitely is a shift in the wind as compared to a decade ago. Hopelessness is giving way to Hope and the conversation is shifting from "nothing can be done" to "something will be possible soon ". However according to us that something soon is already here and available. The hope is not in the future anymore. It is present right here and now. And it exists in the form of stem cell therapy.

A major hindrance to the availability of cellular therapy for muscular dystrophy patients has been the regulations in place for cellular therapy in different countries. However that too is changing. Japan passed a new legislation in November 2014 which has put in place a fast track procedure for making stem cell therapy more accessible to patients in need of it. The new law states that cells are not a drug and so they do not have to go through the process drugs go through for their approval as accepted treatments. The law states that if in 10 patients a significant improvement is shown or if in 100 patients a minor improvement can be show then provisional approval would be given for a seven year period to market the stem cell therapy and insurance companies would have to pay for the same. If such a law was in force in the USA and other countries thousands of muscular dystrophy patients would be able to benefit from the beneficial effects of stem cell therapy.

Its time families as well as muscular dystrophy associations looked at the published clinical results and data available on the safety and efficacy of cellular therapy and worked to put pressure on their governments to bring a law similar to the one in Japan into their countries. Our regulatory bodies are doing a great job in ensuring public safety in connection with new medical treatments. However our Duchenne Boys do not have the luxury of time. Every year many of our courageous boys are losing their battle against their weakening muscles. 10 years ago we could do nothing since there was nothing available anywhere that could save them, That's not true anymore. Now there is a treatment available. Hundreds of patients have received

that treatment. The safety of the treatment is established. There are many scientific publications that document this. Therefore its a real tragedy that there is a treatment available on the planet whose safety and efficacy have been documented and recorded and published and yet we are losing our Duchene boys just because the regulators and other members of the medical fraternity will in different countries will not accept it. Ethics, principles and regulations are meant to protect the individual. If a sticking rigidly to a principle will cost someone their lives then those principles are not respecting the human rights of that individual. This has to change. If Japan can do it so can the USA and other European countries. And it's only the collective voice of the patients and their families that can make this happen.

There is therefore a lot to be done. But we need to make a beginning somewhere. There is a Chinese saying that says "The march of a million miles begins with a single step". We are hoping that we are able to inspire at least some of the readers of this book to take that single step. What are at stake are human lives and nothing should come in the way of doing whatever has to be done to save them.

Dr. Alok Sharma

Views of Two World Leaders on
1. Muscular Dystrophy
2. Stem Cells

Prime Minister of ***India Narendra Modi***
interest in Stem Cell Therapy
and
Views on Muscular Dystrophy

President of the United States of America ***Barack Obama***
Views on Stem Cells

The Prime Minister of India , Shri Narendra Modi, visited the NCBS and inStem in banglore india in February 2015 and was taken to some of the laboratories to see cutting edge stem cell research. He then had a vibrant and truly interactive engagement with faculty, students on subjects ranging from international collaborative research, the use of stem cell based therapies and scientific outreach.

Narendra Modi met Shinya Yamanaka, Japan's stem cell pioneer and 2012 Nobel Prize winner, at Kyoto University Japan in August 2014

Prime Minister Narendra Modi's letter published in our Gujrati translation of our 1st edition of the Patient and Parent Guidebook for Muscular Dystrophy

સત્યમેવ જયતે

તા. ૨૬-૦૨-૨૦૧૩

સંદેશ

પ્રકૃતિનો અપ્રતિમ ઉપહાર એટલે જનનીની કૂખેથી શિશુનું અવતરણ. શિશુ જન્મની વધામણી છે તો ખૂબ જ લોભામણી. આ સુઅવસર કોઈ અસાધ્ય બીમારીને સાથે લઈને આવે તો બાળકની તકલીફ અને માતા-પિતાની મુંઝવણભરી અવસ્થા વિષમ હોય છે. પરંતુ દરેક પળે અને દરેક ક્ષણે બદલાતા અને વિકસતા મેડીકલ કેરના સમયમાં અસાધ્ય રોગોના ઈલાજ શક્ય બનવા લાગ્યા છે. નિરાશાના વાદળ જ્યાં જ્યાં ઘેરાયા હોય ત્યાં રિસર્ચ અને સાયન્સની કમાલ થકી ટેસ્ટટ્યુબ બેબી જન્મતા હોય ત્યારે હવે કશું જ અશક્ય રહ્યું નથી.

અસાધ્ય રોગોથી પીડિત બાળકની અવસ્થાની વાત થાય, જ્યાં બાળકને સાચવવું એક પડકાર હોય, એના રોગની ગંભીરતા લાખોમાં એક જેવી હોય. **મસ્ક્યુલર ડીસ્ટ્રોફી** એ બીમારીની એવી અવસ્થા છે, જ્યાં માતા-પિતા અને સારવાર કરનાર ડોક્ટર, થેરેપીસ્ટની ધીરજની કસોટી, સતત તલવારની ધાર પર હોય છે. ત્યારે એ પરિસ્થિતિને કેમ પહોંચી વળવું તે અંગે જે ઉપકારક માર્ગદર્શિકા ગુજરાતી ભાષામાં પ્રકાશિત થઈ રહી છે એ સતત સંતાપમાં સધિયારો સાબિત થાય તેમ છે.

ડૉ. આલોક શર્મા અને અન્ય સાથીઓ દ્વારા તૈયાર થયેલ અંગ્રેજી પુસ્તકના અંતર મને ઉઠેલી આ વિચારસ્ફૂરણા મનનીય મથામણને અમલમાં મૂકવાની વાત સુધી પહોંચી એ અભિનંદનીય છે. **ડૉ. વિભૂતિબહેન ભટ્ટ** દ્વારા ગુજરાતની ચિંતા કરાતાં આ પુસ્તકને ગુજરાતી ભાષાંતર સાથે રજૂ કરવાની વાત અધિક આવકાર્ય છે.... સમસ્યાઓને સરળરૂપમાં સમજવાનો આધાર પૂરો પાડતી આ રચના **મસ્ક્યુલર ડીસ્ટ્રોફી**ના દરદીની સારવાર સાથે સંકળાયેલા સર્વ માટે સુવિધાજનક સમજણ આપનારી બને એ જ શુભેચ્છા.

સૌનો,

(નરેન્દ્ર મોદી)

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નરેન્દ્ર મોદી
મુખ્ય મંત્રી, ગુજરાત રાજ્ય

Translation of Prime Minister Narendra Modi's letter published in our Gujrati translation of our 1st edition of the Patient and Parent Guidebook for Muscular Dystrophy

Date : 26 - 02 - 2013

One of the most valuable gifts that nature can bestow on a woman is the gift of a child. A new born child brings immeasurable happiness to a parent but when the child suffers from an incurable disease at birth this happens quickly turns into a nightmare. Today in the fast paced, ever evolving field of medicine it has become possible to treat such incurable diseases. Science & research has made it possible to develop test-tube babies and this proves that the possibilities are endless.

One of the most challenging task is to take care of the children suffering from such diseases and catering to their special needs. Muscular Dystrophy is one such disease that challenges the patience of the parents, treating doctors and the therapists and often keeps it on the edge. In such a situation a Guidebook on care for such patients in Gujarati proves to be an invaluable resource.

Dr Alok Sharma and his team have done a commendable job in the development of this book in English. Mrs Vibhuti Bhatt has translated this book in Gujarati keeping in mind the plight of the people of Gujarat suffering from such incurable diseases and this is an even more praise worthy endeavor. This book plays a vital role in reaching out to the common man by presenting concepts in a simple and easy to understand language. My best wishes that this book serves as a focal point for all the people associated in the treatment of Muscular Disease facilitates their work.

– Narendra Modi

President Obama Speech on Stem Cell Policy Change

March 9, 2009

"Today, with the Executive Order I am about to sign, we will bring the change that so many scientists and researchers; doctors and innovators; patients and loved ones have hoped for, and fought for, these past eight years: we will lift the ban on federal funding for promising embryonic stem cell research. We will vigorously support scientists who pursue this research. And we will aim for America to lead the world in the discoveries it one day may yield.

At this moment, the full promise of stem cell research remains unknown, and it should not be overstated. But scientists believe these tiny cells may have the potential to help us understand, and possibly cure, some of our most devastating diseases and conditions. To regenerate a severed spinal cord and lift someone from a wheelchair. To spur insulin production and spare a child from a lifetime of needles. To treat Parkinson's, cancer, heart disease and others that affect millions of Americans and the people who love them.

But that potential will not reveal itself on its own. Medical miracles do not happen simply by accident. They result from painstaking and costly research - from years of lonely trial and error, much of which never bears fruit - and from a government willing to support that work. From life-saving vaccines, to pioneering cancer treatments, to the sequencing of the human genome - that is the story of scientific progress in America. When government fails to make these investments, opportunities are missed. Promising avenues go unexplored. Some of our best scientists leave for other countries that will sponsor their work. And those countries may surge ahead of ours in the advances that transform our lives.

But in recent years, when it comes to stem cell research, rather than furthering discovery, our government has forced what I believe is a false choice between sound science and moral values. In this case, I believe the two are not inconsistent. As a person of faith, I believe we are called to care for each other and work to ease human suffering. I believe we have been given the capacity and will to pursue this research - and the humanity and conscience to do so responsibly.

It is a difficult and delicate balance. Many thoughtful and decent people are conflicted about, or strongly oppose, this research. I understand their concerns, and we must respect their point of view.

But after much discussion, debate and reflection, the proper course has become clear. The majority of Americans - from across the political spectrum, and of all backgrounds and beliefs - have come to a consensus that we should pursue this research. That the potential it offers is great, and with proper guidelines and strict oversight, the perils can be avoided.

That is a conclusion with which I agree. That is why I am signing this Executive Order, and why I hope Congress will act on a bi-partisan basis to provide further support for this research. We are joined today by many leaders who have reached across the aisle to champion this cause, and I commend them for that work.

Ultimately, I cannot guarantee that we will find the treatments and cures we seek. No President can promise that. But I can promise that we will seek them - actively, responsibly, and with the urgency required to make up for lost ground. Not just by opening up this new frontier of research today, but by supporting promising research of all kinds, including groundbreaking

work to convert ordinary human cells into ones that resemble embryonic stem cells.

I can also promise that we will never undertake this research lightly. We will support it only when it is both scientifically worthy and responsibly conducted. We will develop strict guidelines, which we will rigorously enforce, because we cannot ever tolerate misuse or abuse. And we will ensure that our government never opens the door to the use of cloning for human reproduction. It is dangerous, profoundly wrong, and has no place in our society, or any society.

This Order is an important step in advancing the cause of science in America. But let's be clear: promoting science isn't just about providing resources - it is also about protecting free and open inquiry. It is about letting scientists like those here today do their jobs, free from manipulation or coercion, and listening to what they tell us, even when it's inconvenient - especially when it's inconvenient. It is about ensuring that scientific data is never distorted or concealed to serve a political agenda - and that we make scientific decisions based on facts, not ideology.

By doing this, we will ensure America's continued global leadership in scientific discoveries and technological breakthroughs. That is essential not only for our economic prosperity, but for the progress of all humanity.

That is why today, I am also signing a Presidential Memorandum directing the head of the White House Office of Science and Technology Policy to develop a strategy for restoring scientific integrity to government decision making. To ensure that in this new Administration, we base our public policies on the soundest science; that we appoint scientific advisors based on their credentials and experience, not their politics or ideology; and that we are open and honest with the American people about the science behind our decisions. That is how we will harness the power of science to achieve our goals - to preserve our environment and protect our national security; to create the jobs of the future, and live longer, healthier lives.

As we restore our commitment to science, and resume funding for promising stem cell research, we owe a debt of gratitude to so many tireless advocates, some of whom are with us today, many of whom are not. Today, we honor all those whose names we don't know, who organized, and raised awareness, and kept on fighting - even when it was too late for them, or for the people they love. And we honor those we know, who used their influence to help others and bring attention to this cause - people like Christopher and Dana Reeve, who we wish could be here to see this moment.

One of Christopher's friends recalled that he hung a sign on the wall of the exercise room where he did his grueling regimen of physical therapy. It read: "For everyone who thought I couldn't do it. For everyone who thought I shouldn't do it. For everyone who said, 'It's impossible.' See you at the finish line."

Christopher once told a reporter who was interviewing him: "If you came back here in ten years, I expect that I'd walk to the door to greet you."

Christopher did not get that chance. But if we pursue this research, maybe one day - maybe not in our lifetime, or even in our children's lifetime - but maybe one day, others like him might.

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. Today, using every resource at our disposal, with renewed determination to lead the world in the discoveries of this new century, we rededicate ourselves to this work.

Thank you, God bless you, and may God bless America."

Scientific Publications on Stem Cell Therapy in Muscular Dystrophy by the Authors

A) MUSCULAR DYSTROPHY

1. Alok Sharma, Hemangi Sane, PrernaBadhe, Nandini Gokulchandran, Pooja Kulkarni, Mamta Lohiya, Hema Biju, V.C.Jacob. A Clinical Study Shows Safety and Efficacy of Autologous Bone Marrow Mononuclear Cell Therapy to Improve Quality of Life in Muscular Dystrophy Patients. Cell Transplantation. 2013; Vol. 22, Supplement 1, pp. S139-S146.

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Scientific Publications on Stem Cell Therapy in Other Neurological Disorders by the Authors

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Introduction

The muscular dystrophies (MD) are a group of inherited genetic conditions that gradually cause the muscles to weaken. MD occurs worldwide, affecting all races. Some types of MD are more prevalent in certain countries and regions of the world. Both the sexes are affected, males being affected more than females. Many muscular dystrophies occur in childhood and others may occur as late as 60 years of age. Duchenne muscular dystrophy is the most common form and estimated at 1 in 3,500 male births while Becker's muscular dystrophy is 1 in 18,518 male births. In the United States, Duchenne MD and Becker MD occur in approximately 1 in 3300 boys.

An estimate of overall prevalence of MD is 29 per 1,00,000 population in India.

There are many different types of muscular dystrophy, and each affects various muscles in a unique pattern. Muscular dystrophy can also affect the heart, lungs, eyes, spine, brain, endocrine system and gastrointestinal system. The age of onset, severity of conditions, distribution of weakness and family history vary greatly with each type. Most of the conditions are progressive, causing the muscles to gradually weaken over time, and can either be inherited or occur without any family history.

A diagnosis of muscular dystrophy can be extremely challenging for the patient and his family. As soon as the diagnosis is made, parents often get depressed and confused, because proper guidance about what to do next is not easily available. Sometimes, guidance comes too late. Many complications, which can be avoided, occur due to lack of timely intervention. Also, many parents and the families are not completely aware about muscular dystrophy, its prevalence, its causes, the problems caused by muscular dystrophy and the treatment options available. But, it is seen that knowing the disease, the management strategies, having support and resources can help increase confidence in managing muscular dystrophy, and thus enhance quality of life of the patient as well as the family members.

There is abundance of information available about muscular dystrophy on the internet, books, magazines, etc. This information can become overwhelming for the patient and parents. Hence, this book is intended to provide a step by step guideline for patients and caregivers of muscular dystrophy. Its main aim is to help them understand the disease better by providing holistic information, so that they can be prepared for managing the disease and challenges put by the disease.

In this book signs and symptoms of more common forms of muscular dystrophy Duchenne and Becker muscular dystrophy are classified in to five stages. Here we discuss the presentation of symptoms of these disorders stage wise. Also, the

management and prevention of complications is discussed stage wise. The less common forms like Limb girdle muscular dystrophy, Emery Dreifuss muscular dystrophy, etc are discussed in two stages. This book emphasizes on a holistic approach to muscular dystrophy which includes medical and surgical management, cardiorespiratory management, physiotherapy, aquatic therapy, occupational therapy, speech therapy, psychological counseling, yoga therapy, diet and nutrition, cardiorespiratory rehabilitation, and vocational rehabilitation. Also, a detailed discussion on care for care givers is included.

So this book is written with an intention to provide simple and easy-to-follow text with clear illustrations. We hope that this helps the parents of children afflicted with muscular dystrophy and adult patients to cope with this condition better.

SECTION - I :

About Muscular Dystrophy

1.

Clinical Symptoms and Types of Muscular Dystrophy

Muscular dystrophy is a progressive condition in which the muscles get weaker day by day. Muscle weakness is the core symptom of muscular dystrophy which leads to various postural deviations and compensations to carry out the daily functional activities. The muscles that are affected are the skeletal muscles or the voluntary muscles (muscles used for body movements). Weakness of the muscles in muscular dystrophy is not uniform across the body. Some muscles depending on the function they perform become weak earlier than others. This creates imbalance between the strength of various muscle groups and changes the alignment of the bones that they move. In turn, the muscles have to spend more energy in moving these mal-aligned bones and weakness sets in even faster. They may also become shorter in the length and lose their extensibility due to these mal-alignments. Loss of extensibility leads to structural deformities which are seen as the disease progresses and cause severe limitation of the function and movement. This limitation leads to further imbalance in the muscle weakness and the vicious cycle continues.

Individuals with muscular dystrophy may also present with cardiovascular, respiratory, orthopedic, neurological and gastrointestinal symptoms. It is these symptoms that considerably limit the span of the individuals.

Let's get to the root of the problem

The cause of muscular dystrophy is an abnormality in the gene producing proteins required to build muscle fibers. Genes are the microcellular units in the human body that dictate and monitor functions of each cell in human body including the muscle cells. Abnormality of the responsible gene leads to a defective protein which is not capable of executing its function in the muscle cell. Muscle cells are therefore vulnerable to damage and degeneration due to daily functional activities. The damage is so rampant that the reparative body processes are not sufficient to bridge the deficit. This uncontrolled degeneration leads to progressive muscle death and therefore weakness, causing muscular dystrophy.

These abnormal genes could be carried from one generation to the other or sometimes may even exist due to poor prenatal nutrition or in a sporadic form as a spontaneous deviation.

Different types of muscular dystrophy

Different genes are responsible for different protein components of muscle cells. Muscular dystrophies are divided into various groups of disorders depending upon the type of gene affected, the protein it produces, symptoms of the disease and progression of the disease.

More common forms of muscular dystrophy are Duchenne Muscular Dystrophy (DMD), Becker's Muscular Dystrophy (BMD) and Limb Girdle muscular dystrophy (LGMD). The less common forms are FacioScapulo Humeral dystrophy (FSHD), Congenital muscular dystrophy (CMD), Myotonic muscular dystrophy, Occulopharyngeal muscular dystrophy, distal muscular dystrophy, Emery Dreiufuss muscular dystrophy.

Duchenne Muscular Dystrophy (DMD)

What is Duchenne Muscular Dystrophy?

Duchenne muscular dystrophy (DMD) is the most severe forms of the muscular dystrophies. It is rapidly progressive and shortens the life span of the individual.

Gene affected:

Dystrophin gene (Mutation, deletion or duplication)

Protein affected:

Dystrophin

Role of the protein in maintaining the structure of the muscle cell:

It forms the part of the skeleton or inner structure of the muscle cell, cytoskeleton. Dystrophin is crucial to bridge the inner cell skeleton to the outer cementing material that holds the cells together, extracellular matrix.

An absent or affected dystrophin gene gives rise to faulty and less potent dystrophin protein. The muscle cell can therefore be disrupted very easily and is prone to damage even with regular activities.

Inheritance patterns:

X-linked recessive inheritance pattern (Further details explained in Chapter 3, Diagnosing muscular dystrophy and Chapter 4 Genetic counseling). This means that it is transmitted to the children by a carrier mother (with faulty gene but no disease). One affected X chromosome in boys will cause the disease and in girls it will make them carriers but no disease.

Symptoms and disease progression:

The progression of the disease is described in five stages as follows:

- Stage 1: Pre-symptomatic (0-4 years)
- Stage 2: Early ambulatory stage (4-8 years)
- Stage 3: Late ambulatory stage (8 - 13 years)
- Stage 4: Early non- ambulatory stage (13 to 16 years)
- Stage 5: Late non- ambulatory stage (16 years onwards)

Stage 1: Pre-symptomatic (0-4 years)

Muscular dystrophy is a congenital disease. The symptoms become evident much later in life. The time between the birth of the child till the symptoms become evident is the pre-symptomatic stage. The children may not have any difficulty in carrying out activities of daily living during this phase. Some warning signs are still present in this stage and if detected early can help in better management of the disease.

In pre-symptomatic stage of DMD the children seem near normal in their physical performance. Physical milestones like standing and walking may be delayed in some children. Some children may also present with floppy limbs early in childhood with increased flexibility of finger joints, elbows and knees. The children may perform physical activities slower as compared to other children of their age. However there are no evident symptoms suggestive of muscular dystrophy.

In the pre-symptomatic individuals with muscular dystrophy the muscle cells are constantly getting damaged but repaired very slowly. Thus the symptoms are not seen. Although no symptoms are evident, serum Creatine Phospho-Kinase (CPK) levels are found to be elevated. Creatinine phosphokinase is a cellular enzyme, when the muscle cells die or are injured the concentration of CPK in blood increases .

Stage 2: Early Ambulatory stage (4-8 years)

Stage 2 is the stage at which the symptoms first start to manifest and are clinically detectable. The child may lag behind in physical performance as compared to peers. There may be frequent falls while walking, especially on an uneven surface. There may be postural deviations while walking like walking on toes. The child can still climb stairs and may need support infrequently. The child may get tired or fatigued after a strenuous physical activity. The calves or shoulder muscles may seem bigger or swollen and more firm than other children (Pseudo-hypertrophy) (Figure 1.1) Along with the progressing muscle

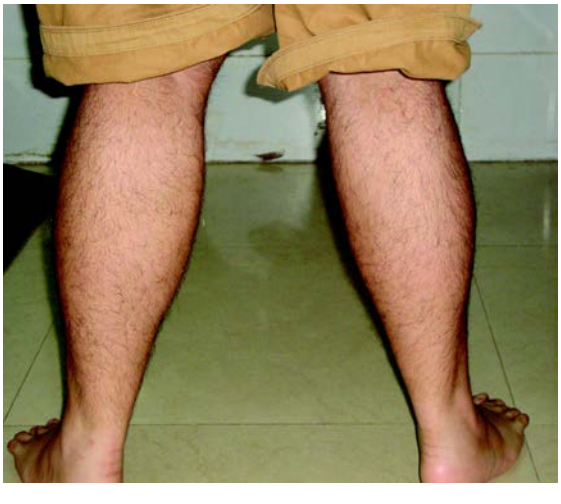

Fig. 1.1: Calf Pseudohypertrophy

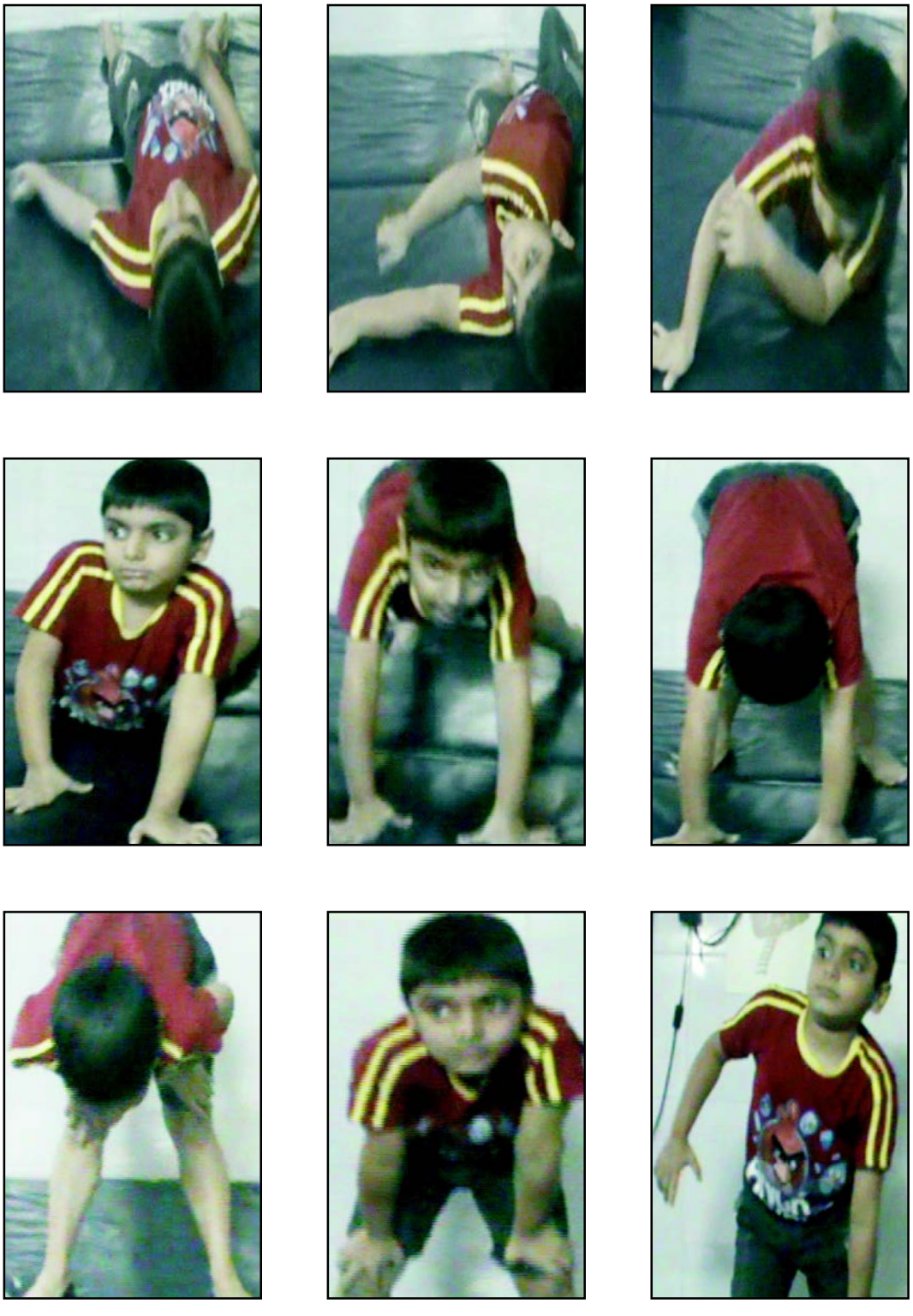

Fig. 1.2: Gower's sign: the child walks up his thighs with his hands.

weakness and postural deviations children may show impairment of function of heart (cardiovascular system), breathing ability (respiratory system) appetite and bowel movements (gastrointestinal system).

Impairments of muscles and postural deviations (Musculo-Skeletal system)

Symptoms:

1. Gower's maneuver positive (Figure 1.2) - Gower's sign is when the patient makes use of his hands to climb up on his body while getting up from the floor. This is mainly to compensate for the weakness of the hip muscles (Glutei) (Figure 1.3) and knee muscles (Quadriceps) (Figure 1.4).
2. Frequent falls while walking, running or jumping
3. Child gets tired soon, and cannot perform physical activities as well as or as long as his peer (Easy fatiguability)
4. Child need to hold the railing while climbing up the stairs (Figure 1.5)
5. There may be over straightening of the knees observed while walking down the slope or climbing down the stairs
6. Poor balance in standing and walking
7. Waddling (Figure 1.6)
8. Toe walking (Figure 1.7)

Muscles that most commonly undergo weakness:

1. Muscles that are required to take the leg behind while standing, Hip extensors (Gluteus maximus) (Figure 1.3)
2. Muscles required to lift the foot up to clear an obstacle on the floor, Ankle dorsiflexors (Tibialis anterior, Extensor digitorum, Extensor halluces longus and brevis, peroneus tertius)
3. Muscles that are required to take the leg away from the body, Hip abductors (Gluteus medius, Gluteus minimum, Tensor fascia lata, Sartorius, Pyriformis) (Figure 1.3)
4. Muscles that are required to take the leg towards the bodyHip adductors (Adductor magnus) (Figure 1.3)
5. Muscles required to bend forward or come to sitting while lying on the back, Abdominals.
6. Muscles that are required to bend the head forwards or lift the head while lying on the bed, Neck flexors (Sternocleidomastoid)
7. Muscles requires to move the arms behind or pull the shoulders down, Shoulder extensors and depressors (Lower trapezius & Latissimus dorsi)
8. Muscles required to move the arm away from the body, Shoulder abductors (Deltoids) (Figure 1.8)
9. Muscles required to straighten the elbow, Elbow extensors (Triceps) (figure 1.8)

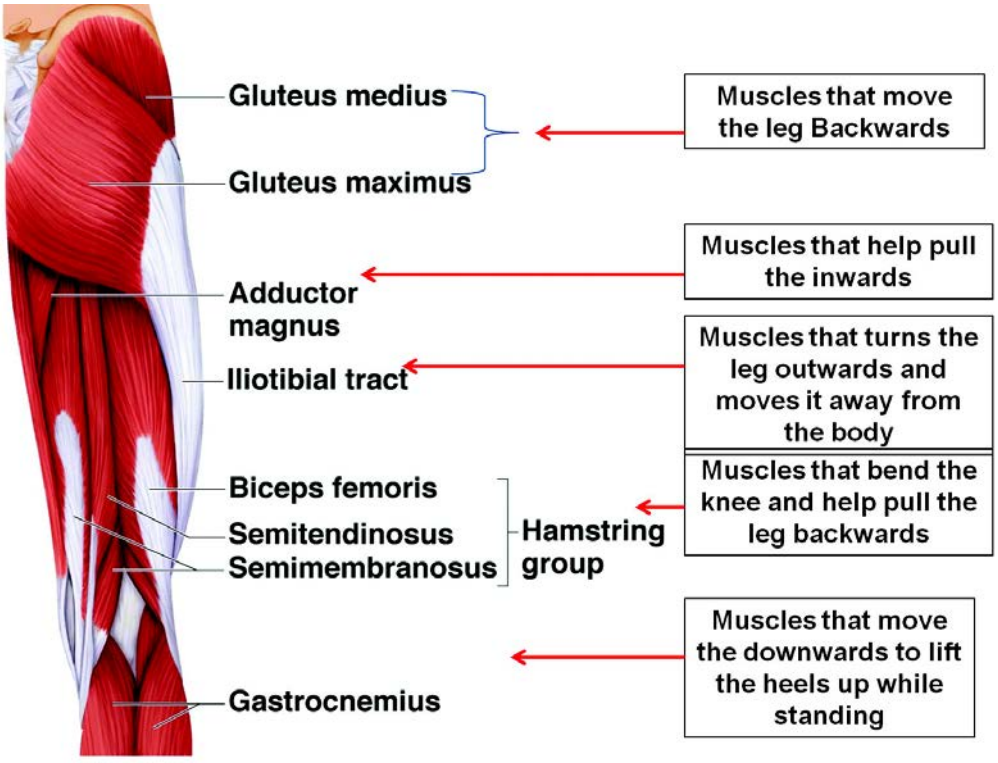

Fig. 1.3 : Muscles of lower limb (Back view)

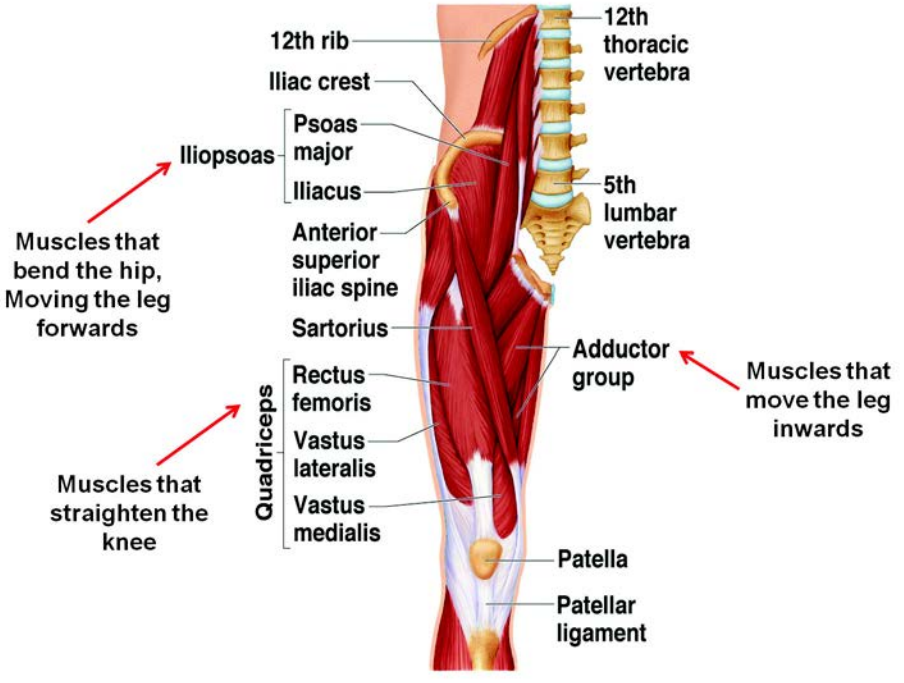

Fig. 1.4 : Muscles of lower limb (Front view)

Fig. 1.5 : Child climbing with the support of a railing

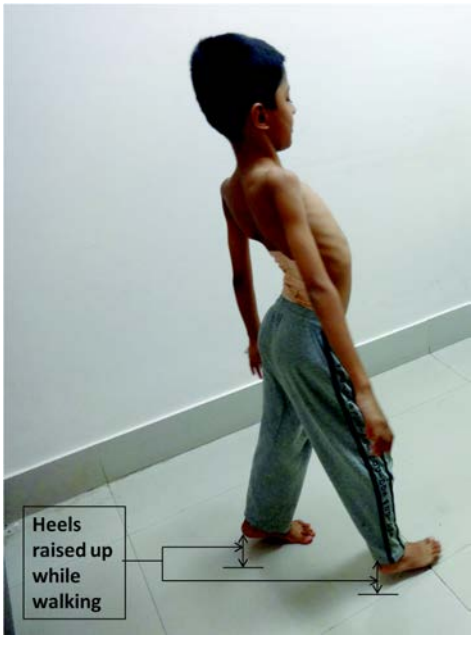

Fig. 1.7 : Toe walking

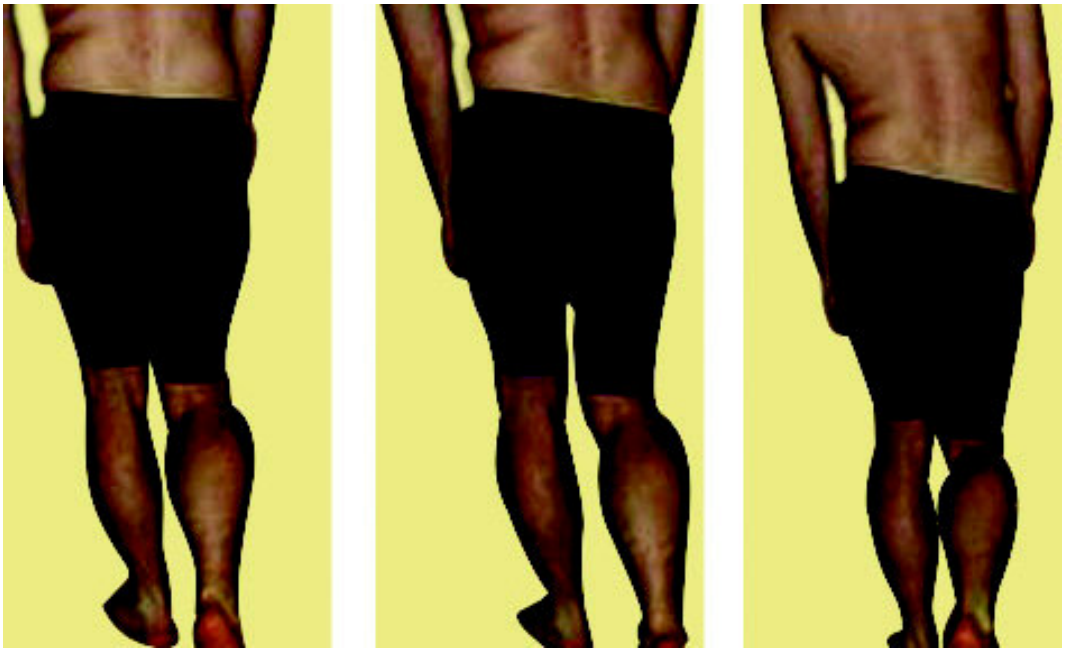

Fig. 1.6 : Waddling

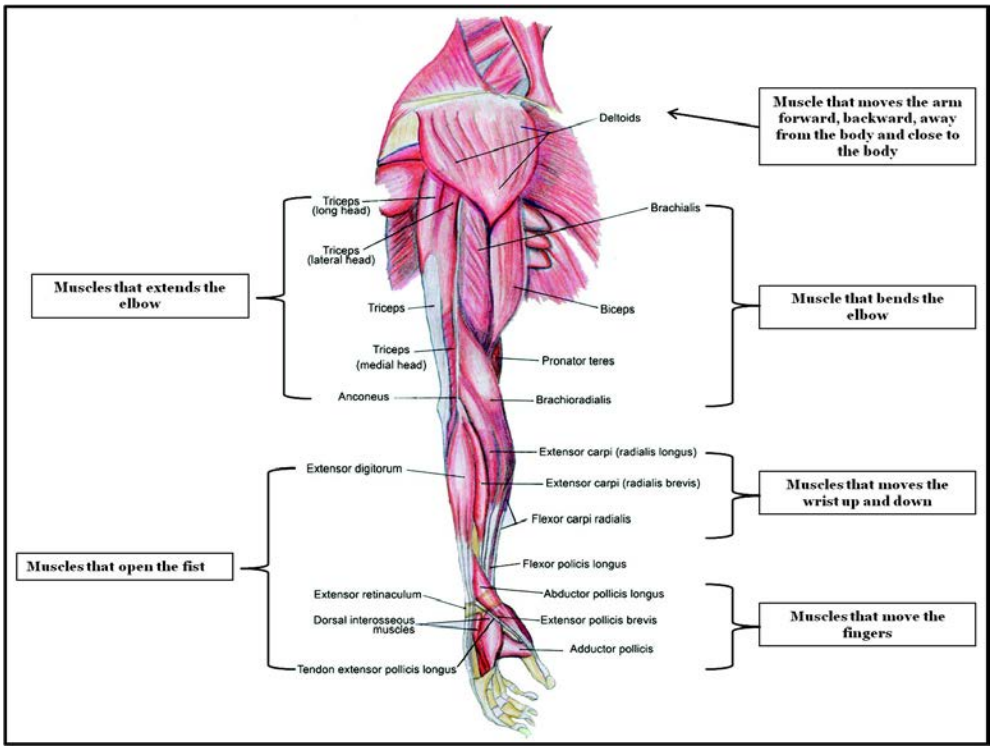

Fig. 1.8 : Muscles of upper limb.

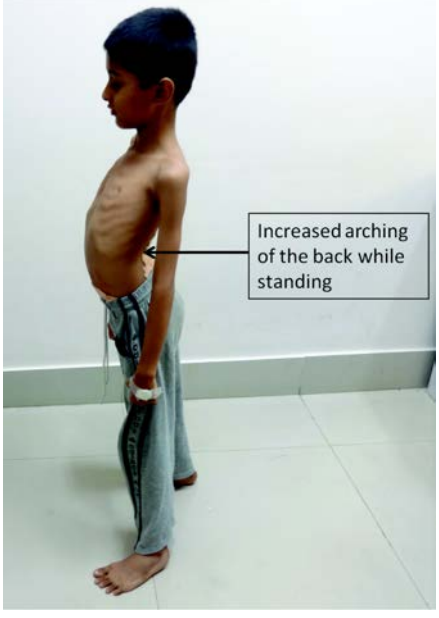

Fig. 1.9 : Increased lumbar lordosis

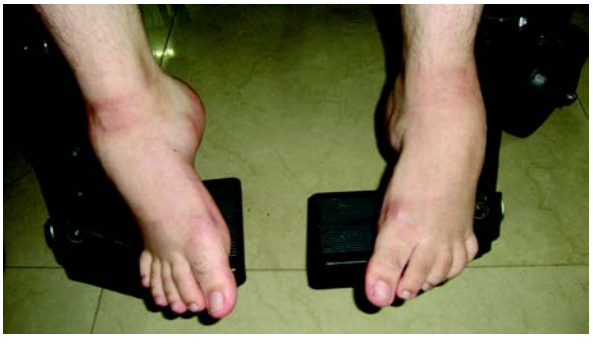

Fig. 1.10 : Foot Deformity

Functional and postural changes observed due to this weakness:

1. Positive Gower's maneuver while getting up from the floor (Figure 1.2)
2. Increased arching of the lower back or posterior trunk lean (Increased lumbar lordosis) to keep force line behind hip joint to maintain balance while walking. (Figure 1.9)
3. Toe walking
4. Increased hip bending to clear the ground while walking
5. Foot may be turned inside and downwards (inverted and pronated) (Figure 1.10)
6. Sometimes flattening of arches of the foot is also observed
7. Child may waddle shifting weight from one side to another while walking

Heart function and breathing ability (Cardio-respiratory system)

Typically there is rarely any cardio-respiratory impairment observed in the early stages of the disease. Cardiac impairment is due to the replacement of the muscle tissue of heart with fatty tissue, this is predominantly seen in left ventricular posteriobasal and lateral walls. The cardiac impairment usually starts with increase heart rate (sinus tachycardia) and abnormal ECG changes [2].

Respiratory muscle weakness also sets in at this stage and the respiration may be labored. Ability to take a deep breath may be compromised. Ability to forcefully blow out the air may also be reduced.

Cognitive ability and brain function (Nervous system)

Although DMD is predominantly a disease of the muscles, some individuals may exhibit some neurological symptoms. The IQ or intelligence quotient of some of the children suffering from DMD is found to be subnormal [10]. At this younger stage it is mainly the verbal IQ or verbal performance that is greatly affected. The cognitive impairment in these children is found to be due to lower than normal metabolism of some of the areas of brain like cerebellum and cortical areas [11]. This is an observation in a relatively smaller number of patients, however if detected early the management strategies could be designed accordingly.

Stage 3: Late ambulatory stage (8 - 13 years)

Muscle weakness continues to progress through this stage and the symptoms advance. Children are able to walk but may require extreme postural compensations or support.

The child cannot climb stairs with or without support. The lower back is markedly arched and the child cannot maintain balance while standing without posterior trunk lean. The children are now habitual toe walkers with marked waddling.

Impairments of muscles and postural deviations (Musculoskeletal system)

Symptoms:

1. Increased falls due twisting of ankle and buckling of the knee while standing or walking.

2. Inability to rise from the floor with or without support
3. Inability to climb stairs with or without support
4. Inability to get up from the chair with or without support
5. Poor balance while standing
6. Child gets tired easily while performing the overhead tasks with upper limbs.
7. Child is able to walk only with support or with extreme arching of the back, way up on his toes and keeping the legs wide apart.
8. Child may lurch on one side while standing, walking and sitting. This lurch or curvature may disappear on lying down.
9. Increased contracture keeping the limbs in a fixed position even when moved passively by others.

Muscles that most commonly undergo weakness:

Muscles mentioned in Stage 2 continue to become weaker. In addition following muscles undergo profound weakness

1. Muscles required to maintain the knee straight while walking providing structural stability or to straighten the bent knee, knee extensors (Quadriceps)
2. Muscles required to move the foot away from the body, Ankle everters (Peroneals)

Functional and postural changes observed due to this weakness:

In this stage most of the postural deviations are to maintain the upright posture in standing and maintain the stability while walking.

1. To maintain the balance mechanics of the body while walking children continue to arch their lower back bringing the hips back and the abdomen forwards. This limits their ability to move the leg behind and therefore to achieve a more stable posture they keep their legs apart (Increased lumbar lordosis with limited hip extension and wider base of support) (Figure 1.11)
2. The legs may roll outwards due to tightness of Ilio tibial band (thick band like structure running across the length of the thigh). (Figure 1.12)
3. Increased foot deviations, foot turns inside and downwards (Increased plantar flexion and equinus)
4. Various muscles undergo tightness as follows
    - Ilio-tibial band
    - Hip flexors - Muscles that are required to lift the leg up with the knee bent in sitting, or bring the leg forward in standing and while walking.
    - Hamstrings - Muscles required for bending the knee and taking the led behind.
    - Gastrosoleus, Tibialis posterior (Plantar flexors) - Muscles that are required to move the foot downwards while lying down or come up on the toes while standing.

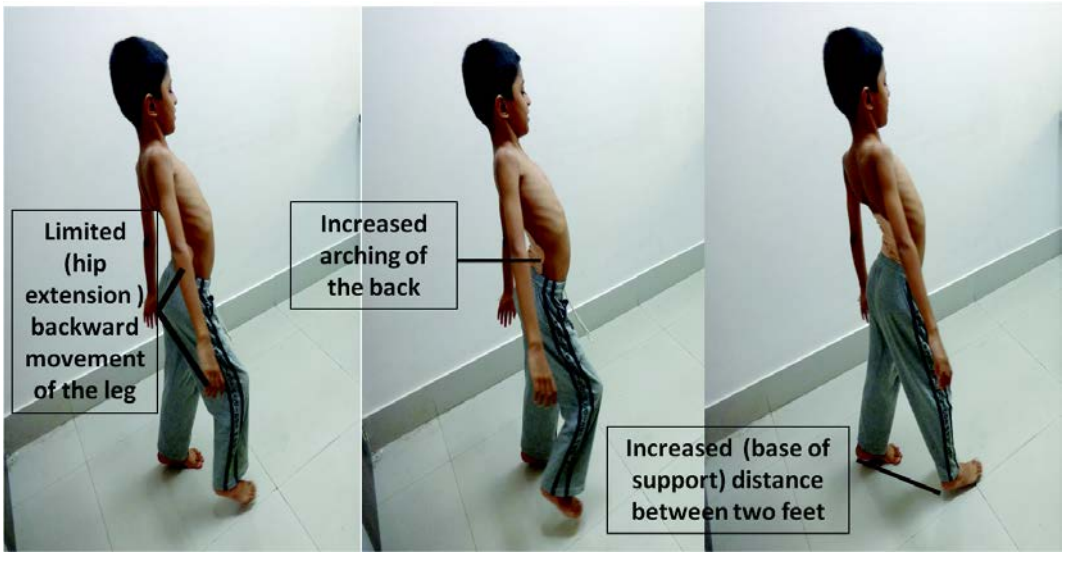

Fig. 1.11 : Child walking with increased lumbar lordosis and wide base of support.

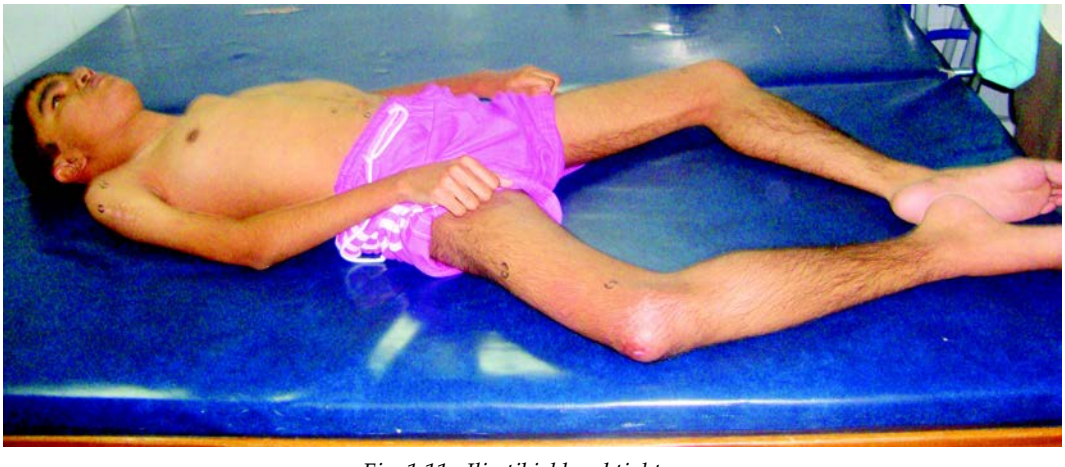

Fig. 1.11 : Ilio-tibial band tightness

- The muscles that undergo tightness first are the muscles that pass over two joints.

5. Deviation of the spinal alignment that may lead to an abnormal curvature of the spine, Scoliosis. (Figure 1.13&1.14)

Heart function and breathing ability (Cardio-respiratory system)

The cardiorespiratory systems are increasingly impaired in this stage. The weakened heart muscles are unable to pump out normal amount of blood with each heartbeat (low ejection fraction/left ventricular dysfunction). There might be some associated changes in the right ventricle. Some other symptoms are palpitations, easy fatigability,

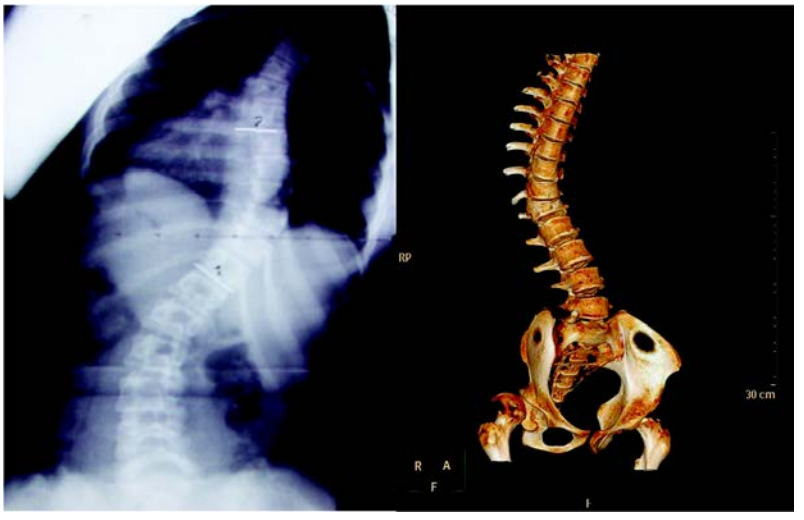

Fig. 1.13 : Scoliosis as seen in X-Ray and CT-Scan

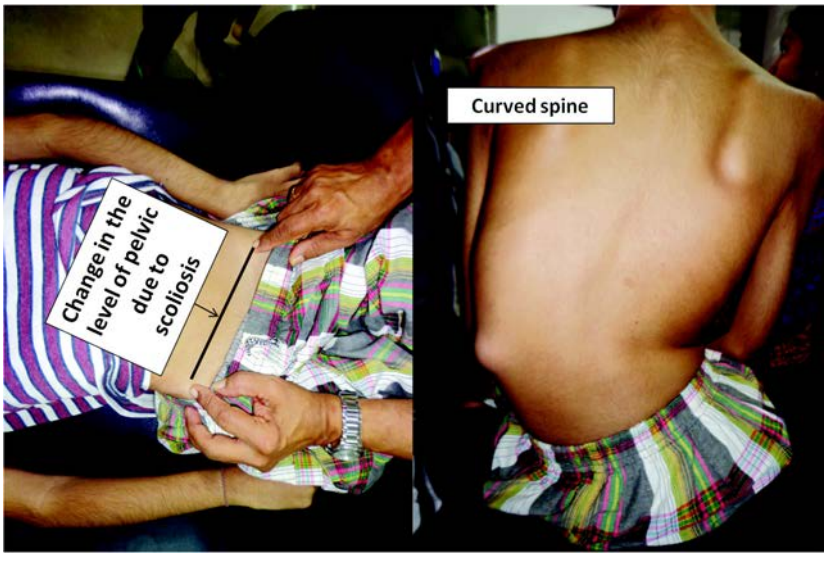

Fig. 1.14 : Scoliosis

shortness of breath, swelling of feet, increased heart rate (tachycardia) and irregular beating of the heart (arrhythmias).

Cognitive ability and brain function (Nervous system)

The verbal IQ of the children at this age may still be lower than peers. Cognitive impairment may be evident in this phase exhibited as poor performance in the school and poor memory.

Cognitive growth of children with normal IQ is age appropriate and is not affected by the disease process.

Gastrointestinal system

Because of limited mobility children may exhibit some problems with the digestive systems. Most commonly children complain of irregular bowel movements, constipation, lack of apetite and very rarely regurgitation [14].

Stage 4: Early non- ambulatory stage (13 to 16 years)

This is the stage where the disease is advanced and children lose their ability to walk. There is significant weakness of upper extremity leading to limitation of upper extremity movement. Postural deviations are pronounced. Respiratory and cardiac muscle weakness leads to enhanced expression of cardio-respiratory symptoms.

Impairments of muscles and postural deviations (Musculoskeletal system)

Symptoms:

1. Inability to walk
2. Poor sitting balance
3. Inability to perform overhead activities
4. Limited upper extremity movement
5. Inability to come to sitting from lying on the back
6. Inability lift the head up while lying on the back
7. Inability to do upper limb activities while sitting unsupported

Muscles that most commonly undergo weakness:

Weakness of all of the muscles listed above becomes more prominent. Following muscles undergo profound weakness in addition and there is increasing imbalance in the muscle groups

1. Muscles responsible for straightening the elbow (elbow extensors) are weaker than the muscles required to bend the elbow (elbow flexors).
2. Muscles required for turning the forearm to face the palm upwards, (supinators) become weaker than the muscles turning the palm downwards (pronators).
3. Muscles that lift the wrist up with palm facing down and open the fingers from a closed fist (wrist and finger extensors)become weaker.

Functional and postural changes observed due to this weakness:

Unlike the late ambulatory stage the postural deviations in this stage are to maintain the upright posture and stability in sitting to assist upper limb function.

1. Leaning on one side for stability (Figure 1.15).
2. Leaning on the opposite side during upper limb function to substitute

   for shoulder girdle weakness in arm lifting
3. Leaning backward while lifting the arms up

4. Leading with head to compensate for trunk weakness
5. Catching fingers in the mouth for overhead activities
6. Tightness develops in
    - Elbow flexors and pronators (Fingure 1.16)
    - Wrist and finger flexors (Figure 1.17)
7. Scoliosis

Cardiorespiratory system

The cardiorespiratory system can be severely compromised towards the end of this stage. There is severe left ventricular dysfunction. Easy fatiguability, Increasing irregularity of heartbeat, cardiac arrhythmias and low ejection fraction.

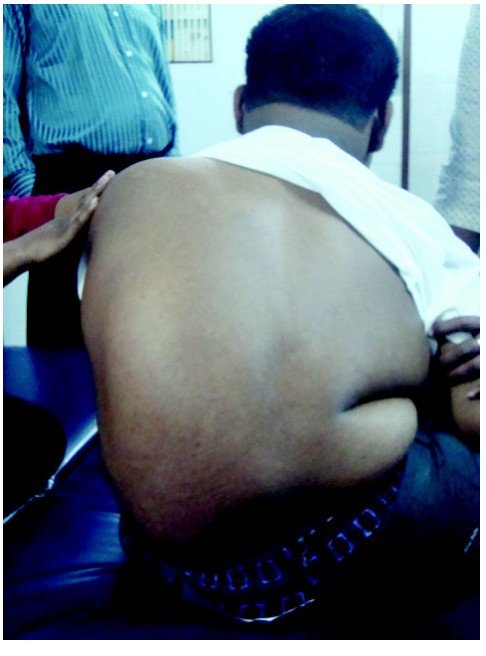

Fig. 1.15 : Leaning on one side for stability

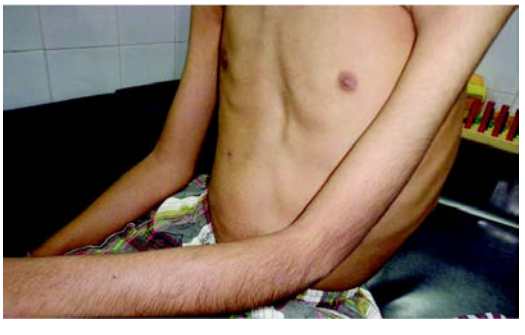

Fig. 1.16 : Elbow Flexion Contracture

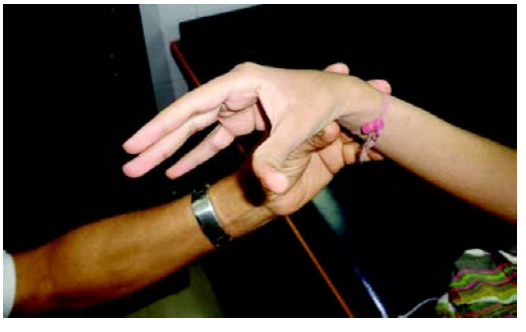

Fig. 1.17 : Wrist and Finger Flexion Contracture

Respiratory system is compromised due to abnormal curvature of the spine restricting the movement of the rib cage. The lung expansion is in turn compromised. The amount of air that can be taken in during inhalation is reduced significantly. The amount of air and the speed at which the air can be thrown out during exhalation is also reduced.

Nervous system

Although the verbal IQ of the children is lower in the early years as they grow the verbal IQ improves. Children in this stage may not show any intellectual or cognitive deficits [11].

Gastrointestinal system

Due to limitation of ambulation and significantly reduced mobility, the gastrointestinal symptoms increase further. The nutrition may be compromised at this stage due to lack of apetite. Towards the end of this stage children may have difficulty in swallowing and chewing which increase the bowel irregularities and nutritional deficiencies.

Stage 5: Late non ambulatory stage (16 years onwards)

This is the last and the most advanced stage of the disease. There are severe limitations in all the physical movements, cardiorespiratory function and gastrointestinal functions.

Musculoskeletal system

The weakness of the above muscles continues and the muscle power reduces to nil in most of the muscles with inability to move any of the proximal muscles. Distal muscles are relatively preserved with ability to use fingers for some functional movements. Postural deformities are very severe and cannot be corrected at this stage. Children are bed ridden.

Cardiorespiratory system

The cardiorespiratory function is greatly compromised and children may require assistance of artificial ventilation and regular cardiac monitoring.

Nervous system

The intellectual ability of children remains unaffected.

Gastrointestinal system

Children develop difficulty in swallowing and chewing and may require to be fed by gastrointestinal tube.

Becker's muscular dystrohpy (BMD)

What is Becker's Muscular Dystrophy?

Becker's muscular dystrophy (BMD) is one of the severe forms of the muscular dystrophies but with a slower progression compared to that of DMD.

Gene affected: Dystrophin gene - In frame mutation (Please note in DMD it is out of frame mutation)

Protein affected: Dystrophin is deficient or abnormal but not completely absent

Inheritance pattern: X-linked recessive inheritance, further information available on page - / / / / / / / /

Symptoms and disease progression:

The disease progresses in the same stages as DMD. The muscle weakness, postural and structural deviations and compensations remain identical. The functional loss is also same as observed in DMD. However the rate of progression of the disease is much slower.

The presymptomatic stage can be extended to second decade of life. The ambulatory stages may span till around fourth decade of life. The life expectancy is much more that in DMD.

The distinct difference in BMD is however a very early involvement of cardiovascular system. Individuals may present with cardiomyopathy as the first symptom of the disease without any muscle weakness or problems in physical performance. Early cardiovascular involvement is related to a mutation at the 5' end of dystrophin gene.

The symptoms of cardiomyopathy are palpitations (increased heart rate) with minimal physical exertion or at rest, irregularities of heartbeat, easy fatigability and palpitations. On investigations reduced ejection fraction and left ventricular dysfunction is evident.

Limb girdle muscular dystrohpy (LGMD)

What is Limb Girdle Muscular Dystrophy?

Limb Girdle muscular dystrophy (LGMD) is one of the slow progressive muscular dystrophies, where the muscles of the hip and shoulder region are involved earlier than other muscles. Slowly the muscles undergo thinning causing severe weakness in other parts of the body as well.

Gene affected, Protein affected, Role of protein in the cell structure and inheritance pattern:

There are several types of LGMD. Each of these have a distinct gene involved responsible for a different protein. The way they are passed on from one generation to other also differs. Different types of Autosomal recessive LGMD, the gene and protein involved, function of the gene and inheritance pattern is summarized in Table 1 [17]. Different types of Autosomal Dominant LGMD, the gene and protein involved, function of the gene and inheritance pattern is summarized in Table 2 [17].

Each of the types shows different genetic involvement and the proteins affected are also different. The role of the proteins in the cell structure is described in Table 1 and 2.

Symptoms and disease progression

It is difficult to differentiate between different limb girdle muscular dystrophies based on the clinical features alone. Although there are some differences

Stage 1: Early Phase

The onset and progression of the symptoms is variable in different forms of LGMD. How fast the symptoms progress cannot be predicted with certainty for these disorders. Onset of the disease ranges from first to fourth decade of the life. Life expectancy may be reduced in many of the individuals suffering from LGMD but may also be preserved in some cases [15,17]. Symptoms and impairment of different systems in various forms of LGMD is given in Table 3.

Impairments of muscles and postural deviations (Musculoskeletal system)

Symptoms

1. Difficulty in getting up from the floor without support
2. Difficulty climbing up the stairs
3. Difficulty in walking on uneven surfaces
4. Frequent falls while walking
5. Difficulty of lifting arms overhead
6. Difficulty of sitting up
7. Difficulty in picking up an object bending down
8. Poor standing balance
9. Difficulty to perform overhead activities
10. Difficulty of holding arms outstretched
11. Difficulty to do upper limb activities while sitting unsupported

Muscles that most commonly undergo weakness:

Weakness in most cases begins in the muscles of Hip followed by Shoulder region. Muscles that undergo weakness at this stage are

1. Muscles responsible for backward and sideways movement of the legs (Gluteal muscles)
2. Muscles responsible for straightening the knee (Quadriceps)
3. Muscles responsible large arm movements like lifting the arm overhead (Deltoids)
4. Muscles used in sitting upright from supine position and curling the legs up to the chest (Abdominal muscles)
5. Muscles that help in keeping the spine erect (Back extensors)

Functional and postural changes observed due to this weakness:

The postural deviations at this stage are adaptations to compensate for the muscle weakness. The function of the muscles of shoulder and hip is to provide stability of these joints when other joints further from the midline of the body (distal joints) like elbow, wrist and fingers, knee, ankle and foot are being moved. Due to weakness of

these muscles the stability is lost and movement of the distal joints is compromised. In absence of the muscle control the only option of stabilizing the joints is by assuming extreme postures to lock hip and shoulder joints.

The postural deviations observed are:

1. Increased arching of the lower back or posterior trunk lean (Increased lumbar lordosis) to keep force line behind hip joint to maintain balance while walking
2. Lack of heel strike while walking
3. Increased hip bending to clear the ground while walking
4. Foot may be turned inside and downwards (inverted and pronated) (Picture)
5. Sometimes flattening of arches of the foot is also observed
6. Child may waddle shifting weight from one side to another while walking
7. Over straightening of the knees while walking

Cardiorespiratory system

Cardio-respiratory systems are not involved in the early stage of the disease.

Stage II: Advanced stage

Advanced stage of the disease is marked with profound weakness of the muscles of arms, legs and trunk. Patients may also develop severe tightness and contractures of various joints. The function is severely limited and patients are non-ambulatory. Respiratory weakness and cardiac impairment is also profound.

Table 1: Autosomal Recessive Limb Girdle Muscular Dystrophies

Type	Protein involved	Role of the protein in the cell structure	Gene (Locus)
LGMD2A	Calpain	Plays a role in cell death and cell cycle progression, regulate clotting of blood and diameter of blood vessels, facilitate the process of protein degeneration essential for integrity of the cell walls	CAPN3 (15q15.1)
LGMD2B	Dysferlin	Essential in muscle cell membrane repair and cell membrane resealing after injury	DYSF (2p13.2)
LGMD2C	Gamma Sarcoglycan	Essential in connecting the muscle cell membrane to extracellular matrix and maintain the integrity of muscle cells under stress	SGCG (13q12.12)
LGMD2D	Alpha sarcoglyacan		SGCA (17q21.33)
LGMD2E	Beta Sarcoglyacan		SGCB (4q12)

LGMD2F	Delta sarcoglyacan		SGCD (5q33.3)
LGMD2G	Telethonin	Putting together the components in the muscle cell structure	TCAP (17q12)
LGMD2H	Actin, Dysbidin	Essential for muscle cell contranction	TRIM32 (9q33.1)
LGMD2I	Fukutin	Maintenance of muscle integrity, also found in brain cells	FKRP (19q13.32)
LGMD2J	Titin	Putting together the components in the muscle cell structure, serves as a skeleton for micro muscle fibers	TTN (2q31.2)
LGMD2K	unidentified		POMT1 (9q34.13)
LGMD2L	Anoctamin		ANO5 (11p14.3)
LGMD2M	Fukutin	Maintenance of muscle integrity, also found in brain cells	FKTN (9q31.2)
LGMD2N	unidentified		POMT2 (14q24.3)
LGMD2O	unidentified		POMGNT1 (1p34.1)
LGMD2Q	unidentified		PLEC (8q24.3)

Table 2. Autosomal dominant muscular dystrophies

Type	Protein involved	Role of the protein in the cell structure	Gene (Locus)
LGMD1A	Myotilin	Skeletal muscle cell protein responsible for integrity of cell wall	MYOT (5q31.2)
LGMD1B	Lamin	Responsible for disassembly of the central portion of the cells and putting it back together during the process of cell generation and growth	LMNA (1q22)
LGMD1C	Caveolin	Responsible for transport of various molecules in and out of the cell	CAV3 (3p25.3)
LGMD1D	Unknown		DES (2q35)
LGMD1E	Desmin	It is important in maintaining the cell structure and structure of sarcomere, small units in the muscle cells which bring about contraction of muscle fibers	DNAJB6 (7q36.3)
LGMD1F	Unknown		TNPO3 (7q32.1-q32.2)
LGMD1G	Unknown		HNRPDL (4q21)
LGMD1H	Unknowm		Unknown (3p25.1-p23)

Less common forms of muscular dystrophies

The less common forms of muscular dystrophy are:

- Facioscapulohumeral muscular dystrophy (FSHD)
- Congenital Muscular Dystrophy (CMD)
- Myotonic Muscular Dystrophy
- Occulopharyngeal Muscular Dystrophy
- Emery-Dreifuss Muscular Dystrophy
- Distal Muscular Dystrophy

These forms of muscular dystrophies are divided in two phases.

Initial stage : This is the stage where the symptoms begin to manifest but, are evident but may not severely restrict the function.

Advanced stage : This is the stage where the disease has progressed and leads to severe functional limitations.

Facioscapulohumeral dystrophy (FSHD)

What is Facioscapulohumeral muscular dystrophy?

As the name suggests the disease affects the muscles of arms, shoulder, neck and face. In the later stages of the disease other muscles may also get involved and severely limit the function.

Gene affected: Gene 4q35.2, 10qter, 18p11.32 (Dominant)

Protein affected: Double homeobox protein 4 (DUX4), D4Z4

Inheritance patterns: Autosomal dominant

Symptoms and disease progression:

There is a repetition of a sequence in the gene 4q35, known as D4Z4 [17]. It is inherited in an autosomal dominant pattern [15].

Early stage

The onset of symptoms could be ranging from congenital to late third decade of life. Congenital onset is related to more generalized weakness where as adult onset presents with predominant muscular weakness in the scapular and facial muscles. In rare and sporadic forms it may occur even at the fourth of fifth decade of life. In such cases facial muscle weakness may not be presesnt. Disease starts with weakness of the shoulder girdle muscles and facial muscles. This could be asymmetric, sometimes presenting with weakness of one side (unilateral). The weakness then progresses to arm and forearm muscles. Weakness of these muscles leads inability to perform overhead movements progressing to inability to perform distal hand movements. Some of the variants show predominant weakness of facial muscles. Female patients more commonaly exhibit weakness in the proximal as well as distal leg muscles. In

some rare cases foot drop is an evident symptom. In the early stage symptoms may be only limited to musculoskeletal system.

Symptoms

- •• Facial muscle weakness (eyelid drooping, inability to whistle, decreased facial expression, depressed or angry facial expression, difficulty pronouncing the letters M, B, and P)
- Shoulder weakness (difficulty working with the arms raised, sloping shoulder)
- Hearing loss
- Abnormal heart rhythm
- Unequal weakening of the biceps, triceps, deltoids, and lower arm muscles
- Loss of strength in abdominal muscles (causing a protuberant abdomen and lumbar lordosis) and eventual progression to the legs
- Foot drop
- Some may show delayed speech and mental retardation [16].

Late stage

The weakness progresses in a descending fashion to the groups of trunk and lower extremity. More commonly involved trunk muscles and pectoral muscles and lower abdominal muscles. Profound weakness of the muscles mentioned in the early stages combined with weakness of trunk muscles severely limiting the function of upper extremities. About 20% of the patients may be confined to wheel chair for ambulation.

Symptoms

- Inability to chew and swallow
- Inability to speak
- Increasing breathing difficulty at rest or on minimal exertion
- Ambulatory disturbances
- Inability to climb stairs
- Inability to get up from the chair
- Sleeping with eyes open
- Bulbar dysfunction difficulty of using straws, blowing up balloons
- Unclear speech especially labial consonants, easy fatigability while talking
- Transverse smile
- Pouting mouth

Other systems

- Sensorineural hearing loss may be observed in some patients. It is progressive and may remain assymptomatic in some while as with infantile onset it is found to be very severe.

- Coats' disease (Vasculopathy) may be observed with assymptomatic retinal detachment. In rare cases blindness may be observed.
- Various cardiovascular complications may be observed in later stages like Labile hypertension, Arrhythmia and Conduction block.
- Mental retardation and Epilepsy may be prevalent in individuals with large deletions.

Congenital muscular dystrophy (CMD)

What is Congenital Muscular Dystrophy?

CMD consists of a group of disorders divers in their clinical features and genetic causality. It presents with muscle weakness at birth or during infancy. Children typically appear "floppy" due to low muscle tone and lack of spontaneous movement. Although muscle weakness can stabilize short term, it progresses with time. This leads to rigidity of spine, contractures and spinal deformities. In later stage respiratory complications may arise. These affect quality of life and life span [17,18].

Genes Affected: laminin alpha-2, Collagen IV, POMT1, POMT2, FKTN, FKRP, LARGE, POMGNT1, and ISPD

Proteins affected: Merosin, Dystroglycan, Collagen

Ingeritance pattern: Autosomal recessive

Symptoms and disease progression:

CMD is muscular dystrophy that is present at birth. CMD includes a number of autosomal recessive] diseases of muscle weakness and possible joint deformities, present at birth and slowly progressing. Life expectancies for affected individuals vary, although some forms of CMD do not affect life span at all. The disease affects the skeletal growth of the child. The life span varies, some children may die in infancy while others may survive till late adulthood [17]. CMD not only affects the muscles but also affects nervous system. Some of the children with CMD also present with impaired cognition and seizures.

Early stage

- Delayed motor milestones, child able to turn, roll, sit, stand and walk later than other children
- Low tone, floppy extremities
- Slow movements
- Lack of co-ordination
- Possible hip dislocation early in the infancy
- Tendency to avoid bearing weight on the extremities
- Poor neck holding
- Child may look famished due to sever muscle wasting

- Facial muscle weakness
- Spine or joint deformities

Advanced stage

- Stunted skeletal growth
- Severe muscle wasting
- Inability to chew or swallow
- Severe breathing difficulty
- Contractures and scoliosis
- Vision abnormalities
- Expressionless face

Myotonic muscular dystrophy

What is Myotonic Muscular Dystrophy?

Myotonic dystrophy is slowly progressing disease with high variability and involvement of multiple organs. The characteristic of the disease is Myotonia, which means delayed relaxation of the muscle after voluntary action or prolonged contraction. Along with myotonia and muscle weakness it presents with cataract, heart conduction defects, hormonal variations and mental retardation [19]. There are two types of myotonic dystrophy based on the gene involved. The onset may vary from immediately after birth to late in the teenages.

Gene affected: Type 1 - DMPK, Type 2 - ZNF9/CNBP

Enzyme affected: Myotonin protein kinase

Inheritence pattern: Autosomal dominant

Symptoms and disease progression:

Early stage

- Delay in motor milestones
- Hypotonia and feeding difficulties
- In some forms children may be born with mental retardation
- Some forms show cognitive symptoms like lack of organization, concentration and inability to choose correct words to express and hypersomnia.
- They may present with insulin resistance.
- Muscle weakness predominantly in the muscles of fingers, face and neck
- Excessive sleepiness during day time (Hypersomnia)
- Hormonal disturbances, reduced formation of sex hormones (hypogonadism)

Advanced stage

- Profound generalized muscle weakness
- Tongues muscle weakness causing slurring of speech
- Difficulty in closing eyes and mouth
- Drooping of eyelids
- Cataract
- Retinal degeneration
- Ciliary body weakness
- Reduced secretion of growth hormones resulting in stunted skeletal growth
- Severe breathlessness during sleep (Sleep apnoea)
- Eosophageal dysfunction, giving rise to frequent infections of the respiratory tract (Aspiration paneumonia)

Occulopharyngeal muscular dystrophy

What is Occulopharyngeal Muscular Dystrophy?

Occulopharyngeal muscular dystrophy occurs in early middle age with weakness of the muscles controlling movements of the eyeballs, eyelids, mouth and throat.

Gene affected: 14q11.2

Protein affected: Polyadenylate-binding protein

Inheritance patterns: Some types are autosomal dominant and some are recessive

Symptoms and disease progression:

Early stage

- Onset varies from early 20's to 60's depending the type
- Progressive ptosis (drooping of eyelids) and weakness of the extraocular muscles is the initial clinical finding.
- With severe genetic mutations limb weakness may also be observed
- Minimal difficulty in swallowing, patient may be able swallow but the speed of swallowing is slow
- There may tongue weakness with minimal slurring of speech
- Mildly elevated serum creatinine phospho kinase and myopathic or denervation abnormalities noted in electromyography.
- Weakness of the muscles that control movement of the eyeballs leading to some visual deficits and slow movement of the eyeballs
- Weakness of the facial muscles, expressionless face inability to flare up the nostrils,

move the eyebrows, blow air forcefully, inability to close the lips tight while drinking water, inability to smile

Advanced stage

- Severe difficulty of swallowing liquids and solids (Dysphagia)
- Proximal limb weakness may develop in types with severe genetic mutation [2]
- There may be some sensory loss with inability to perceive vibrations in the exteremities
- Some patients may not be able to walk due to weakness of proximal muscles of the leg.
- Inability to use muscles that control movement of the eyeballs (Opthalmoplegia)

Emery-Dreifuss muscular dystrophy

What is Emery-Dreifuss Muscular Dystrophy?

It is a relatively benign form of the disease. The onset varies from very early in childhood to late 20's or 30's however the disease progression is very slow.

Gene affected: Emerin Xq28

Protein affected: Emerin

Inheritance patterns: X-linked Recessive

Symptoms and disease progression:

Early stage

- Weakness of the muscles of the shoulder and ankle in an humeroperoneal pattern.
- Weakness is usually symmetrical
- Scapular winging is present in early stages
- Unlike other forms the contractures are seen earlier in the disease, contractures are mainly seen in the neck, elbow and arm region.
- One of the characteristic features of the disease is involvement of the cardiovascular system by the third decade of life leading to cardiomyopathy.

Late stage

- Muscle weakness and wasting progressess to the muscles of lower limbs
- Facial muscle weakness is observed
- Severe wasting or thinning of the elbow and calf muscles
- Rigid spine with severe spinal deformities
- Cardiac involvement is severe in the late stage of the disease.
- Towards the end of the disease there might be some respiratory involvement.

Distal Muscular Dystrophy

What is Distal Muscular Dystrophy?

Distal muscular dystrophy connotes a group of disorders that result in weakness of the muscles of small joints like wrist, fingers, ankle and feet. Rarely weakness of proximal bigger joints like shoulder, hips and trunk is observed.

Gene affected: Multiple depending on the type

Protein affected: Multiple depending on the type

Inheritance patterns: Some types show autosomal dominant and some types present with autosomal recessive inheritance patterns

Symptoms and disease progression:

Early stage

- Weakness of wrist and finger muscles
- Foot drops down while walking which requires lifting the leg up higher than usual to be able to walk
- Subclinical neuropathy and sensory abnormalities may be present
- Hypotonia
- Muscle pain

Advanced Stage

- Proximal muscle weakness
- Drooping of eyelids
- Facial muscle weakness
- Breathlessness on exertion
- Scoliosis and other spinal deformities

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2.

What Really Happens in Muscular Dystrophy?

PathophysiologyAs we have discussed in the earlier chapter, muscular dystrophy is a result of gene mutations. In this chapter we will be focusing on how the abnormal protein produced due to these mutated genes affects the muscles in muscular dystrophy. These genes are majorly responsible for producing proteins which help build the muscle fibres. The defect in protein production causes damage and degeneration of muscles leading to muscular dystrophy. Herein, we will be discussing the molecular mechanism of the muscle in detail.

Normal muscle physiology

Skeletal muscles are a comprehensive unit made up of different tissues like smaller fibers muscles of (myofibers), nerve cells (neurons), network of blood vessels (vascular networks) and cementing or binding tissue with (connective tissues). Myofiber is the structural and functional element of skeletal muscle. Myofibers possess unique contractile properties that allow these to shorten in length resulting in muscle contraction. In a normal muscle, the myofibers are evenly spaced, angular, and are of a relatively uniform size. Each myofiber is surrounded by the basement membrane. Basement membrane is the thin layer of fibrous tissue. It does not possess the special contractile properties of myofibers. Beneath the basement membrane are situated the satellite cells. These cells help maintain, repair and regenerate the muscles. They are normally inactive, but are stimulated as a response to growth or injury and give rise to regenerated muscle and more satellite cells hence forming a reserve pool of cells. In a healthy muscle, the wear and tear is a remarkably efficient process which is regulated by these satellite cells.

Dystrophin-glycoprotein complex (DGC):

Dystrophin-glycoprotein complex (DGC) is a large complex of proteins made up of dystroglycan, sarcoglycan and syntrophin complexes. Studies have revealed that the DGC is a multifunctional complex and a highly dynamic structure in the muscle. It

forms a bridge across the muscle membrane, stabilizes the covering of the muscle cells (sarcolemma) and protects muscle fibers from long-term contraction-induced damage and cell death. Any defect in the different components of the DGC causes muscular dystrophies that vary in terms of severity, age of onset, and selective involvement of muscle groups. Different types of muscular dystrophies are caused by absence or abnormalities in different proteins from this complex. Figure 2.1. shows different proteins responsible for different types of muscular dystrophies and their location in the DGC complex.

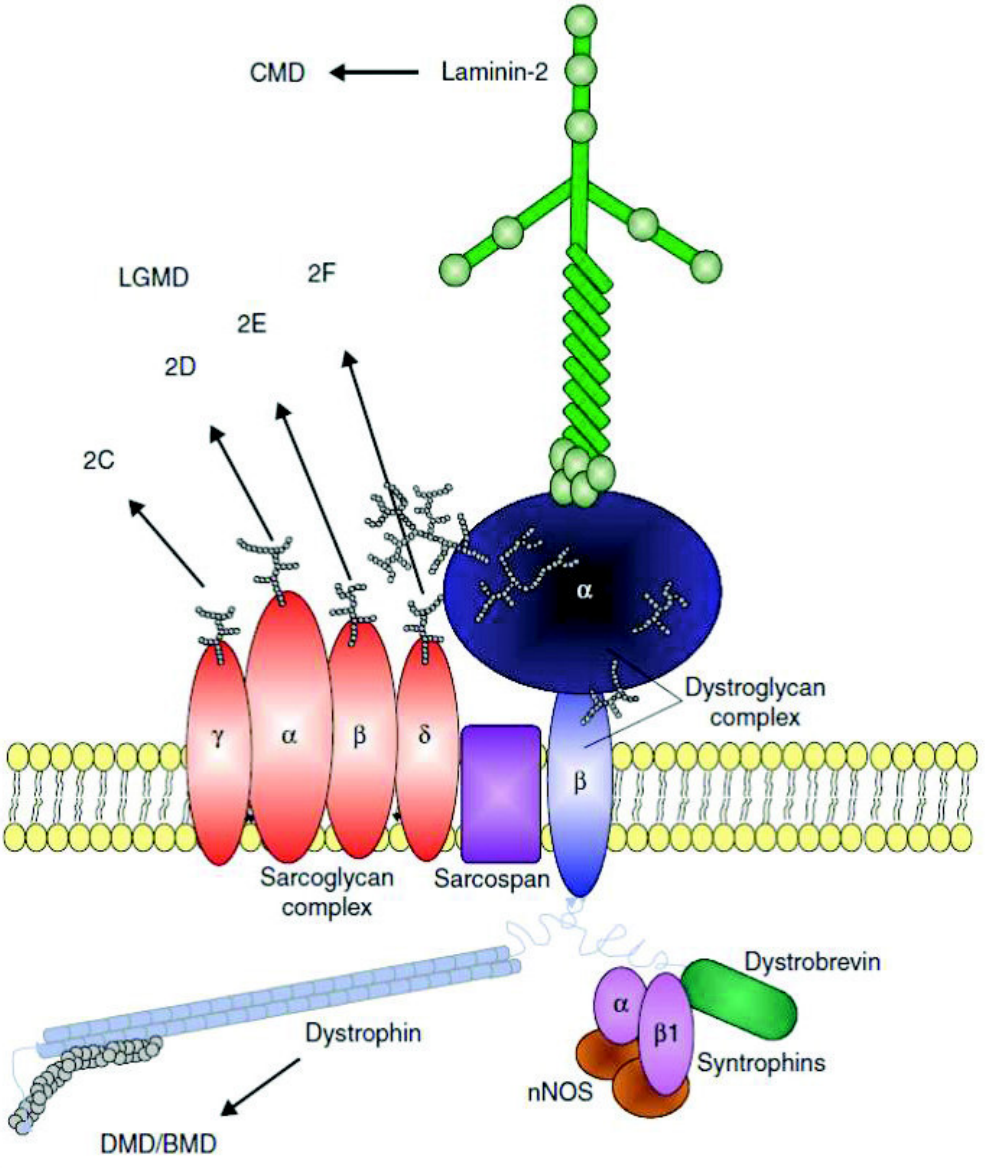


Figure 2.1: Different protein responsible for different types of muscular dystrophies and their location in the DGC complex

Muscular dystrophy Pathophysiology:

In this section, we have mainly described about Duchenne Muscular Dystrophy (DMD). In DMD, the protein dystrophin is either absent or semi functional. Dystrophin is known to bind to DCG complex and maintain the integrity of the membrane. Lack of dystrophin not only leads to muscle degeneration but also affects the nerves and blood supply. In DMD, the satellite cells which carry out the natural repair process ultimately get exhausted and are unable to regenerate new muscle fibres. Hence muscle degeneration outweighs muscle regeneration eventually leading to irreversible damage and death of the tissue.

(A) Effects of lack of dystrophin on muscle fibre

1. Membrane Integrity disruption:

Lack of dystrophin in DMD causes damage to the plasma membrane and makes it fragile leading to leakage of substances like proteins and enzymes (creatine kinase) into circulation and exposing the muscle to hypoosmotic conditions which leads to membrane blebbing. The enzymes and chemicals that leak out are responsible for certain chemical reactions and produce energy required for muscle contraction. Simultaneously, the extracellular substances leak into the fiber through the fragile membrane damaging the fiber and disrupting the process of muscle contraction.

2. Calcium influx:

Regulated levels of calcium molecules are critical for various muscle functions. Studies have shown that these levels are disturbed in muscular dystrophy. Due to compromised membrane integrity, there is a large spike and fall of intracellular calcium which further leads to cell death.

3. Oxidative stress:

Oxidative stress is one of the main reasons of degeneration in dystrophin deficient muscular dystrophies. Increase in reactive oxygen and oxidative stress leads to cellular damage by damaging the proteins, membrane lipids and DNA. It also causes irreversible damage to the membrane and alters its integrity.

4. Apoptosis:

Apoptosis is programmed cell death. Muscle fibers are subjected to constant stress from contractile activity. In dystrophin deficient muscles, the membrane is disrupted and the permeability is altered followed by homeostatic dysbalance and increased cytosolic Ca2+-influx. These events initiate apoptosis in DMD muscle.

5. Inflammation:

In muscular dystrophy, a major part of the muscle damage is caused due to inflammation. The inflammation causing molecules such as cytokines and chemokines are expressed directly by the muscle fibers. This indicates that the muscle tissue is directly responsible for chronic inflammation.

5. Vascular problems

Dystrophin under normal circumstances localizes nNOS (neuronal-type nitric oxide

synthase) to the membrane which is further responsible for production of NO (Nitric oxide). NO in healthy muscles is responsible for regulating the blood flow and facilitating smooth muscle vasodilation by blunting vasoconstrictor response. This response in dystrophin absent DMD is affected as vasoconstrictor response is not blunted, further affecting the blood flow and oxygen levels in the muscles. NO is also responsible for activation of satellite cells. Hence, in its absence the satellite cells become exhausted, and ultimately lose their ability to repair muscle damage leading to breakdown of muscle fibres, and inflammation.

6. Fibrosis:

Fibrosis is one of the chief pathological features of DMD. In DMD, there is a constant breakdown of muscle fibres resulting into chronic inflammation. As the pool of satellite cells in DMD is eventually exhausted, the muscle repair and regeneration is greatly affected. The muscle tissue is then ultimately replaced by fatty cells and fibrotic tissues. Hence, causing muscle dysfunction. This phenomenon is first recorded in the calf muscle of the DMD patient.

(B) Effects of lack of dystrophin on nerves:

Along with the muscle tissue, dystrophin is also found to be present in the neurons. Hence, lack of dystrophin may also have a major impact on the neuronal function. Similar to the muscles, the nervous system is also subjected to external as well as internal forces such as brain growth, body movements, environmental insults, etc. Dystrophin could play a role in maintaining the integrity of the neurons. Studies show that lack of dystrophin may also affect the structure and function of neuromuscular junctions. These neuromuscular junctions are more susceptible to damage and might aggravate the damage of muscles.

In case of LGMD, there is loss of sarcoglycan complex of DCG. This complex comprises of α-sarcoglycan, β-sarcoglycan, γ-sarcoglycan and δ-sarcoglycan. Any defect to even one of these may destabilize the whole complex. The integrity of this complex is important for normal muscle physiology. Hence, any alteration may affect the membrane permeability and also lead to apoptosis.

In conclusion, abnormalities in elements of the DGC seem to be the underlying pathology that triggers muscle damage and degeneration in muscular dystrophy.

3.

Diagnosing Muscular Dystrophy

Diagnosis of muscular dystrophy is guided by clinical features, blood tests, electromyogram and confirmed by muscle biopsy, Musculoskeletal MRI or genetic testing. Genetic testing helps to give the most accurate estimation of the type of muscular dystrophy.

Clinical examination:

For muscular dystrophies that affect children at a younger age, symptoms are most commonly observed by parents. Early symptoms remain common in children as well as adults. The onset of these symptoms varies according to the type of muscular dystrophy. When you visit a clinician with the present symptoms, onset and progression of the symptoms will be discussed thoroughly. The clinician will also ask information about your immediate family and close relatives to identify if anybody had similar symptoms. The discussion will be followed by performance of series of physical tasks like getting up from the floor, walking on a plane surface, stair climbing, getting up from the chair, getting up from supine to sit, standing one leg and squatting. Based on the performance of these tasks the clinician will decide the tests to be done. Further investigative tests in MD are Serum CPK testing, muscle biopsy, EMG, musculoskeletal MRI, ECG and 2D-echo cardiography.

Serum CPK testing

What is serum CPK testing?

CPK is an enzyme found in muscles, brain and heart. This enzyme is released in blood when the muscles are injured. During our day to activities there is some damage to the muscles and some mount of serum creatine kinase is released in the blood however if there is significant injury to the muscles then the levels increase beyond regular range.

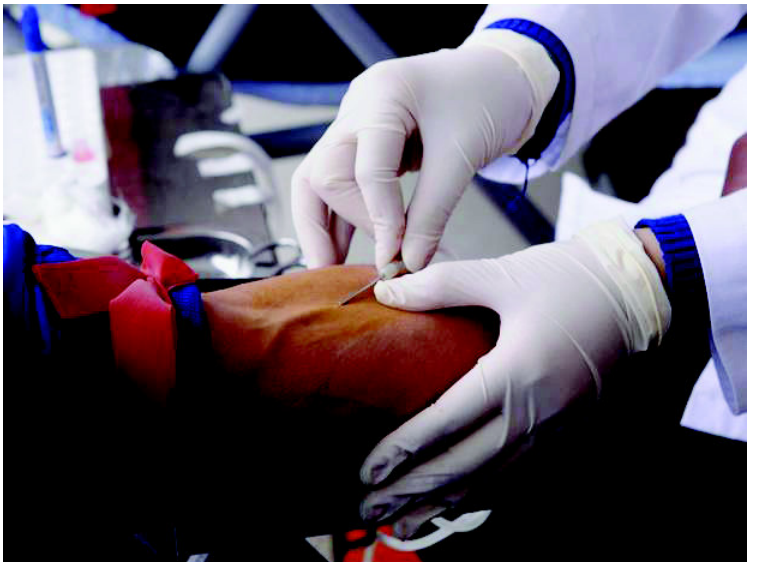


Fig. 3.1 : Blood test to measure serum CPK

The procedure for serum CPK testing: (Fig. 3.1)

Preparation for the procedure

- No special preparation or fasting is required for this test.
- Avoid any physical exertion before the test.
- Inform your doctor if you have consumed any of the following
  - Medication like amphotericin B, certain anesthetics, statins, fibrates, dexamethasone
  - Alcohol
  - Cocain

During the procedure

- Blood samples will be drawn by means of a venopuncture (puncture to the vein), maintaining the stipulated standards of sterilization.
- The clinician or technician will clean the area (usually the area on the inside of your arms or back of your hand) with topical antiseptic.
- An elastic band will be wrapped around your arm. You will be asked to make a fist.
- The needle will be inserted to draw blood samples.
- You may feel moderate intensity pain, prick or stinging sensation. The pain will reduce immediately after the needle is drawn out.

Post procedure guidelines

- The blood sample will be labeled and sent to the lab for further analysis. You may feel some minor dull pain or soreness after the blood test.

Interpretation of the results:

Serum CPK can be elevated due to various reasons, in muscular dystrophy it is exponentially higher than the normal levels sometimes even up to 10 times higher. It is important to understand that the diagnosis cannot be confirmed only on the basis of elevated serum levels and clinical correlation is a must. It is therefore advise to meet you doctor with the results of the test. Who may ask to perform further confirmatory tests.

Normal range of total serum CPK:

- Male: 38 - 174 units/L
- Female: 96 - 140 units/L

Muscle biopsy

What is muscle biopsy?

A muscle biopsy is a tool to diagnose neuromuscular diseases by viewing the muscle cell structure under microscope. Depending upon where the symptoms are observed a needle is inserted for sectioning the biopsy or a small piece of muscle is excised by your doctor.

The procedure of muscle biopsy

Preparation for the procedure:

- Thorough assessment will be performed.
- Your doctor will explain the procedure to you in detail.
- Inform your doctor if you have any allergies to medication or anesthetic agent.
- Inform your doctor of all the medications you are consuming.
- Your doctor may ask you to fast for sometime before the procedure.
- You may also be given mild sedative to help you relax.

During the procedure:

- You will be asked to change in to a hospital gown. The area from where the muscle is to be taken will be exposed and cleansed with an antiseptic solution. The doctor will inject anesthetic to numb the area. As the needle pricks you will feel a stinging and pricking pain for some time.
- Your doctor will insert the biopsy needle or make a small cut on your skin and remove a small piece of muscle. If the cut on the skin is too big your doctor may put some stitches or use adhesive tapes to seal the wound. A sterile bandage and dressing will applied on the wound. The muscle tissue will be sent to the laboratory to be analyzed.

Post procedure precautions:

- Keep the area of biopsy clean and dry.
- Follow the bathing instructions given by your doctor accurately.

- Stitches will be removed in a few days it is important to take care of the wound site to make sure it does not get infected. The adhesive tape will fall off, on its own.
- You may feel tenderness and pain at the site of biopsy for next 2 to 3 days. If pain is unbearable please talk to your doctor and take appropriate pain medication.
- **In case of fever, redness, swelling, bleeding, oozing of pus or increased pain around the biopsy site notify your doctor immediately.**
- **Avoid any excessive physical exercises for 24 to 48 hours after biopsy.**

Interpretation of the results:

The muscles will be observed under miscroscope for specific features suggestive dystrophy. Your neurologist and pathologist will give a report to confirm presence of muscular dystrophy.

Disadvantages:

It is an invasive procedure which involves taking out a piece of muscle tissue. In already weak muscles, this procedure can make the muscle more weak. Secondly, if the procedure is done without imaging guidance, the biopsy may be taken from the non affected part of the muscle, thus giving a false negative report.

Electromyogram (EMG) and Nerve conduction velocity (NCV) testing

What is EMG-NCV testing?

EMG is a procedure used to measure the response of the muscles upon electrical stimulation by the nerves. The test is used to detect abnormalities in the transmission of electrical impulses from the nerves to the muscles and back to the nerves. Most commonly EMG is accompanied by the measurement of nerve conduction velocity (NCV). Abnormalities in the speed of nerve conduction help identify the location of the damage to the nerve. Hence EMG-NCV testing helps to find out the exact location of damage. Electrical activity of muscle and nerves can be recorded using various methods and placements of the electrode. For the diagnosis of muscular dystrophy Needle EMG is required. Needle EMG is an invasive technique as explained below.

The procedure needle of EMG and NCV testing (Fig. 3.2)

Preparation for the procedure:

- No special preparation or fasting is required for the test.
- You may be advised to refrain from any caffeinated drinks 2 - 3 hours before the test.
- Wear clothes that allow access to all the regions of the body or that can be easily removed.
- Inform the doctor if you have any metallic implants in the body or pacemakers.
- Do not use any oils and lotions on the day of the examination.

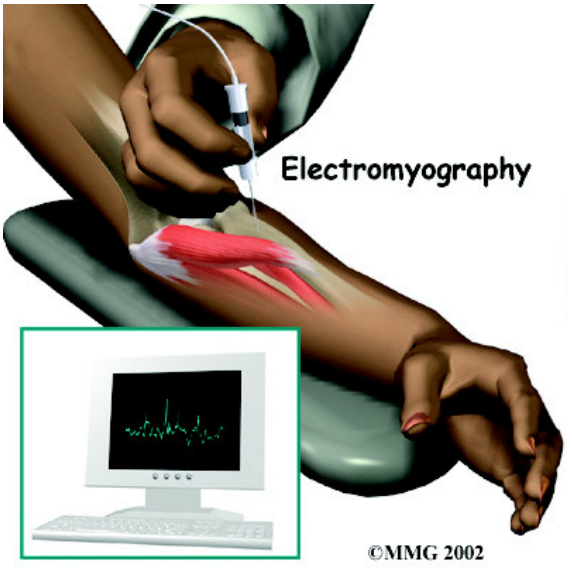


Fig. 3.2 : Needle Electromyography

During the procedure:

- You will be advised to remove any clothing, hairpins, eyeglasses, hearing aids, or other metal objects that may interfere with the procedure.
- The test can be performed in sitting or lying down.
- The muscles to be studied will be located. The skin region will be cleansed using an antiseptic solution.
- An electrode to complete the circuit (ground electrode) will be placed under your arm or leg depending on the muscle to be stimulated.
- Multiple needles may be inserted to record the impulses. There may be mild to moderate pain due to needle insertion. However if pain is severe inform the doctor as it may interfere with the results. Children may find it more painful than adults.
- Once the needle is securely placed in its location, you will be asked to perform a small movement of that muscle and later on a more forceful movement. The electrical activity will be recorded during these contractions. Multiple such muscles will be tested in the regions of arms and legs.
- For NCV testing, two superficial electrodes will be placed on the skin one of them will be a recording electrode and the other stimulating electrode. A small current will be passed through the stimulating electrode. The time taken to carry this impulse to the recording electrode and the distance between the two electrodes will determine the conduction velocity of the nerve. Multiple nerves may be tested. You may feel mild discomfort as the current is passed through your body but generally it is pain free.

Post procedure precautions:

- You may experience dull soreness to moderate pain at the site of needle insertion.
- Notify your doctor immediately in case of any swelling, pus, persistent severe pain and tenderness.

Interpretation of the results:

EMG and NCV studies are performed to diagnose many disorders. A careful clinical evaluation along with findings from other tests is required in case of muscular dystrophy. In early stages of the disease the muscles will demonstrate abnormal activity (Action potentials) due to interruption of the electrical signals by fibrous tissues in the muscles. Nerve conduction velocity remains unaffected during early stages however in later stages it may show some alterations.

Advantages: It is diagnostic and helps to differentiate from muscle weakness due to nerve problem. Also, it can monitor the progress of the disease.

Disadvantages: It can be a somewhat painful procedure.

Musculoskeletal Magnetic Resonance Imaging (MRI-MSK)

What is MRI-MSK?

MRI-MSK is a non-invasive imaging technique used to identify any structural abnormalities in the body. MRI uses a powerful magnetic field, radio frequency pulses and a computer to produce detailed pictures of organs, soft tissues, bone and virtually all other internal body structures. MRI does not use any X-ray (Ionizing radiation). The images obtained can be studied on the computer or printed out. (Fig.3.3)

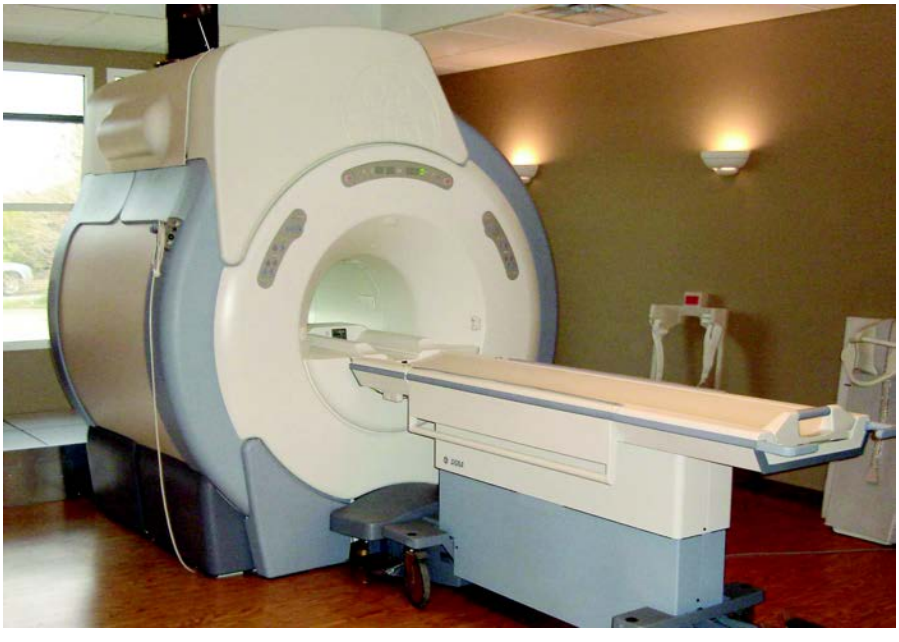


Fig. 3.3 : Magnetic Resonance Imaging Tunnel

The procedure of MRI-MSK

Preparation for the procedure:

- Wear loose clothes that can be easily removed.
- Do not wear any jewelry, glasses with metal in the frames, clothing with metal hooks and button or metal any other metal articles on your body.
- Do not carry any electrical devices like mobile phones, pagers etc. in the examination room
- Fasting and food restrictions vary from center to center and the type of MRI. Unless instructed otherwise carry on with your daily routine.
- Inform your radiologist of any allergies that you have, any medication you take and any recent injuries, surgeries or metal implants.
- Women must inform the radiologist if they are pregnant and MRI testing should be avoided during the first trimester. So for no documented ill effects of MRI on pregnant women or fetuses have been noted.
- The procedure involved will take place inside a tight closed tunnel (figure) for 30 to 45 mins.
- If you feel anxious or are fearful of closed spaces (claustrophobic) inform you physician and radiologist in advance. If counseling and reassurance does not relieve your fear, your physician may prescribe mild sedative for the examination. Children will require sedative or anesthesia to complete the exam to stop them from moving. The amount of sedation and anesthesia required depends upon child's age and the type of MRI. If sedation or anesthesia is required for your child the child may be required to be kept nil by mouth for some duration prior to testing and such instructions will be provided to you by your radiologist.
- Implanted devices like artificial heart valves, pacemakers, metal pins, screws, plates, stents, implanted nerve stimulators etc. will have a pamphlet explaining the risks during MRI. If you have the pamphlet, bring that to the attention of the radiologist before scheduling your exam. It is advisable to consult the doctor who has fitted the implant for detailed information regarding MRI compatibility in addition to the information on the pamphlet.
- Dyes used in tattoos may contain iron and could heat up during MRI, but this is rarely a problem.
- Tooth fillings and braces usually are not affected by the magnetic field, but they may distort images of the facial area or brain, so the radiologist should be aware of them.
- Parents or family members who accompany patients into the scanning room also need to remove metal objects and notify the technologist of any medical or electronic devices they may have.

During the procedure

- To conduct an MRI you will be positioned on a movable table.
- You will then slowly moved into a tunnel like magnet of the MRI (Figure).
- Your radiologist will be sitting outside the MRI room and will be able to see you and communicate with you through a two way intercom.
- The entire examination is usually completed within 30 to 45 minutes.
- You will be asked to remain still during this examination. It is absolutely essential to remain steady while the images are being obtained.
- The part under investigation may feel a bit warm but if it is uncomfortable, painful or you feel any burning sensation inform your radiologist immediately.
- You will hear and feel loud tapping or thumping sounds while the images are being recorded. Some centers provide earplugs, while others use headphones to reduce the intensity of the sounds made by the MRI machine.
- You will be able to relax between imaging sequences, but will be asked to maintain your position without movement as much as possible.

Post procedure precautions

- As there is no contrast injected during this type of MRI the recovery is instant, you can resume your activities as soon as the examination is done.
- If any sedation is used you would be taken to the recovery room to rest. As the effect of the sedative wears out you may feel some nausea and vomiting sensation. But it should reduce within a couple of hours.

Interpretation of the results:

MRI images help identify the amount of fibrous tissue and muscles in a given body part. Based on this proportion and distribution and appearance of muscles and fibrous tissue, radiologists will be able to assess the severity of the disease.

Advantages: It is a non invasive and painless investigation. It reveals a detailed muscle involvement with regards to number of muscles affected, extent and severity of damage. It also gives information about the amount of fatty infiltration in the muscles. It can also be used as a monitoring tool.

Electrocardiograph (EKG/ECG)

What is Electrocardiograph?

An electrocardiogram measures the electrical activity of the heart muscles and is one of simplest and fastest ways of evaluating heart muscles. Small plastic patches (electrodes) will be stuck to your chest arms and legs. These measure the electrical activity which recorded and represented in graphical format for the doctor to interpret. EKG is not a diagnostic test in MD however it is essential to prevent and treat any heart related complications.

The procedure of EKG (Fig. 3.4)

Preparation for the procedure

- No specific preparation is required for the test. No fasting is required.
- Be sure to inform your doctor of the medications you are taking prior to fixing an appointment for EKG.
- Your doctor may give you specific instructions about the medication.
- If you are on pacemaker, artificial valves or any other implants inform your doctor in advance.

During the procedure

- Remove all the jewelry, metallic and electronic objects that may interfere with procedure.
- You would require to remove clothing from waist up.
- You would be lying on the table for the test to begin.
- It is important to remain still as the test begins.
- Electrodes will be stuck on your chest and arms, these areas will be shaved off and cleaned prior to fixing the electrodes.
- It will take 15 - 20 mins to complete the recording. You will not feel anything during the recording.

Post procedure precautions

There are no specific precautions to be taken after the test and you may resume your routine activities immediately.

Interpretation of the results

Based on the graphs your doctor will be able to identify any damage and subnormal functioning of the cardiac muscles and will advice medication accordingly.

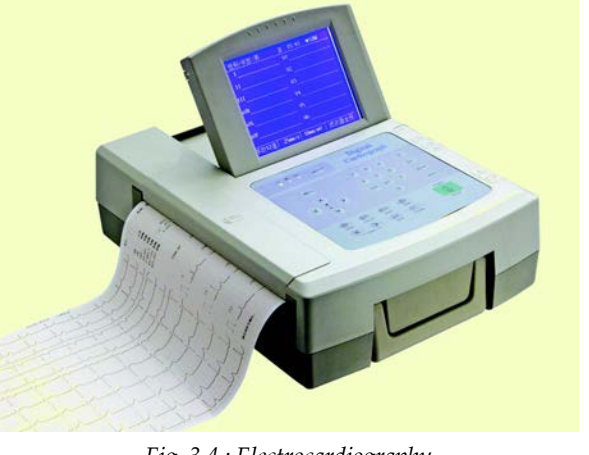


Fig. 3.4 : Electrocardiography

2D-Echocariography

What is 2D-Echocardiography?

2D-echcardiography like ECG is not a diagnostic test in MD however it is essential to prevent any heart related complications. It is a noninvasive procedure wherein sound waves are sent through the heart and recorded. Based on the echo of these waves an image is built by the computer which is then analyzed by the clinician.

The procedure of 2D-Echocardiography (Fig. 3.5)

The pre-procedure precautions are identical to ECG testing.

During the procedure

- You will be required to remove clothing waist up.
- ECG electrodes will be placed and connected to the monitor.
- The clinician will place warmed gel on your chest and place the device that emits sound waves (probe).
- You may feel a slight pressure as he moves the device.
- The room may be dimly lit to allow better viewing of the images.
- It may take upto 20 mins to obtain the images of the heart.

Fig. 3.5 : 2D Echo-cardiography

Post procedure precautions

- There are no precautions to be taken after the procedure and you can resume your routine immediately.

Interpretation of the results

Echo cardiograph helps to give a better understanding of the heart function and structures. It tells about any abnormality of the heart valve function, chambers and walls of the heart. It also shows if the amount of blood pumped by the heart is adequate and if any particular part is performing subnormal.

Genetic testing

What is Genetic Testing?

Genetic testing is the gold standard to identify MDs. Genetic testing identifies the faulty genes. It is performed by drawing blood which is then analyzed by array of tests to find out the faulty gene.

The procedure of genetic testing

The sample for genetic testing is blood and is collected as standard methods of blood

collection as explained above in CPK testing. The details about the genetic testing and its implications are explained in detail in the next chapter on Genetic Counselling.

What next after the diagnosis of Muscular Dystrophy?

Once the diagnosis is confirmed it is important that the patient/parents approach an appropriate team of specialists who can guide in the management of the condition. The team may comprise of a physician, neurologist, pediatrician, orthopedic surgeon, neurosurgeon, physiotherapist, occupational therapist, speech therapists, social worker, dietician and psychologist. These specialists can give proper advice regarding the outcome and treatment options.

What are the treatment options for muscular dystrophy?

Till date, no cure is available for muscular dystrophy, although, medicines like steroids can delay the progress of the disease. Stem cell therapy and rehabilitation are found to be very beneficial in improving the condition. These treatments certainly ensure the patients an improved quality of life and increased life expectancy.

4.

Genetic Counseling

Muscular dystrophies are mostly genetically inherited disorders barring the exceptions of the instances where it could be caused by a spontaneous mutation. After the diagnosis of a child or an individual with MD, knowing that it is incurable and progressively deteriorating, there are many daunting questions in the minds of the patients and caregivers. They are anxious about the progress of the disease as well as its implications on other family members. In general they may be unaware of the exact transmission and the possibility for the children to inherit the disease. They may find themselves overwhelmed due to the vast knowledge available on internet and may feel confused about what to do next. To answer these doubts in your mind you need to seek a consultation from a genetic counsellor.

Who can be your genetic counsellor?

Ideally a genetic counsellor is a professional trained in genetics like a physician geneticist. However a range of health professionals can provide genetic counselling as follows:

1. Physician with relevant knowledge and experience in genetics
2. Neurologists with relevant knowledge and experience in genetics
3. Pediatrician with relevant knowledge and experience in genetics
4. A professional trained in human genetics

If a genetic counselor is not available, then the pediatrician, neurologist or physician that diagnoses the patient can also provide genetic counselling. In some instances he may refer to an expert or support groups that provide genetic counselling.

What is genetic counselling?

Genetic counselling provides information about the causes of the disease, symptoms, complications, prognosis, management strategies, prevention strategies and patterns in which the disease can be inherited from one generation to the other. It is a key component for prevention of muscular dystrophy.

National society of genetic counsellors defines genetic counselling as the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following:

- Interpretation of family and medical histories to assess the possibility of inheriting the disease and passing it on to future generations, genetic testing, management and prevention of the disease.
- Providing information about the resources and current research.
- Counseling to empower the patients and caregivers and help them make their own decisions regarding marriage, pregnancy and genetic testing of children and/or siblings etc..

Who requires genetic counseling?

Patients and immediate family members of the patients with muscular dystrophy require genetic counseling to understand and better manage the disease. The risk of the disease does not stop at the immediate family it also extends to other close relatives. Thus genetic carrier or diagnostic testing for the relatives at risk may be required.

When will you be advised to undergo genetic counselling?

You may be asked to undergo genetic counselling in variety of situations as explained below:

1. Diagnostic genetic counselling:

You would be advised to undergo a diagnostic genetic counseling if you or your child has exhibited symptoms likely of MD. There will be two parts of the counseling process; however it may not be strictly adhered to.

Pre-test counseling: Before the test the counselor will mainly focus on the causes and genetic inheritance pattern of the disease. Details about how the testing procedure and interpretation of the results will be provided.

Post-test counseling: After the test is performed and the results are available. Based on the findings; further practical steps to be taken will be discussed.

2. Predictive genetic counselling:

You or your child may be asked to undergo the counseling in absence of any symptoms if there is a high risk of the disease. A high risk of the disease would be estimated based on the members of your family diagnosed with the disease or diagnosed to be the carriers of the disease. Pre-test and post-test counseling will be undertaken in the similar manner as described above.

3. Carrier genetic counseling:

If your child or brother or nephew or a close relative has been diagnosed with DMD/ BMD; you may be asked to undergo carrier genetic counseling and testing. Pre-test and post-test counseling will be undertaken in the similar manner as described above. Further you will be examined thoroughly for presence of any symptoms of the disease.

4. Prenatal genetic counseling:

If you have a son or a brother or a close relative who has been diagnosed with the disease and are contemplating to have a child you and your partner would be asked to undergo prenatal genetic counseling and testing. If in the carrier testing you were tested positive and want to conceive a child you and your partner would be asked to undergo prenatal genetic counseling. After the counseling prenatal testing would be undertaken during your pregnancy to detect the risk for the fetus to have the disease.

Genetic counseling can be divided in three parts

1. Providing education
2. Providing emotional counseling
3. Genetic testing

Providing education and emotional counseling

This will be the mainstay of the genetic counselling sessions. Educational and emotional counseling is aimed at providing appropriate information and guidance about the disease and providing support to be able to manage the disease well [2].

What will be discussed in the consultation?

1. Genetic causes of the disease
2. Symptoms of the disease and disease prognosis
3. Treatment options for the disease
4. Practical information of what to do next?
5. Co-ordination and explanation of genetic testing
6. Risks, consequences and limitations of genetic testing
7. Alternatives that could be considered in case genetic testing facilities are unavailable or if you choose not to undergo the testing
8. Identification of the carriers of the abnormal gene
9. Identification of the potential risk to the children of the carrier
10. Making the carries aware of the risks of pregnancy
11. Identification of the disease manifestations in the carriers and further management.
12. Appropriate research studies to pursue
13. Genetic information to promote health
14. Strategies to minimize psychological distress
15. Support groups available
16. How to increase personal control.

Important points for you to keep in mind are that; counsellor should make sure to take an informed consent prior to counselling. There should be absolute anonymity maintained regarding the familial involvement and test results. The counselling should be provided to you in the language you understand the best. Genetic counsellor will act as a guide or an advisory to you. Issues that you discuss during the counselling are a choice and not a compulsion. Genetic counselling could be overwhelming with information to be understood and decisions to be made and hence don't do it in a haste. Make sure to discuss with your counsellor all the doubts you have, repeatedly if you need to do so for a clear understanding. Give yourself adequate time to understand the information given to you and think about all the possible options in front of you. If you are a parent and are taking decisions for your child you may take into consideration their views about the disease. If you are an adult consider to involve your family members for the genetic counselling session.

Inheritance patterns for different muscular dystrophies

Some terms that you should be familiar with before we discuss about the inheritance patterns:

1. **Affected individual:** is the individual who has been diagnosed with the disease.
2. **Carrier:** Carrier is the person who shows the presence of a faulty gene but is not affected by the disease and can transmit the disease (faulty gene) to the children.

X- Linked recessive inheritance patterns

X - Linked inheritance patterns are present in case of Duchenne's muscular dystrophy, Becker's muscular dystrophy and some forms of Emery Dreifuss muscular dystrophy. The gene responsible for DMD and BMD is located on the X-chromosome. Girls have a two X-chromosomes whereas boys have One X chromosome and one Y chromosome. Therefore the faulty gene can be present in both boys and girls. However boys have a higher chance of manifesting the symptoms. The expression of the gene, meaning, if or not presence of the gene will lead to clinical manifestation of the disease can be explained as below. The expression on dystrophin is in an X-linked recessive pattern. This means the gene will express itself only in absence of the normal gene counterpart. In a girl child there are two copies of X chromosome and therefore if on one there is an abnormal gene and on the other there is a normal gene the girl will not suffer from the disease. She may however carry the abnormal gene and therefore her sons may be at the risk of developing this disease. Figures 1-5 simplify the inheritance pattern of DMD and BMD; it also depicts the percentage risk of a child being a carrier or patient.

What are the genetic causes of DMD and BMD?

DMD and BMD are caused by an abnormality in the gene dystrophin at locus Xp21on the X chromosome of human DNA. Genes are the molecular units of DNA that hold the information regarding formation and maintenance of the cells and tissue in human body. This gene is crucial to make the structural protein of the muscles dystrophin. Without dystrophin muscle cells are prone to early degeneration. This leads to

progressive weakness of all the muscles. The rate of degeneration in DMD is much faster than in BMD. The type of abnormality in the dystrophin gene also varies with BMD and DMD. The abnormality in the dystrophin gene is caused by deletion of exonsin majority of the cases of both BMDand DMD. A smaller percentage shows point mutations and a still smaller proportion of patients shows duplication of the exons responsible for the mutation. Deletion, duplication or mutation of the exons therefore occurs in both BMD and DMD. Weather the patient exhibits clinical features of DMD or BMD is currently diagnosed on the basis of reading frame hypothesis. Our DNA is made from smaller molecules called amino acids. These amino acids are sequenced in a particular manner to form different genes. In each gene these form a group of 3 amino acids that are responsible for the correct translation and production of the necessary proteins. In DMD the deletion or duplication or mutation leads to disruption of this pattern of group of 3 amino acids and the resultant protein is non-functional. In BMD the deletion or duplication or mutation is such that it can still maintain the pattern of group of 3 amino acids. The resultant protein therefore has only subnormal function and therefore the rate of degeneration of the muscles is much slower.

Figure 4.1: Inheritance probabilities for unaffected but carrier mother and unaffected father (DMD and BMD)

(In the below figure X = normal X chromosome, X' = faulty X chromosome)

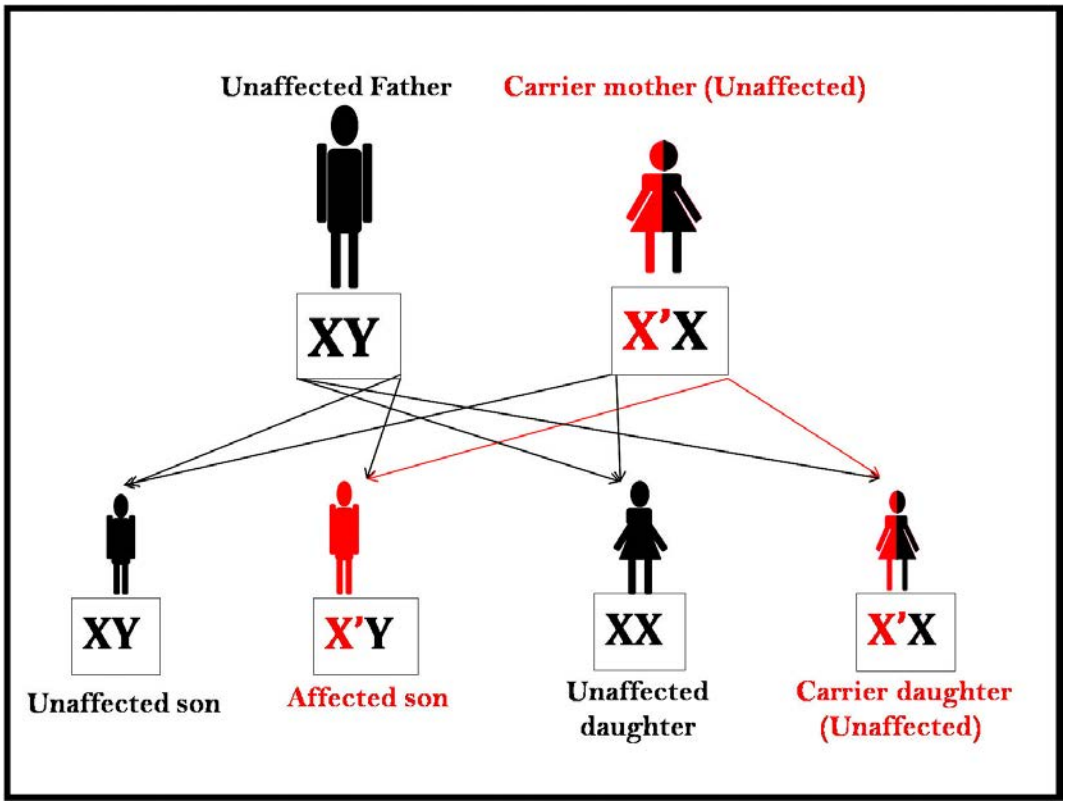


Figure 4.1

Above scenario is the most common clinical observation in DMD and BMD. In the above considered pairing where the mother is a carrier and father is unaffected.

1. Every male child that is born is at 50% risk of being affected with DMD/BMD.
2. Every female child that is born is at 50% risk of being a carrier.
3. Every child that is born is at 50% risk of inheriting the faulty gene.

In such a scenario a genetic counsellor will advise the mother as well the sister of the affected boy to undergo carrier testing and brother who may not be exhibiting any symptoms to undergo the diagnostic genetic testing.

Figure 2: Inheritance probabilities for affected father and unaffected mother (BMD)

(In the below figure X = normal X chromosome, X' = faulty X chromosome)

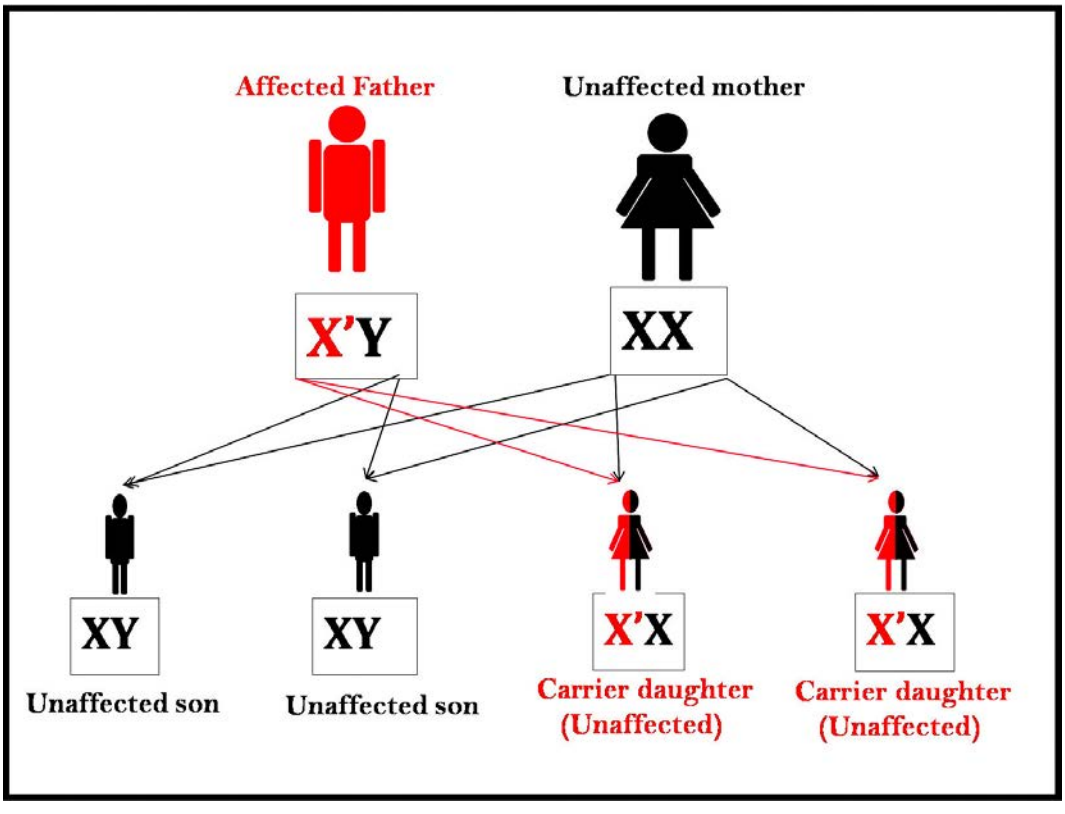


Figure 4.2

Above scenario could be a clinical observation in case of BMD. This scenario may not be applicable for DMD.

In the above considered pairing where the father is affected and mother is unaffected.

1. Every male child that is born is at no risk of being affected with DMD/BMD.

2. Every female child that is born is at a 100% risk of being a carrier.

In such a scenario a genetic counsellor will advise the daughters and sisters of the affected male to undergo carrier testing and brother who may not be exhibiting any symptoms to undergo the diagnostic genetic testing.

Figure 3: Inheritance probabilities for affected father and carrier mother (BMD)
(In the below figure X = normal X chromosome, X' = faulty X chromosome)

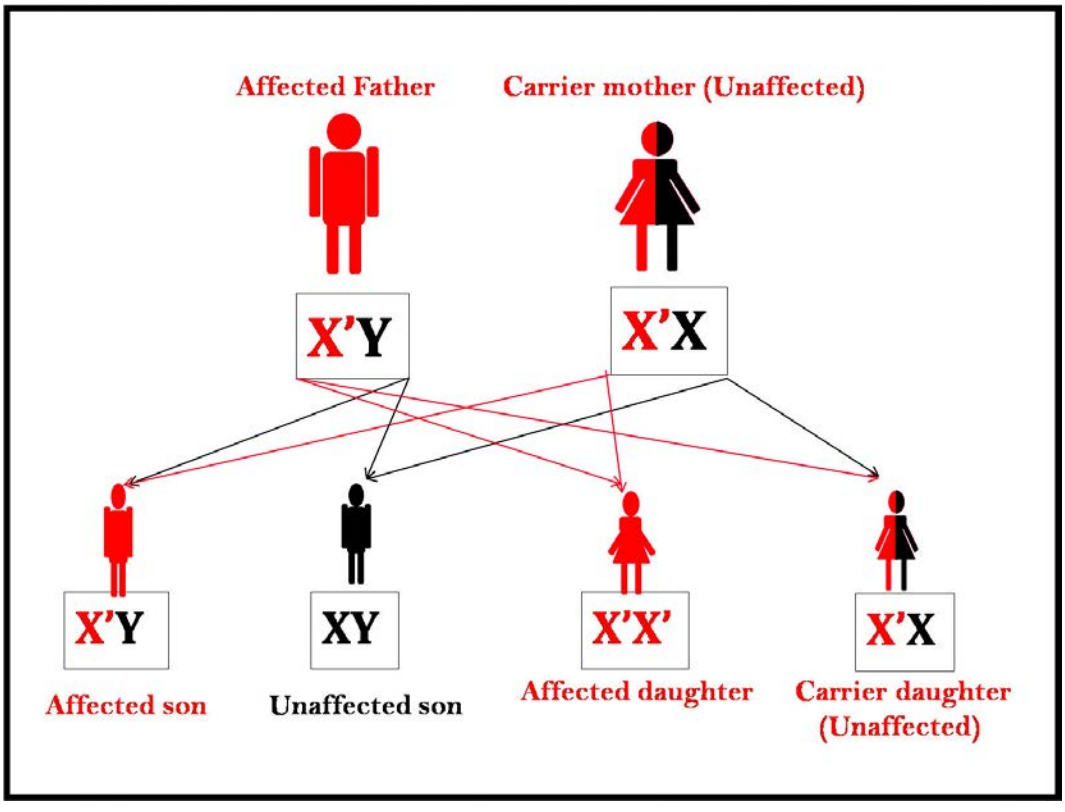


Figure 4.3

This scenario also is only a possibility in case of BMD. In the above considered pairing where the father is affected and mother is unaffected.

1. Every male child that is born is at 50% risk of being affected with the disease.
2. Every female child that is born is at 50% risk of being a carrier or being affected with the disease.

In such a scenario a genetic counselor will advise the daughters and sisters of the affected male to undergo carrier testing as well as diagnostic genetic testing and brother who may not be exhibiting any symptoms to undergo the diagnostic genetic testing.

Autosomal patterns of inheritance

Autosomal patterns of inheritance are independent of the sex chromosomes (chromosomes responsible for the sex of the child). Therefore both male and female children are at an equal risk of having the disease. There are two chromosomes inherited from each parent. The genes on either of these chromosomes are identically placed. For any gene therefore there is a counterpart (allele) on the other chromosomes. Based on this there are two different patterns in autosomal inheritence.

Autosomal recessive: Refers to an inheritance pattern where the faulty gene cannot express itself on its own in presence of a normal gene counterpart from the other chromosome.

Muscular dystrophies that are show autosomal recessive inheritance patterns are

1. Congenital muscular dystrophy
2. Distal muscular dystrophy (some types)
3. Emery-Dreifuss muscular dystrophy (some types)
4. Occulopharyngeal muscular dystorphy
5. Limb girdle muscular dystrophy - Type 2 (A-Q)

Figures 4.4 - 4.6 simplify the inheritance pattern of autosomal recessive muscular dystrophies and depict the percentage risk of a child being a carrier or patient.

Figure 4.4: Inheritance probabilities for one affected parent and the other unaffected parent

(In the below figure C = normal chromosome, C' = faulty chromosome)

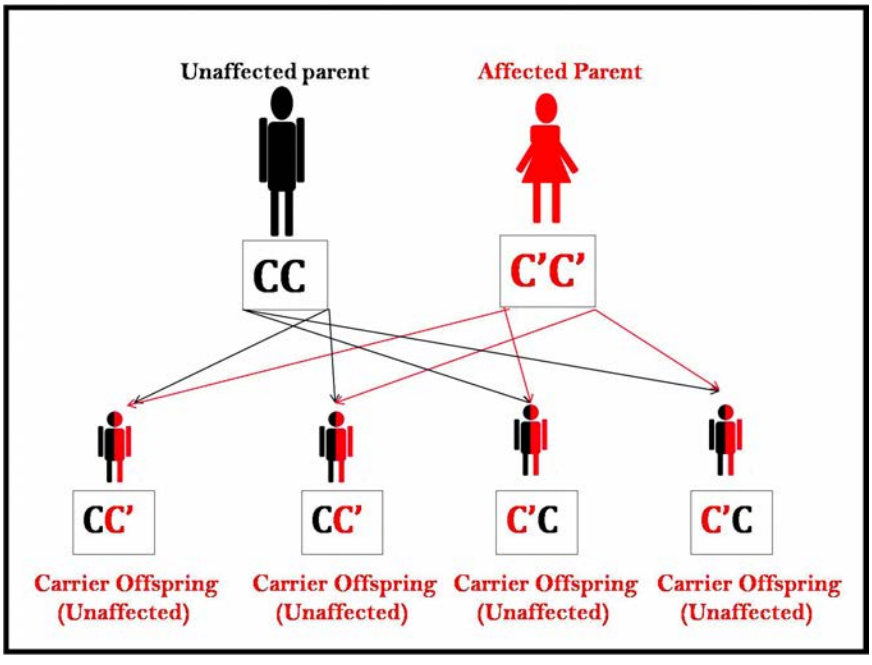


Figure 4.4

In the above considered pairing one parent is affected and the other is unaffected. The outcome and probabilities remain the same whether the affected parent is father or mother as the gene is not located of the sex chromosomes.

In this case

1. None of the children will suffer from the disease.
2. All of the children will carriers of the disease.

In such a scenario a genetic counselor may not advise any further testing.

Figure 4.5: Inheritance probabilities for one affected parent and the other carrier parent

(In the below figure C = normal chromosome, C' = faulty chromosome)

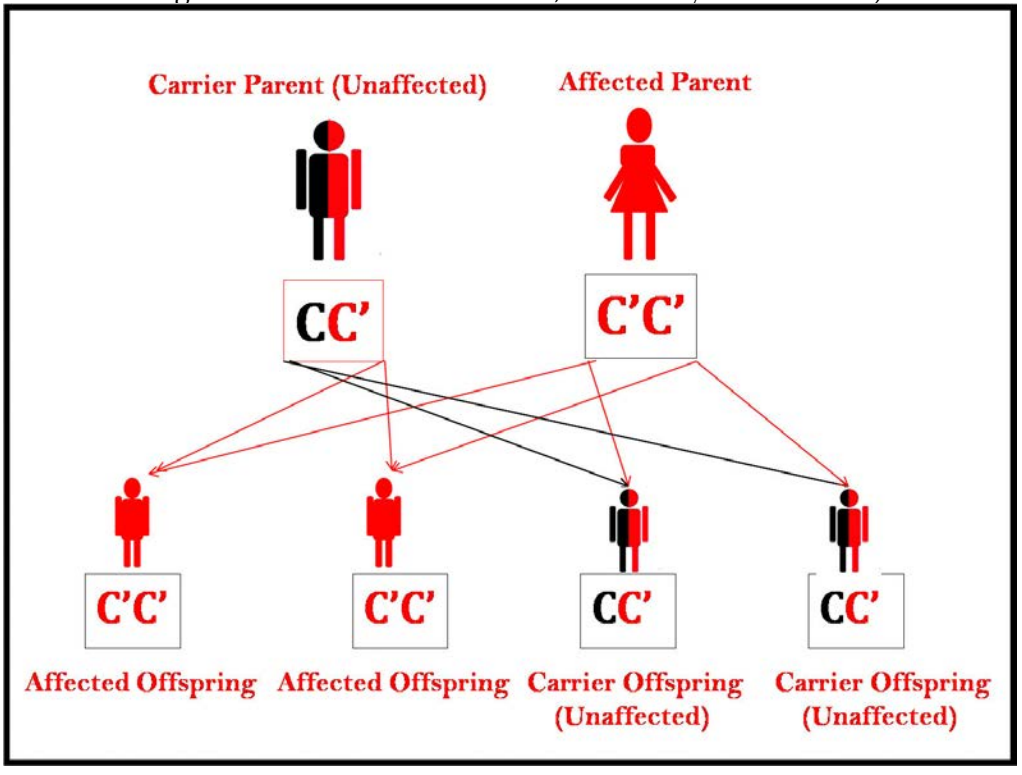


Figure 4.5

In the above considered pairing one parent is affected and the other is a carrier. The outcome and probabilities remain the same whether the affected parent is father or mother as the gene is not located of the sex chromosomes.

In this case

1. 50% of the children born will be affected
2. Remaining 50% will be carriers

In such a scenario a genetic counselor may advise further testing to identify carriers and pre-symptomatic affected children.

Figure 4.6: Inheritance probabilities for both affected parents

(In the below figure C = normal chromosome, C' = faulty chromosome)

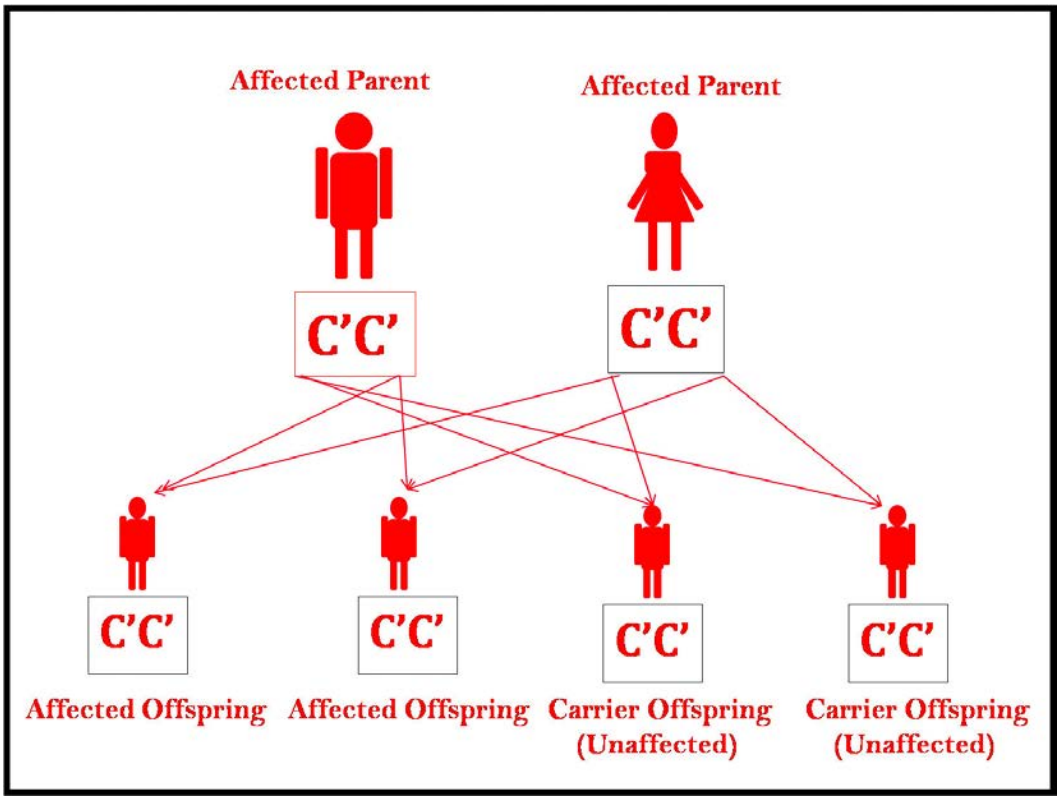


Figure 4.6

This is a very rare possibility where both the parents are affected with the disease. In such a scenario all the children born will also be affected with the disease.

Pre-natal genetic counseling may be advised in such a scenario.

Autosomal dominant: Refers to an inheritance pattern where the faulty gene can express itself on its own in presence of a normal gene counterpart from the other chromosome. Therefore in autosomal dominant inheritance patterns there are no asymptomatic carriers of the disease.

Muscular dystrophies that are show autosomal recessive inheritance patterns are

1. Facio Scapulo Humeral muscular dystrophy (FSHD)
2. Myotonic muscular dystrophy
3. Occulopharyngeal muscular dystrophy
4. Limb girdle muscular dystrophy - Type 1 (A-H)

Figures 7 & 8 simplify the inheritance pattern of autosomal dominant muscular dystrophies and depict the percentage risk of a child being a carrier or patient.

Figure 4.7 : Inheritance probabilities for one affected and one unaffected parent
(In the below figure C = normal chromosome, C' = faulty chromosome)

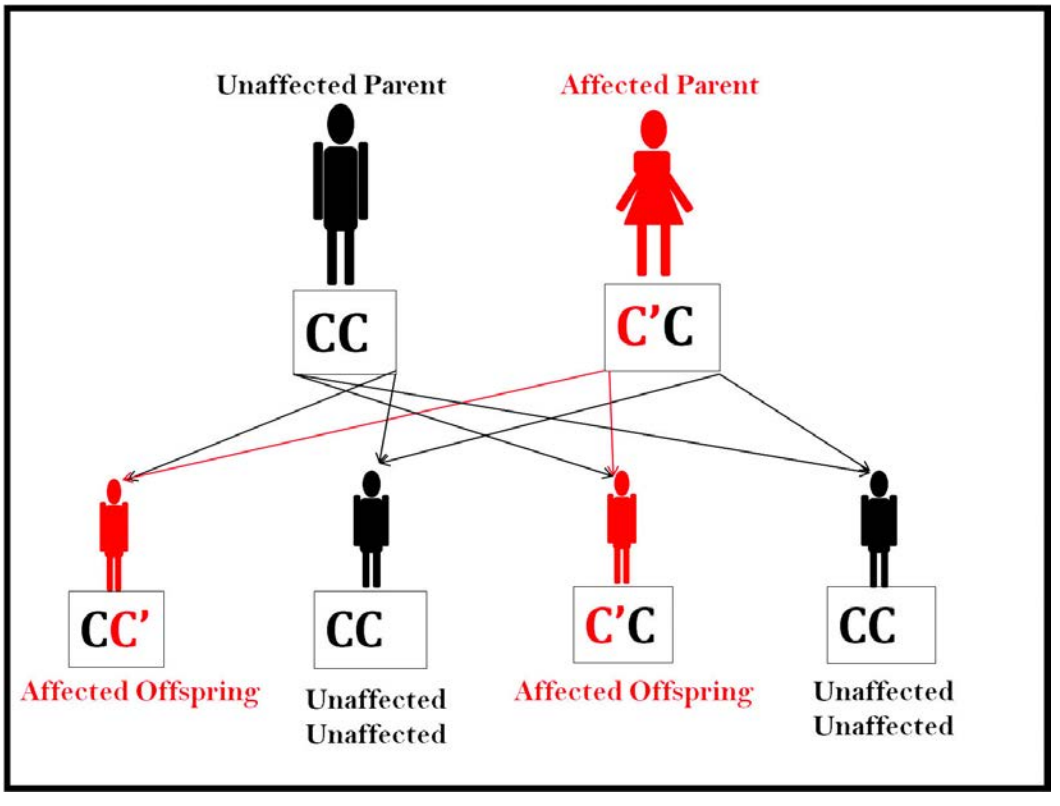


Figure 4.7

In the above scenario one parent is affected but carries only one faulty gene and the other is unaffected. This inheritance pattern too is gender independent and the outcome and probabilities remain the same with affected mother or father.

Children born to these parents are at

1. 50% risk of inheriting the disease
2. 50% chance of not inheriting the disease

Prenatal genetic counseling is very important in such cases. Genetic testing of the children may also be advised.

Figure 4.8: Inheritance probabilities for both parents affected
(In the below figure C = normal chromosome, C' = faulty chromosome)

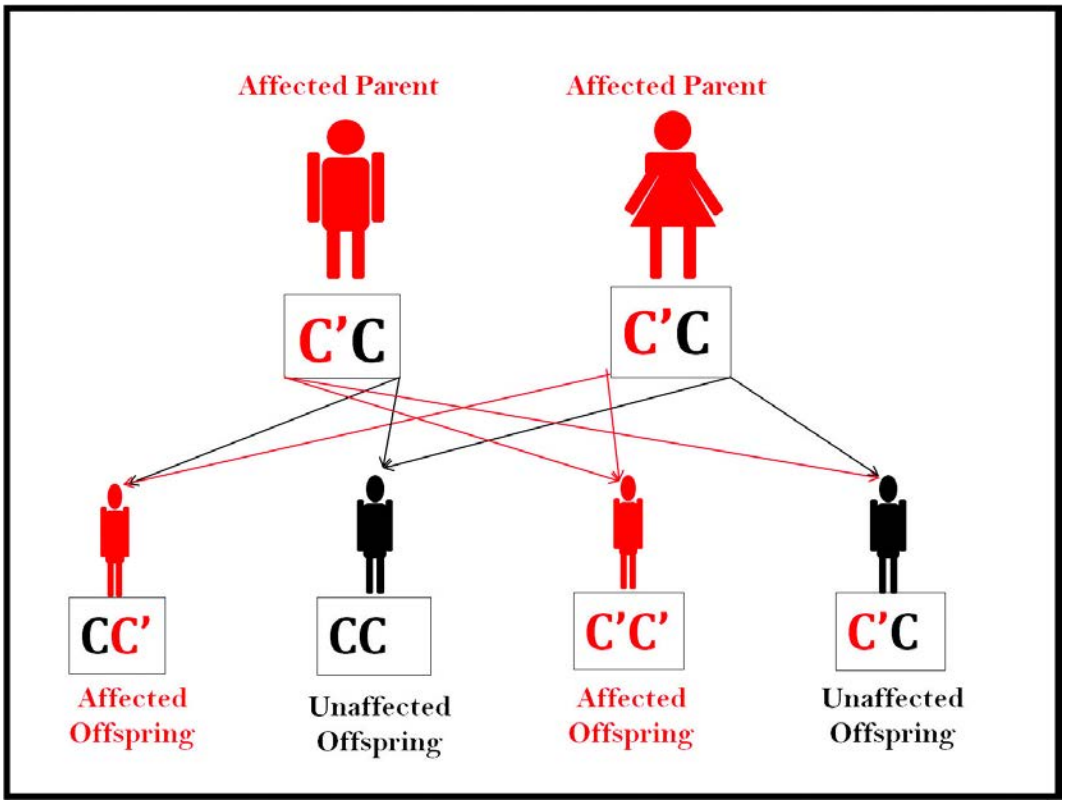


Figure 4.8

In the above scenario both the parents are affected. Being an autosomal dominant pattern, an affected parent may have only one copy of the faulty gene.

In such case

1. There is a 75% risk of the child being affected with the disease
2. However there is a 25% chance of the child being unaffected

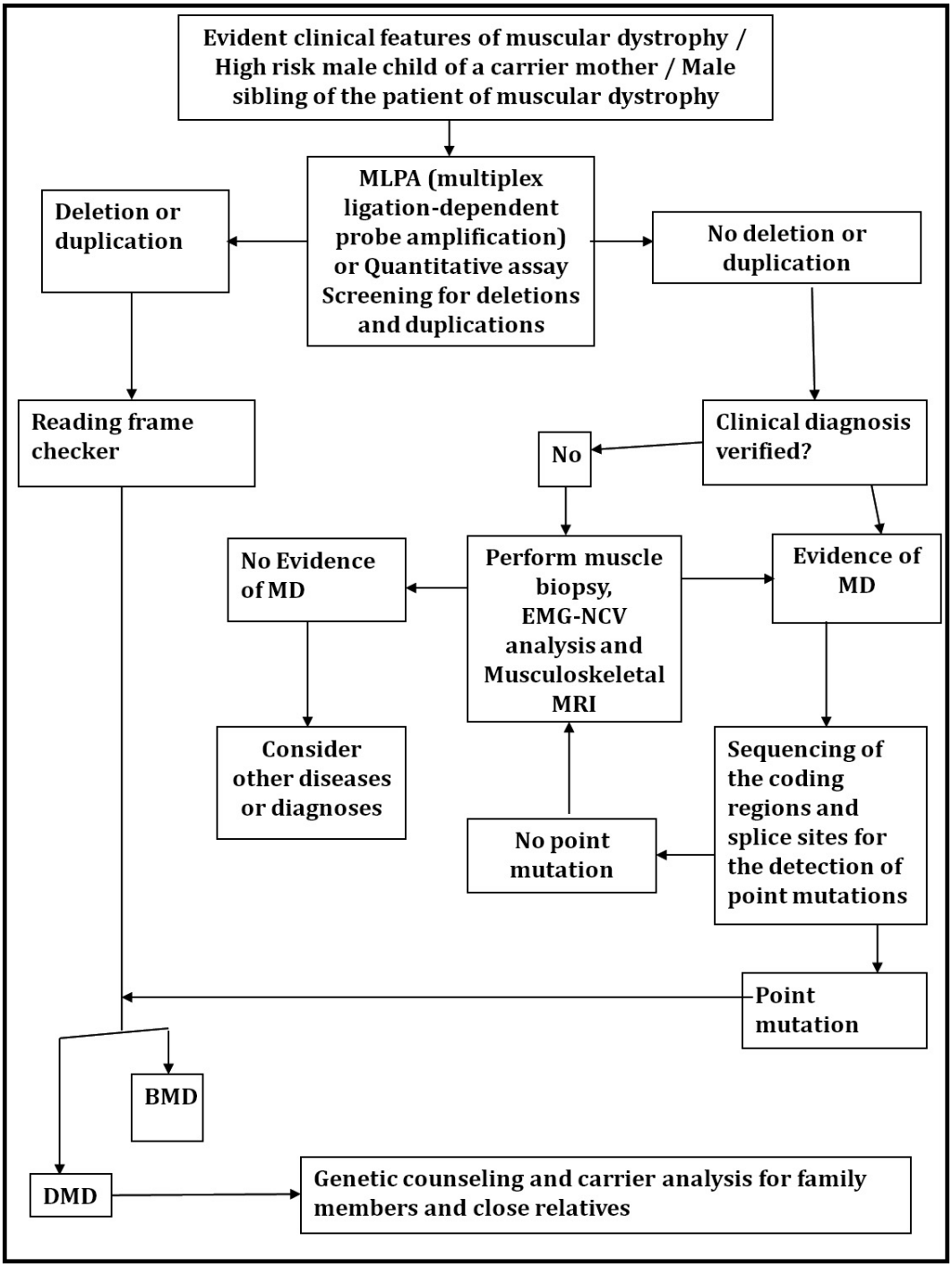
If any one of the parents however have a both the copies of the gene faulty then all the children born to them will also inherit the disease.

Prenatal Genetic counseling is therefore very crucial. The children may be advised to be tested genetically.

Genetic testing for DMD and BMD

Genetic diagnostics for DMD/BMD are generally carried out as explained in Figure 4.9.

Figure 4.9: Molecular diagnosis of DMD/BMD



Diagnostic genetic testing for DMD and BMD

Testing for deletion, duplication and mutation:

This can be performed by multiplex polymerase chain reaction (PCR) assay looks for the deletions in only the exons that are known to be most commonly deleted. It does not give the end points of all the deletions. However with the recent advances 98% of the cases of DMD can be detected using this technique.

When a deletion is not identifiable using the above method, quantitative assay of each exon using various methods is performed. Earlier quantitive multiplex PCR and southern blot hybridization using cDNA probes were used. Most recent development in these techniques is multiplex ligation-dependent probe amplification (MLPA).This is the current method of choice as it is able to identify DMD cases and carriers even when multiplex PCR analysis fails to identify these [10].

To assay the mutations in the gene an array of techniques is used like SSCP, dHPLC, FM-CSCE, PTT, HRM

From the results of these tests if a whole exon deletion or duplication is present then the individual can be diagnosed of muscular dystrophy. Based on if these deletions or duplications affect the translational frame of amino acids distinction between BMD and DMD is confirmed. Severity of the disease and clinical features are dependent on the eons deleted [11].

Carrier analysis by genetic testing of known and unknown familial mutation:

For carrier analysis where the mutation of a family is member is known and has been identified, the DNA sample is used for comparison. Above methods are used to detect the genetic abnormality. These methods are capable of detecting the abnormal gene even with the overshadowing by the normal gene.

When the sample of the member of family with the known mutation is not available a detailed analysis as explained in the 'diagnostic genetic testing' is carried out [12].

It is important to interpret the results of these tests properly. Absence of similar mutation in the mother of a child with known mutation does not rule out the risk for subsequent children. Prenatal testing is highly recommended for such instances.

Once the woman is identified as a carrier the range of diagnostic tests used for an individual suffering from the disease should be carried out to rule out any disease manifestations in the mother [13,14].

Prenatal genetic testing

Prenatal genetic testing is carried out with through amniocentesis or chorionic villi sampling and the same array of tests is run on these samples. If a mother is known carrier and has a child affected with the disease, his samples are used for comparison. Maternal cell contamination needs to be ruled out during this assessment as it may misguide our interpretation.

Using the current techniques abnormality in the mail child can be detected but it

cannot be detected for a female child. Inability to detect any abnormality does not rule out the presence of abnormality.

The report of prenatal genetic testing clearly states the presence or absence of mutation in the fetus.

Conclusion:

Genetic testing is important to identify whether the disease has occurred due to spontaneous anomaly or due family history (familial) of the disease. In case if there is familial origin then the mother and female relatives should be tested and made aware of their carrier status to take informed decision about future pregnancies. Sometimes the carriers also develop weak hearts and other mild symptoms of the disease, genetic testing helps for a prompt treatment in such a scenario. Lastly, eligibility to clinical trials may be dictated by the presence or absence of certain mutations and familial or spontaneous nature of the mutations. Therefore one should be aware of this information.

- Genetic testing confirms the presence of the disease and gives the prognosis.
- Genetic counseling helps you to understand the risk of inheriting muscular dystrophy or transmitting it to your children.
- Carrier testing helps in prenatal diagnosis, prevention and management

  Genetic counseling should be availed at the earliest if you or your close relative has been diagnosed with muscular dystrophy.

5.

Complications

Complications are the difficulties and limitations that arise due to the disease process but are not the actual symptoms of the disease. Most common complications in patients of muscular dystrophy are the complications arising due to muscle weakness and imbalance. This causes skeletal and postural deviations which may be fixed after sometime resulting in compromised function. The muscle weakness also leads to inability to swallow and breathe resulting in various respiratory complications. In addition to these, medications used in muscular dystrophy may also have implications on the health of the patients. Steroids especially are known to cause severe adverse effects and these lead to medical complications due to prolonged use. The complications differ a lot depending upon the type of muscular dystrophy and how advanced is the disease. Some forms of muscular dystrophy will exhibit symptoms sooner than the others.

It is important to understand the possible complications of the disease and how to prevent them in order to prevent rapid progression of the disease. Some of these complications can be prevented if identified and treated on time. Therefore early identification of the complications is of key importance while providing multidisciplinary care to patients with muscular dystrophy. Apart from patients themselves, parents and caregivers are in a position to detect subtle changes at an early stage. Thus it is important for them to be aware of the possible complications and how to identify and prevent these.

Duchenne Muscular Dystrophy

The secondary complications are usually seen in the late ambulatory stage when there is considerable imbalance in the strength of different muscle groups. This imbalance leads to postural deviations causing secondary complications. As the disease progresses, body systems that are not affected by the primary disease pathology also get affected. This is primarily due to inactivity and sluggish contractions of muscles responsible for respiratory function, bowel and bladder movement, heart muscles and muscles in the walls of the blood vessels.

Late ambulatory stage

Tightness of the muscles:

Muscles of calves and hip tend to undergo tightness in this phase, if not stretched appropriately this may lead to permanent tightness or contracture of the muscles. Further tightening of the muscles can be prevented by using night and day splints that prevent abnormal position of the foot. (Figure 5.1)

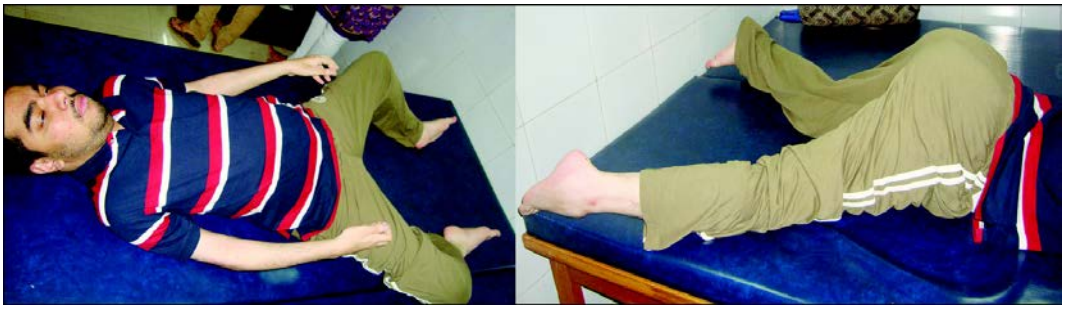


Fig. 5.1 : Contractures of hip, knee and foot joints

Sleep disturbances:

Capacity of the lungs to inhale and exhale reduces due to respiratory muscles weakness. This leads to inability to cough effectively. Muscle weakness may cause episodes of breathlessness while asleep. Such episodes may alternate with episodes of shallow breathing. This leads to reduced oxygen levels in the blood. The child may complain of breathlessness at night or may present with some sleep disturbances. The child may complain of nightmares.

As muscle weakness increases, the person with Muscular dystrophy will not be able to change his position on his own and may find it difficult to sleep.

Respiratory infections:

Due to weakness in the respiratory muscles and inability to cough the chances of respiratory infections is high during this stage. However it may not be as frequent. If your child presents with recurrent respiratory infections, complete respiratory system assessment is warranted.

Excessive sleep during the day (Daytime Somnolence):

Due to sleep disturbances and breathing difficulties while asleep, children may be unusually sleepy during the day. They may be lethargic and reluctant for any physical activities. They may get tired easily (easy fatigability).

Cardiomyopathy:

In this stage the cardiomyopathic changes may be noted in a small percentage of patients. Cardiomyophathy is weakening of heart muscles that leads to inefficient pumping of the blood and thickening of muscles of the heart due to fibrotic changes. The fibrotic changes also bring about conduction deficits that lead to irregular heartbeats.

The children may exhibit following symptoms like easy fatigability, difficulty to perform exercises or physical activity as good as others, difficulty in breathing, tiredness and swelling of ankles and feet.

Left ventricular dysfunction:

The chambers of the heart that pump the blood out to the whole body work inefficiently and therefore not enough blood is pumped out. Blood pools in the heart chambers increasing the back pressure on the lungs. This causes swelling of the lungs seen as breathing difficulties and excessive cough.

Early non-ambulatory stage

Joint contractures:

Increasing joint contractures are observed during this stage due to reduction in muscle extensibility, inability to move the joints through full range and immobility.

Scoliosis:

Scoliosis is abnormal curvature of the spine it could be C - shaped or S - shaped. It usually develops as the child reaches non ambulatory stage and is wheelchair bound. Scoliosis can also be accompanied by unusual slouching (kyphosis) (figure 5.2)or forward arching of the upper back (thoracic lordosis) (Figure 5.3). The abnormal curvature of the spine also affects the respiratory function, feeding, seating and comfort, loss of sitting balance, shortening of trunk and compression of vital organs like heart and the lungs. This stage is also the stage of pubertal growth of these patients, thus progression of scoliosis is faster. Progression of spinal curve is an indication for spinal fusion. Care needs to be taken about the pulmonary and cardiac status before deciding for a spinal fusion surgery.

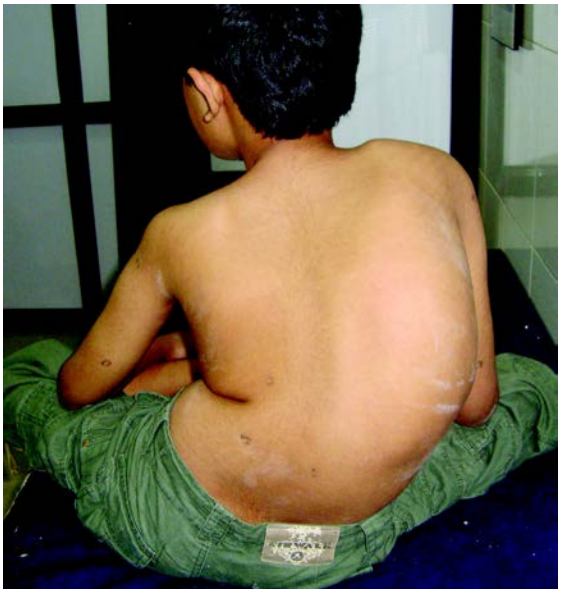


Fig. 5.2 : Kyphosis Secondary to Scoliosis

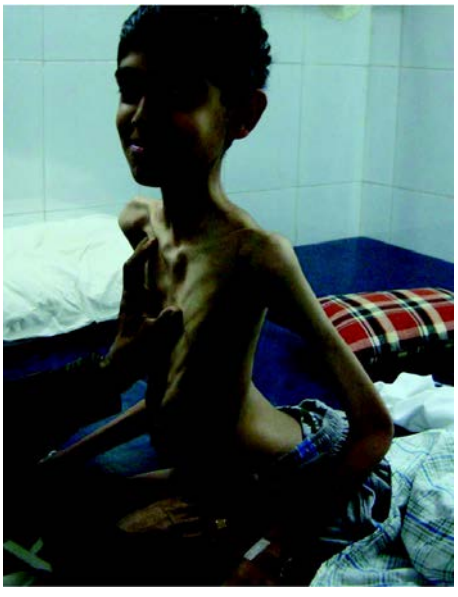


Fig. 5.3 : Thoracic Lordosis

Respiratory infections

Breathing difficulty with minimal activity

Profound cardiomyopathy

Loss of appetite and nutritional deficits

During this phase the activity levels of the child reduce significantly. This leads to sluggish bowel movements. Sluggish bowel movement and reduced levels of oxygen in the blood caused by breathing difficulty during sleep can lead to loss of appetite. Some unresolved psychological problems may also lead to loss of appetite. Because of this the nutritional levels deplete.

Late non-ambulatory stage

Poor appetite and increased frequency of respiratory infection:

As the weakness progresses in patients with DMD, chewing and swallowing becomes difficult as a result of weakness of chewing muscles. As a result, patients may be at a risk of food entering the respiratory tract (food aspiration). In these patients, involvement of muscles of the stomach (gastric muscle) is also seen. Weakness of muscles of the stomach interferes with the mobility of food inside, causing loss of appetite.

Regurgitation of the food and constipation:

The loss of normal movement of the food in stomach and digestive system leads to regurgitation or reflux of food. It may also lead to constipation, which is commonly seen as a problem in patients with DMD.

Severe scoliosis and respiratory restriction:

Due to loss of ambulation, increase in weight is observed due to reduced activity. Excessive weight may have an unfavorable impact on the already ongoing weakness of muscles and increasing the amount of scoliosis. As the scoliosis increases the twisting of the spine and bending on side restricts the movement of the rib cage and adds onto the respiratory effort. As the respiratory muscles undergo weakness at this stage this added restriction further declines respiratory capacity. It is therefore very important to prevent scoliosis using braces and splinting or other supportive devices.

Respiratory complications:

In respiratory complications, there are spiral of events, which decline the respiratory events. It usually begins with loss of lung volumes, followed by progressive weakness of inspiratory and expiratory muscles, chest infections, sleep-disordered breathing and ultimately daytime ventilatory failure. Though this is a general process of ventilatory failure in patients with muscular dystrophy, its evolution varies in different types of dystrophies.

Severe weight loss:

In older patients, or patients who are in the complete non-ambulatory stage for a long time, a progressive weight loss is observed as a result of feeding problems and gastrointestinal problems mentioned above. This weight loss corresponds to the nutritional deficits seen in children with DMD. It may be beneficial to use supplementary feeding methods like

Complications due to long term use of steroids

- **Obesity -** Obesity is a common side effect of long term steroid treatment and increasing physical limitations restricting mobility. It is recommended to timely monitor the weight of the child and to proactively start diet regimens for the whole family not just the child. Encourage physical activity. If the weight cannot be controlled consult the dietitian for diet modification, your physician for steroid dose adjustment and physiotherapist for the activity modification. (Fig. 5.4)
- **Hirsutism -** Hirsutism is excessive hair growth on the body parts. It is of psychological and asthetic concern mainly for the women as the hair growth is similar to that of masculine patterns.

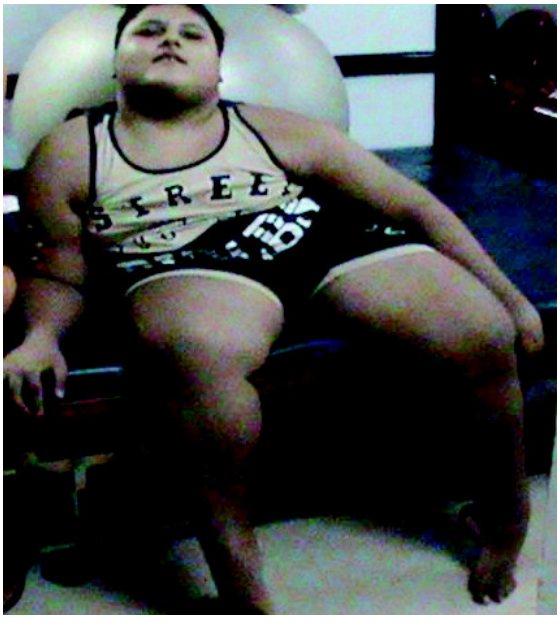


Fig. 5.4 : Obesity

- **Acne, Tinea, warts -** Skin conditions like blackhead, whiteheads, inflammation of sebatious glands (glands observed in skin pores responsible for producing wax like secretions to waterproof and lubricate the skin) and pus in the sebatious glands may aggravate due to steroid intake. Mostly these can be treated however if it is unmanageable consult your physician for dose readjustment.
- **Delayed puberty and stunted skeletal growth -** Delayed puberty can be identified by the growth history of the child and when consuming steroids it is important to keep the record of the increase in height, weight and secondary sexual characteristics of the child. A child with delayed puberty will exhibit stunted height, will look a lot younger than his age and will have a high pitched voice as compared to boys his age. Consult your doctor regularly to ensure early detection and appropriate treatment. It is not always essential to treat delayed puberty but regular monitoring is very important. (Fig. 5.5)

Fig. 5.5 : Short Stature due to stunted growth

- **Bone porosity -** Corticosteroids hinder bone growth and formation through various mechanisms. Some of these mechanisms are
    1. Reducing the amount of calcium absorbed by the body and increasing the amount of calcium excreted in the urine. Calcium is an important mineral for bone growth.
    2. Increased production of cells that cause the bone cells to break down
    3. Reducing the number of bone forming cells

The signs of porous bones are aches and pains in the joints after moderate physical activity and postural deviations. However in most cases brittle bones go unnoticed until a bone is fractured due to stress. To prevent this it is important the child is screened for reduced bone density every six months, take calcium supplements as advised by the physician and engage in regular physical activity.

- **Mood swings** - The child can be irritable and sensitive. Children with long term steroid use are susceptible to manic depression. However usually the mood changes are mild and reversible.
- **Hormonal imbalance** - Corticosteroids suppress certain hormones responsible for bone growth, developing secondary sexual characteristics etc. promoting hormonal imbalance.
- **Immune suppression** - Steroids play a part in the immune feedback system that are responsible for diminishing the immune response. Therefore children may be more susceptible to infections and may frequently fall ill. Contact your physician immediately in case of frequent illness to monitor and readjust the steroid dosage.

- **Hypertension** - One of the effects of steroids is increased blood pressure. It is important to monitor blood pressure of the child to prevent further cardiac complications.
- **Glucose intolerance** - Glucose intolerance could lead to excretion of glucose through urine, excessive thirst and frequent urination. Encourage a dialogue with your child regarding the color, frequency and any irritation while passing urine. Consult your doctor in case any of these symptoms persist for a long time.
- **Gastro-esophageal reflux (Heart-burn)** - Gastro-esophageal reflux is regurgitation of undigested food from stomach to esophagus, causing burning or vomiting sensation.
- **Peptic ulcer** - Stomach pain and sometimes blood in stood are the common signs of peptic ulcers. Peptic ulcers should be treated at earliest, contact your physician immediately if such symptoms are seen.
- **Cataract -** Children may develop cataract due to long term steroid consumption (Figure 5.6). Children may complain of visual impairment due to cataract in which case it will have to be treated immediately. It is advisable to carry out an eye examination every year for early detection and prevention of cataract.

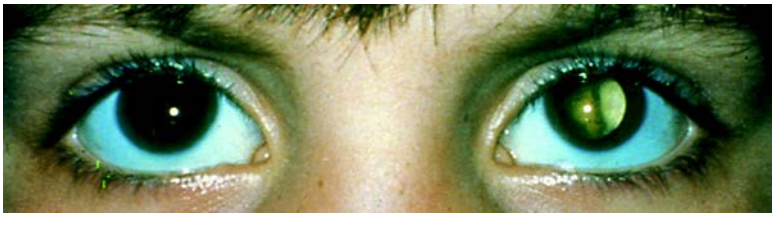


Fig. 5.6 : Cataract

- **Myoglobinuria -** Myoglobinuria is presence of products of muscle cell breakdown in urine. This causes the color of the urine to change to dark brown. Keep a check on the color of the urine after exercise or physical activity. In case of myoglobinuria limit physical activity, drink plenty of water and consult your physician.

Becker's Muscular Dystrophy:

- **Muscle contractures:** The course of disease is more benign in patients with BMD, as compared to DMD. Weakness of muscles sets in by 11-12 years of age and involves mainly the proximal muscles, which is progressive. The continued weakness leads to decline in mobility of the patient, reduction in the extensibility of the muscles and inability to complete full range of motion is seen evidently in the early non ambulatory stage, progressing to late non ambulatory stage. These impairments lead to development of contractures of the joints mainly seen in the shoulder and hip joints (proximal joints) progressing to the elbow, knee, wrist, hand, ankle and foot joints (distal joints).

- **Scoliosis:** Imbalance in the postural muscles leads to alterations in the spinal curvature (Scoliosis).
- **Pressure sores:** Becasue of prolonged sunstained positioning the individuals with MD in terminal stages are also at a great risk of developing pressure sores (Figure 5.7). Pressure sores are the wounds caused by sustained pressure, which reduces the blood supply to that part. Lack of blood supply leads to tissue which is easy to rupture due to mechanical forces exerted during body movements and passive transfers.

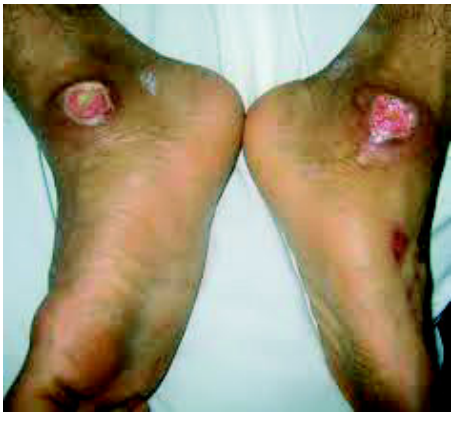


Fig. 5.7 : Pressure sores

- **Gastrointestinal impairment:** As the patients become immobile, complications like constipation, gastroeasophageal reflux and malnutrition become more prevalent.
- **Respiratory inefficiency:** The contractures and immobility of the patients restricts their breathing and reduces in efficiency. Though in childhood, respiratory problems are uncommon; respiratory difficulties and failure is common in the 3rd or 4th decade of life in patients with BMD.
- **Cardiac complications:** Cardiac abnormalities and complications arise earlier and are more frequent in BMD. Cardiac involvement begins by the age of 20 in patients with BMD. In a study done on patients with BMD, 76% of patients showed abnormal Electrocardiogram (ECG), and the function of the left side of the heart was affected. Common cardiac complications seen are impaired function of the left side chambers of the heart, inability to pump out blood effectively, irregularities in the heart beats, disproportionate increase in the heart beats on moderate exertion and easy fatigability. Even with the cardiac complications seen in patients with BMD in later stages, the quality of life of these patients is better as a result of pharmacotherapy and cardiac transplants.

Congenital muscular dystrophy:

Congenital muscular dystrophy is associated with early onset muscle weakness, with accompanying features of flabby muscles (hypotonia), rigidity of muscles since birth leading to deformities in two or more joints simultaneously (arthrogryposis) and

progressive tightness in the muscles to compensate for muscle weakness causing joint deformities (contractures).

- Spinal deformities like kyphosis and scoliosis: Forward arching (kyphosis) of the thoracic spine giving a hunched back appearance. This is caused due to muscle weakness. This compromises the breathing pattern with respect to depth and rate of breathing. This vicious cycle of thoracic kyphosis and irregular breathing compromises the respiratory function in the long run.
- Ventilaroty failure: The studies in this field demonstrate that children with CMD need external support for breathing by early teenage period mainly due to weakness of the main muscle of inspiration, diaphragm.
- Cognitive impairment: In congenital muscular dystrophy, several forms are identified, with variable prognosis. Some are with and others are without significant mental retardation, which complicates the course of their disease.
- Feeding and swallowing problems: Weakness of the muscles leads to difficulty in swallowing and chewing food, compromising the nutrition and food intake of the individual.
- Frequent chest infection: As symptoms of CMD progress slowly and do not show cardiac or bulbar involvement, prognosis after giving ventilatory support is seen to be relatively good. Although with long term ventilatory support respiratory system is susceptible to frequent chest infections.

Limb Girdle Muscular Dystrophy:

As there is a vast variability in the types of LGMD, the cardio respiratory complications also differ among different types of LGMD and between individual patients. Overall, these set of patients show reduced capacity to exhale air out of their lungs, as the disease progresses. Development of contractures in the upper limbs, mainly in the shoulder girdle causes restriction and reduced mobility of the ribcage, affecting the breathing pattern. The respiratory muscle involvement is late in the course of their disease.

Facio-Scapulo-Humeral Dystrophy:

In patients with FSHD, involvement of respiratory functions leading to deterioration or failure in ventilation is unusual and occurs occasionally. The heart is not implicated in most cases, though arrhythmias and conduction defects have been described. Mental impairment is not a feature, but retinal vascular disease and hearing loss can arise.

Myotonic muscular dystrophy:

In myotonic muscular dystrophy, the median age of onset of symptoms is usually 20 to 25 years. Respiratory involvement is usually seen in the middle age. There is progressive restriction of the breathing muscles, causing difficulty in expansion of lungs and labored breathing. Manifestations of respiratory problems are sometimes variable. Some patients may develop paralysis of diaphragm, sleep disturbances, central apneas or hypoventilation.

Emery-dreifuss muscular dystrophy:

In these set of patients, the weakness of muscles is primarily seen in the shoulder and chest region, along with stiffness contractures of upper limb and slouching of spine in the chest region. There are associated cardiac complications seen in these patients. Cardiac complications generally occur before the respiratory problems, with the earliest signs of first degree heart block, which is inability of the nerve impulses to pass from the atria to ventricles of the heart affecting the contraction of the heart muscle. Following the heart block, irregular heart rate is observed sometimes leading to atrial paralysis. Respiratory failure is common at this point, thus giving rise to the need of ventilating the patient.

Oculopharyngeal muscular dystrophy (OPMD):

The patients with OPMD become symptomatic in the late adulthood with cardinal symptoms of difficulty in swallowing and drooping of eyelids. These features are slow progressive in nature. Ptosis can be bilateral and is often severe. Vision is not affected in these patients, but visual field is restricted. Due to weakness of muscles of throat (pharynx), pooling of saliva/secretions is seen, with difficulty in speaking. Cessation of breathing is observed during sleep. Involvement of heart and respiratory functions is not seen in these set of patients. The disease is progressive, with death occurring eventually as a result of starvation or aspiration pneumonia, which happens as a result of food particles entering in the wind pipe.

DESIDERATA

Go placidly, amid the noise and the haste and remember what peace there may be in silence.

As far as possible without surrender, be on good terms with all persons. Speak your truth quietly and clearly and listen to others, even the dull and ignorant, they have their story. Avoid loud and aggressive persons; they are vexatious to the spirit. If you compare yourself to others you may become vain and bitter, for always there will be greater and lesser persons than yourself.

Enjoy your achievements as well as your plans. Keep interested in your career, however humble it is a real possession in the changing fortunes of time. Exercise caution in your business affairs, for the world is full of trickery. But let this not blind you to what virtue there is; many persons strive for high ideals, and everywhere, life is full of heroism.

Be yourself, especially do not feign affection. Neither be cynical about love; for in the face of all aridity and disenchantment, it is as perennial as the grass. Take kindly the counsel of the years, gracefully surrendering the things of youth.

Nurture the strength of spirit to shield you in sudden misfortune. But do not distress yourself with imaginings. Many fears are born of fatigue and loneliness.

Beyond a wholesome discipline, be gentle with yourself. You are a child of the universe, no less than the trees and the stars. You have a right to be here. And, whether or not it is clear to you, no doubt the universe is unfolding as it should.

Therefore be at peace with God, whatever you conceive him to be. And whatever your labors and aspirations in the noisy confusion of life, keep peace with your soul.

With all its shams, drudgery and broken dreams, it is still a beautiful world.

Be cheerful. Strive to be happy!

– Max Ehrmann

SECTION - II

Multidisciplinary Management of Muscular Dystrophy

6.

Medical Management

Muscular Dystrophy (MD) has been identified as a disease for over a century, yet there are no medications which provide the answer for a cure. Although its genetic basis, pathogenesis and etiology have been elucidated since decades, due to its debilitating nature we have been unable to provide a definitive treatment. MD being a progressive disorder, available treatment modalities are aimed at controlling the deterioration. Several attempts in the form of medications and rehabilitation have been made but have failed to halt the progression of the disease. Duchenne was the first clinician who attempted faradic stimulation for MD in the 19th century and today in the 21st century; we are no closer to finding an answer. Ongoing research therapies like cell and gene therapies are a ray of hope for the patients of MD and their families. In the future, our hope is that a wide range of drugs will be available for the treatment of MD.

Treatment

Treatment modalities are aimed to:

1) Completely halt or slow down the disease progression
2) Lengthen the period of independent walking
3) Symptomatic improvements
4) Functional improvements to ease activities of daily living
5) Prevent complications of contractures and deformities
6) Preserve cardio-respiratory functions

Duchenne Muscular Dystrophy (DMD) is the most devastating form of MD. In the first five years of life, boys with DMD present with abnormal gait, inability to run and difficulty in rising from the floor. The profound muscle weakness and contractures of the tendo Achilles and iliotibial bands leads to a loss of independent walking at a mean age of 10 years (range 7 to 13 years). Scoliosis develops in over 90% of boys when they become wheelchair bound. Cardiomyopathy develops in the second decade of life. The late teen years are marked by progression of respiratory muscle weakness,

nocturnal hypoventilation, respiratory failure and death in early twenties. This steep down slope of disease progression is the biggest challenge for treatment in MD.

The available medications for MD are described below:

1) Corticosteroids:

A variety of medications have been developed and tried, nevertheless glucocorticoids (steroids) are still the "gold standard" for treatment. Corticosteroids are the hormones produced by the adrenal cortex. The adrenal cortex is located along the perimeter of the adrenal glands (endocrine glands situated at the top of the kidneys). The use of steroids is not very popular in India, though short term usage has found its place in MD treatment regimens. In other countries like USA, Canada, Australia, etc. steroids have become an integral part of the treatment regime for MD. There are two main types of corticosteroids i.e. glucocorticoids (cortisol) and mineralocorticoids (aldosterone). The steroids usually prescribed for muscular dystrophy are synthetic glucocorticoids like prednisone, prednisolone and deflazacort.

Glucocorticoids and their mechanism

Glucocorticoids exert beneficial effects in MD by inhibition of muscle proteolysis, stimulation of myoblast proliferation, stabilization of muscle fiber membranes, increase in myogenic repair, reduction of calcium concentrations, anti-inflammatory and immunosuppressive effect. This results in decrease of muscle damage and maintenance of muscle strength for a longer time. There are many published trials with prednisone, prednisolone and deflazacort showing stabilization of strength for a period of 2-3 years. To record the effects of intervention, the studies used outcome measures such as prolongation of time to loss of walking and muscle strength (average muscle score and ability to lift weights). Functional benefits were measured by time taken to rise from the floor (Gowers' time), nine-metre walking time, four-stairs climbing time, leg function grade (Brooke scale), pulmonary function test (forced vital capacity), scoliosis angle and Quality of life (QoL). The clinical studies with steroids have shown improvements in all these outcome measures. However, it is important to note that none of the studies reported any non-ambulant (wheelchair bound) patient regaining the ability to walk on treatment with prednisone.

Initiating Glucocorticoid Therapy

No generally accepted guidelines exist in the literature about the best time to initiate glucocorticoid therapy in an individual with MD. The initiation of the therapy should be an individual decision based on the functional state, age and pre-existing risk factors for side effects. Recognition of the three phases of motor function in DMD (making progress, plateau, and decline) helps the clinician to make this decision. In all cases, the recommended national immunization schedule should be complete and varicella immunity should be established before steroids are started. Initiation of glucocorticoid treatment is not recommended for a child who is still gaining motor skills, especially when he is under 2 years of age. The plateau phase, which might last only a few months, can be identified when there is no longer progress in motor

skills, but prior to decline, as determined by history and timed testing. A child who takes longer in timed testing, loses a skill (such as climbing stairs), shows less endurance, or has more falls, is in a decline phase. Once the plateau phase has been clearly identified, usually at age 4-8 years, the clinician should propose initiation of glucocorticoids unless there are substantial reasons (such as major pre-existing risk factors for side effects) to wait until the decline phase. Starting steroids when in the full decline phase or when ambulation is more marginal is still recommended, but might be of limited benefit. Long-term use of glucocorticoids requires significant commitment on the part of the family. Essential issues for discussions should include potential side effects, the obligation to closely monitor and manage any adverse issues that might arise, and the requirement to have the child followed closely by their primary care physician and specialty health care team.

Prednisolone/Prednisone:

Prednisolone, a derivative of cortisol is the most commonly used steroid. This steroid has a beneficial effect on muscle strength in boys with DMD and is offered for treatment especially in the ambulatory phase. Prednisone is the inactive precursor form of prednisolone. It is converted into active prednisolone in the liver. Recommended dose for starting prednisone is 0.75mg/kg/day i.e. in a child who weighs 20 kg, the dosage would be 15mg in a day.Prednisolone is available in the form of tablets or syrups. Wysolone (Wyeth) and Deltacortil (Pfizer) are the most common brands of prednisolone found in the market. These are available in strength of 5mg, 10mg and 20mg.

- Ambulatory phase: For a person up to 40 kg, dosage increases with age. Maximum dose of prednisolone is approximately 30mg/day. In ambulatory patients, the dose of prednisolone is commonly increased as the child grows, provided side effects are manageable and tolerable until he reaches approximately 40 kg in weight, with a prednisone cap of approximately 30-40 mg.
- Non ambulatory: For persons usually above 40kgs, long term steroid therapy is maintained. The prednisolone dose is often allowed to come down to 0.3 to 0.6 mg/kg/day. Non-ambulatory teenagers maintained on chronic glucocorticoid therapy are usually above 40 kg bodyweight and the dose per kilogram is often allowed to drift down to the 0·3-0·6 mg/kg daily range for prednisone.

Deflazacort:

Deflazacort, discovered in 1969, is an alternative steroid used for treating DMD. It is a synthetic derivative of prednisolone with similar anti-inflammatory and immunosuppressive effects, but with less severity of side effects. It is administered orally and is rapidly converted to its pharmacologically active form called 21-desacetyl deflazacort. The starting dosage generally prescribed for deflazacort is 0.9 mg/kg/day i.e. in a child of 20kg; the dosage to start with would be 18mg/day (in 2-3 divided doses). In the ambulatory phase, maximum advised dose of deflazacort is 36 mg/day. In India, it is available as Asteride (Dr.Reddys'), Defnalone (Lupin), Cortimax (Zuventus), Deflazen (Torrent), Nestacort (Cipla). They are available in strength of

6mg, 24mg tablets (also available in syrup formulations). Deflazacort is usually considered as the first line of treatment in case of pre-existing weight and/or behavioral issues.

Steroid Regimes

Various steroid regimes developed for treatment of DMD are:

1) Dubowitz regime: Prednisolone 0.75 mg/kg/day on a 10 days on treatment and 10 days off treatment regime OR Prednisolone 0.75 mg/kg/day for the first 10 days of every calendar month (cycles of 10 days on prednisolone treatment, 20 days off treatment)
2) Nigro regime: Deflazacort 0.6 mg/kg/day 20 days on, 10 days off
3) Alternate day prednisone therapy: Prednisolone 0.75 mg/kg on alternate days (+ vitamin D 600 - 1200 units/day)
4) Daily prednisone therapy: Prednisone 0.75 mg/kg/day for two years
5) Long-term daily prednisone therapy: Prednisone 0.3-0.75 mg/kg/day
6) Daily dose deflazacort: Deflazacort 0.9 mg/kg/day, for two years

Side Effects of Steroids

Higher dosages and longer duration of therapy are associated with more side effects as shown in the box below. All three steroids i.e. prednisone, prednisolone and deflazacort have similar benefits on strength and functional activities. They also have a similar side effect profile. The intermittent regimes have a better safety profile. Closed monitoring for side effects is essential and preventive measures like supplementation of calcium and Vitamin D, regular bone mineral density measurement, routine blood pressure, weight, eye check up and blood tests (electrolytes and sugar) should be taken. Caution is required while giving physical therapy as it may easily fracture the fragile bone.

Due to the side-effect profile, the use of steroids is surrounded with lot of controversies. In the western world it is more widely practiced, whereas in India steroids are still prescribed very conservatively in MD. The weight gain and fractures pose great difficulties in transfer and mobility of patients, especially in view of manual wheelchair of majority patients.

2) Antimyotonic drugs

Antimyotonic drugs raise the activation threshold of muscle membranes and improve muscle relaxation in myotonic dystrophy. Various groups of medications used for antimyotonic effect are antiarrhythmic lidocaine analogs (mexiletine and tocainide), sodium channel blockers (phenytoin, procainamide, carbamazepine), antidepressants (amitriptyline, clomipramine, imipramine), calcium channel blockers, benzodiazepines, prednisone, dehydroepiandrosterone, taurine, acetazolamide, and quinine. Phenytoin has good results but is associated with undesirable side effects such as hirsutism, gingival hypertrophy, and blood dyscrasias. Tocainide is associated with bone marrow

suppression therefore Mexiletine is preferred. Mexiletine at dosages of 150 - 200 mg three times daily is effective and well-tolerated.

3) Vitamins

- Coenzyme Q10 (CoQ10) has an effective antioxidant property which helps reduce the damage caused by excessive oxidative radicals and calcium overload in dystrophic muscles. In clinical studies it has been shown that a combination of prednisone and CoQ10 results in increased muscular strength and cardiac function. It has been recommended that the patients with muscular dystrophy may be treated with co-enzyme Q10 indefinitely.
- Omega 3 fatty acids are essential fatty acids (ALA-alpha-linolenic acid, DHA-docosahexaenoic acid, EPA- eicosapentaenoic acid) which are abundant in fish, fish oil and flaxseed. Omega-3s have an anti inflammatory property (by reducing TNF-a) which plays a protective role in muscle degeneration. Research strongly supports cardioprotective effect of omega-3. Since, cardiomyopathy occurs in many muscular dystrophy patients, omega-3 supplements are recommended. It may cause blood thinning and bleeding especially in people on anticoagulants.
- Vitamin E is an antioxidant and exerts an anti- inflammatory action. Experimental studies have revealed that myocytes exposed to an oxidant challenge , show enhanced repair when supplemented with vitamin E. Thus, it helps in maintenance of skeletal muscle homeostasis. The clinical study did not show any practically usable increase of muscle strength during the year of treatment with vitamin E, yet its protective role cannot be underestimated.

4) Others drugs

- Creatine: Research shows high quality evidence from randomized controlled trials that short-term creatine treatment increases muscle strength in muscular dystrophy patients. There is also evidence that creatine improves functional performance in muscular dystrophy. It is well tolerated and supplementation with (0.075 - 0.1 g/kg/day) has shown greater strength (~9%) and fat-free mass (~0.63 kg). One has to remember that due to creatine transport issues it cannot be used in myotonic dystrophy patients.
- Methylphenidate: Myotonic Dystrophy patients frequently complain of excessive daytime sleepiness. Many medications have been tried in vain. Recently, 20-mg methylphenidate (psycho stimulant) has given relief to these patients by reducing day time sleepiness.
- Albuterol: A study illustrated that one of the options to decrease fat mass, increase lean body mass and improve functional measures could be short-term treatment with extended release of albuterol.
- Cardiorespiratory drugs: With progression of the disease, cardiorespiratory function is compromised and ultimately becomes the cause of death. Therefore, recent focus has been to preserve this function by various drugs.[Refer to cardiorespiratory management for details]

Conclusion

Muscular dystrophy is still a devastating disease with no definite cure. We need to put a brake on degradation of muscle and accelerate their synthesis to control the disease. Steroids, though debatable have shown benefits. One should remember the side effects and patients are encouraged to do routine monitoring tests and take preventive measures. The various side-effects e.g. steroid induced osteoporosis to avoid complications should be taken into during physical therapy. Vitamin supplementation is crucial to maintain homeostasis. Cell therapy has also made attempts to control the progression of the disease. But, since the root cause of muscular dystrophy is a genetic defect; correction of gene seems to be a straight forward answer. A lot of research of gene therapy has brought the dream of cure within reach. Till gene therapy comes into practice or cure becomes a reality, we must attempt to control the disease by available medications. A fine act of balancing benefits versus adverse effects of medication may help to provide the patient with a better quality of life.

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7.

Surgical Management

Orthopedic Surgical Management

The primary goal is to prevent development of contractures/deformities and maintain walking for as long as possible. A regular program of physiotherapy and use of orthotics (calipers and splints) prevent joint contractures/deformities which can help in ambulation. Once muscle contracture develops and walking becomes increasingly difficult, soft tissue surgery is suggested to maintain the limb alignment and joint position. Surgery improves the walking balance & prolongs the ability of the child to walk. Surgeries recommended for DMD, based on stage of the patient:

1. Before contracture begins (Early-Extensive ambulatory approach): Release/ opening up of muscles of the hip, thigh and ankle.
2. When difficulty in walking starts due to tightness of muscles: Ankle and knee release. This is called Moderate ambulatory approach.
3. Correction of toe walking (equinus gait) - Minimum Ambulatory approach
4. When the child ceases to walk: Aim of surgery is to re-establish walking. This is Rehabilitative approach.
5. The Palliative approach is the one in which the child is wheel-chair bound and surgery is only done for relief of pain, comfort, ease of nursing care & for shoe wear.

Different experts have different opinions about the timing of the surgery. But a general rule/advice is to perform the surgery within the window period of 3 - 6 months after the child stops walking, to help the child walk again. Early surgery at the onset of contractures can prolong ambulation/walking by 2-3 years more than patients that didn't undergo surgery. Delayed operations after the child has stopped walking for more than a year will not establish ambulation. Also, obesity, osteoporosis and poor cardiovascular status are risk factors for surgery.

Ankle and Knee Surgery:

Ankle surgery comprises of percutaneous heel cord tenotomy, "Z" lengthening, and

recession or transfer of tibialis posterior to correct dynamic varus. (Figure 7.1 and 7.2) Knee surgery consists of hamstring lengthening, or tenotomy. (Figure 7.3 and 7.4) Soft tissue surgery is required when knee deformity exceeds 20 degrees of flexion.

Hamstring lengthening and long leg bracing will be enough to correct this degree of deformity. Rarely a supracondylar osteotomy with rigid fixation is required. Hip flexion release involves recession of the anterior hip muscles including the sartorius,rectus and tensor fasciae latae. Post-operative rehabilitation should be aggressive. Weight bearing should start on the first post-operative day, gradually progressing to assisted walking as soon as possible. Any bed rest or immobilization enhances the muscle weakness and thus casting should be avoided as far as possible. Immediate fitting of orthosis /calipers/splints helps in early ambulation/walking, thus preserving muscle strength.

Percutaneous release of hamstrings and calf muscles

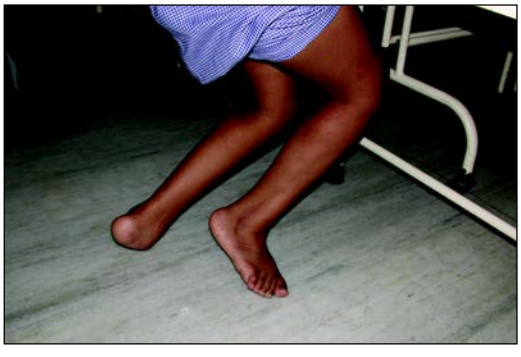

Fig 7.1: Before Surgery Knee and foot deformity

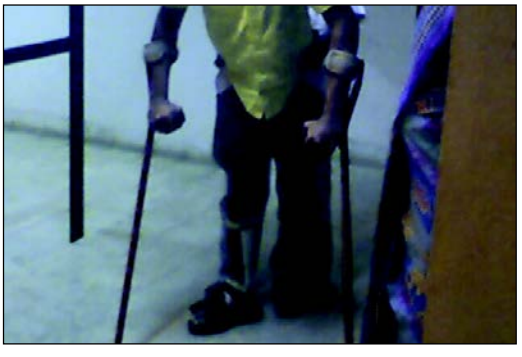

Fig 7.2: After Surgery deformity correction

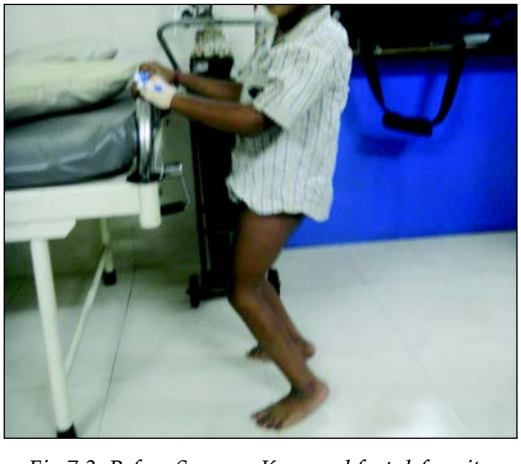

Fig 7.3: Before Surgery Knee and foot deformity

Fig 7.4: After Surgery deformity correction

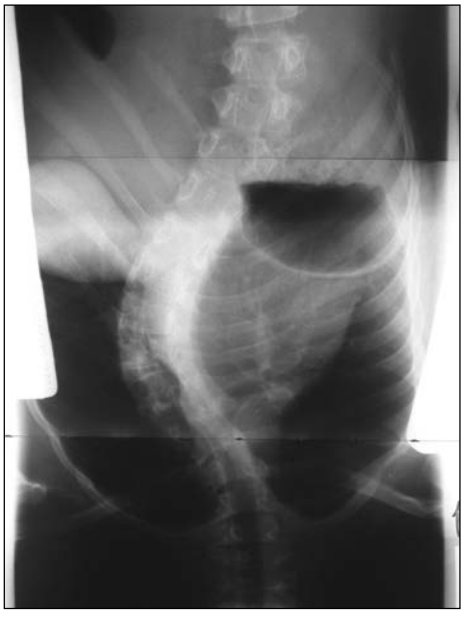

Fig 7.5: Before Surgery Scoliotic deformity

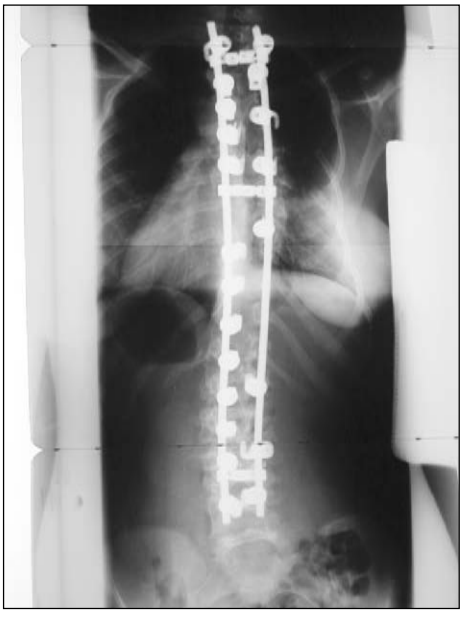

Fig 7.6: After surgery deformity correction

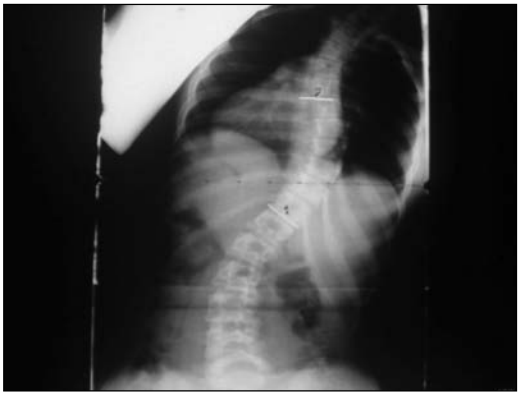

Fig 7.7: Before surgery scoliotic deformity

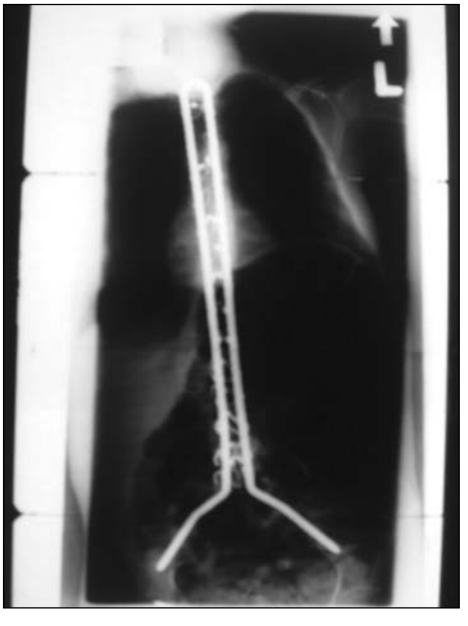

Fig 7.8: After surgery deformity correction

Spinal Surgery: *(Fig 7.5, 7.6, 7.7, 7.8)*

Almost all children with DMD will develop scoliosis once they are non-ambulatory.Thus preservation of walking ability is paramount. Spinal screening for scoliosis is mandatory for all children with DMD. Spinal deformity is common in teenaged boys with Duchenne muscular dystrophy.Approximately 90% of boys with

DMD will develop severe scoliosis. This, many a times, cannot be controlled by nonsurgical means such as bracing or adaptive seating.Surgical stabilization/operation for scoliosis is usually recommended when the curve is more than 20 degrees before pulmonary function worsens. A decreased chest function goes against the possibility of operation.The typical curve pattern is a long sweeping thoraco-lumbar scoliosis (curve of the lower back), flexible and associated with pelvic obliquity (oblique angle of the hip). Mild curves < 10 degrees should be watched closely and as the cobb angle exceeds 20-30 degrees, surgery can be considered. Forced vital capacity/chest and lung capacity decreases by 4`% each year and by 4 % for each 10 degrees of curve. Thus progression of scoliosis and deterioration of pulmonary function go side by side making delayed surgery precarious and unsafe. Specially designed screws and rods are use to fix the spine. This provides good stability allowing better correction of the spinal curve.Surgery improves the seating ability of the child, preserves pulmonary function and prevents skin break down due to improper posture.

Perioperative Care

Perioperative care is aimed at providing better conditions for patients before operation (preoperative), during operation (intraoperative) and after operation (postoperative). It helps in preparing the patient both physically and psychologically for any surgical procedure. Due to the progressive muscle weakness in muscular dystrophies, the perioperative care routines of patients should be carefully planned and monitored. Common perioperative concerns associated with muscular dystrophies include respiratory problems, co-morbid cardiac disease, reduced pulmonary capacity and an increased sensitivity to various anesthetic agents.

Surgical considerations

In MD patients, the use of general anesthesia may become necessary in various situations like muscle biopsy, joint contracture surgery, spinal surgery and gastrotomy. While planning a safe surgery, several condition-specific issues need to be strictly monitored and the surgery should be undertaken in a full-service hospital which has previous experience with muscular dystrophy patients. Furthermore, for patients on chronic corticosteroid treatment, giving steroid cover over the period of the surgery should be considered.

Anesthetic agents

Exposure to inhalational anesthetic agents like isoflurane and halothane pose the risk of malignant hyperthermia-like reactions. Hence, the exclusive use of a total intravenous anesthetic technique is strongly recommended. Depolarizing muscle relaxants, such as suxamethonium chloride/ succinylcholine, are absolutely contraindicated due to the risk of fatal reactions.

Hemorrhage or blood loss

To minimize blood loss following options can be used: (a) mildly hypotensive anesthetics - blood pressure lowering anesthetics, (b) cell-saver technology - a machine

that recycles the blood so it can be given back to the patient instead of being thrown away and (c) crystalloid bone allograft. (d) The use of agents that reduce intraoperative bleeding like tranexamic acid or aminocaproic acid may also be considered. (e) It is inappropriate to use heparin as a postoperative anticoagulatant in MD patients.

Prevention of deep vein thrombosis (DVT)

Compression stockings or sequential compression for prevention of deep-vein thrombosis (formation of blood clots in deeper veins) might also be recommended.

Cardiac considerations

An echocardiogram and electrocardiogram should always be carried out before general anesthesia. These should also be done if the patient is undergoing conscious sedation or regional anesthesia if the last investigation was more than 1 year previously or if there had been an abnormal echocardiogram in the preceding 7-12 months.

Respiratory considerations

Preoperative pulmonary function tests are strongly recommended. Respiratory interventions are aimed at providing adequate respiratory support during induction of, maintenance of, and recovery from procedural sedation or general anaesthesia. They are primarily designed to reduce the risk of post-procedure endotracheal extubation failure, postoperative atelectasis (partial or complete collapsing of the lung due to absence of air) and pneumonia. This can be achieved by provision of non-invasive assisted ventilation and assisted cough after surgery, specifically in patients with significant respiratory-muscle weakness (as indicated by preoperative pulmonary function test results). Patients with significant respiratory muscle weakness might be eligible for surgery only after a thorough and careful consideration of the risks and benefits.

Emergency-care considerations

Many factors must be taken into account on presentation of a patient to an emergency room due to the involvement of different systems in MD. From the outset, the diagnosis, current medication, respiratory status, cardiac status, and associated medical disorders should be made clear to the emergency-room staff. Chronic steroid use (if relevant) should be made clear, as they are associated with risk of reduced stress response, masking of infection, and possible gastric ulceration. Awareness of the risk of arrhythmias and cardiomyopathy is crucial. Anesthetic issues, as previously described, need to be taken into account at all times if surgery or sedation is needed. If nocturnal ventilation is already being used, then access to the ventilator is essential during any acute event or intervention. For patients who are already using ventilation, the team involved in the respiratory care of the patient should be contacted as soon as possible.

8.

Cardiac Management

It is crucial to remember that the heart is made up of muscles and muscular dystrophy (MD) also weakens the cardiac muscles. Cardiac dysfunction is a frequent manifestation of MD and a common cause of death for individuals with this condition. The weakening of cardiac muscles is called dilated cardiomyopathy (DCM see Figure 8.1). The onset of DCM leads to an enlargement of the heart and causes two types of complications; heart failure and arrhythmias. The heart is unable to pump blood around the body efficiently. This can lead to fluid buildup in the lungs, ankles, abdomen and other organs of the body. This collection of symptoms is known as heart failure. The second complication is irregular beating, called arrhythmias. Both high and low heart rate due to arrhythmias can be risk to life.

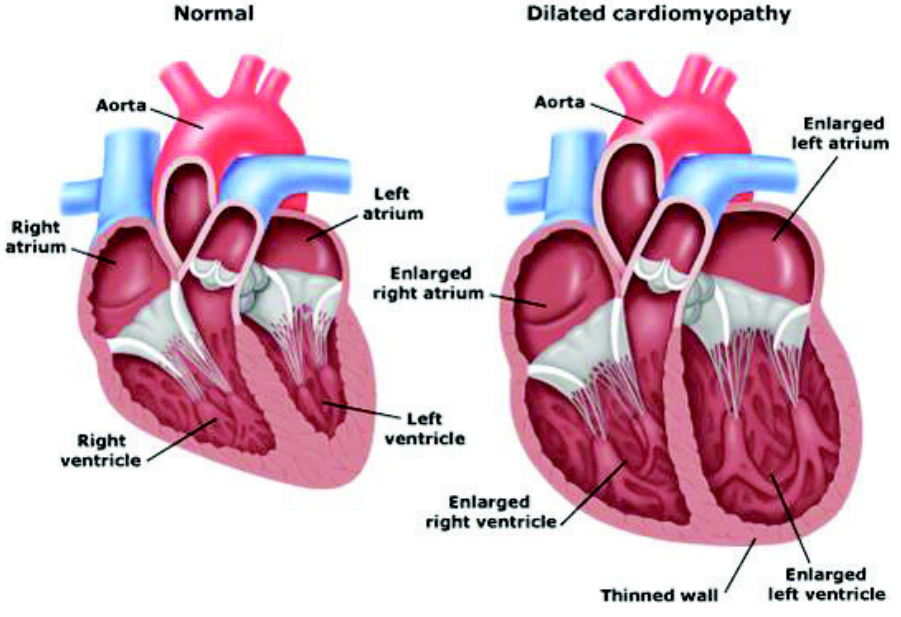

Figure 8.1: Depiction of a normal heart and heart with DCM.

Cardiac Involvement in DMD

Cardiomyopathy in DMD usually starts as a preclinical or intermediate stage, with evolution towards advanced stages characterized by ventricle enlargement but also by symptoms and signs of heart failure such as edema and liver enlargement. The overall incidence of DCM in Duchenne muscular dystrophy (DMD) has been estimated to be 25% by 6 years of age, 59% by 10 years of age. By adulthood, nearly all people with DMD have cardiac involvement. However, the child may not have any symptoms in spite of having cardiomyopathy. Previously, the cardiomyopathy used to be diagnosed only when the disease was in an advanced stage, but today, it is detected even before the onset of any symptoms. This allows early and potentially life-saving treatment. In our practice, screening for cardiomyopathy is routine and co-incident with the diagnosis of MD.

How can DCM be diagnosed?

Electrocardiography:

Electrocardiography (ECG see Figure 8.2) is a quick, simple, painless procedure in which the heart's electrical impulses are amplified and recorded on a piece of paper. This record, the electrocardiogram (also known as an ECG), provides information about the part of the heart that triggers each heartbeat (the pacemaker, called the sinoatrial or sinus node), the nerve conduction pathways of the heart, and the rate and rhythm of the heart. This technique does not accurately access cardiac size or function and is useful for determining cardiac arrhythmias.

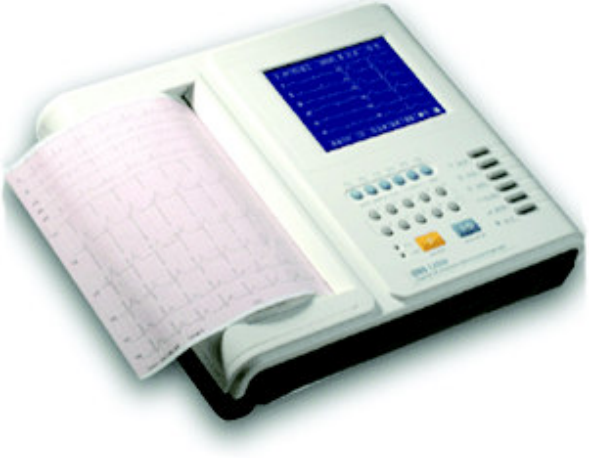

Figure 8.2: ECG machine. The image shows an ECG machine generating an electrocardiogram.

Echocardiography:

Echocardiography often called an echo is a sonography of the heart (see Figure 8.3). It uses sound waves to create pictures of the heart. It allows determination of the heart size, valve function, as well as the strength needed for pumping blood through the body. It can be done while the patient remains in a wheelchair, which is a significant advantage over other methods. It is useful in the diagnosis of heart failure.

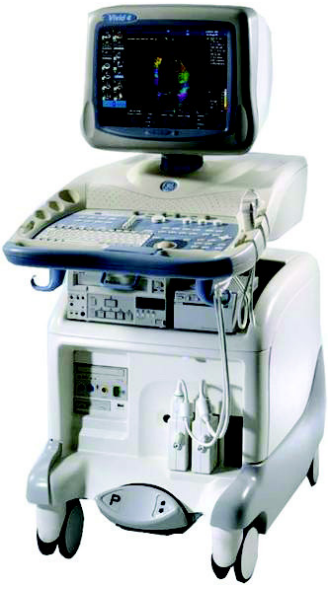

Figure 8.3: Ultrasound machine used for echocardiography

The Holter Monitor:

A Holter Monitor (see Figure 8.4) is a portable device that continuously records and monitor's the rhythms of the heart. This is a painless test that uses small electrodes (conducting patches), which are attached through wires to the Holter monitor device, stuck onto the patient's chest. The monitor can either be carried in the pocket or secured around the waist or wrist of the patient. This test is useful in detecting arrhythmias.

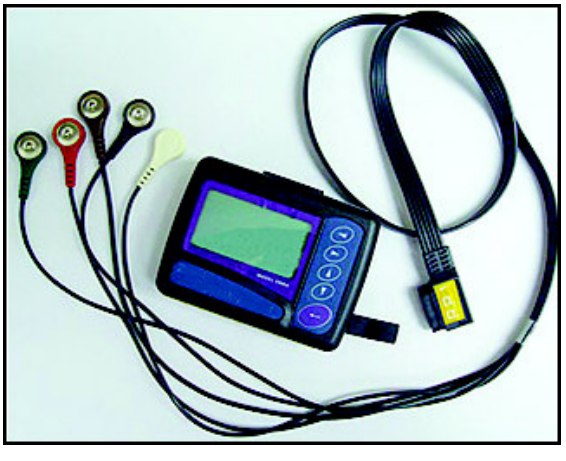

Figure 8.4: Holter Monitor with electrodes.

Cardiac enlargement or dysfunction can also be diagnosed magnetic resonance imaging (MRI) and multiple gated acquisition (MUGA) scan. Cardiac MRI provides one of the most accurate assessments of heart size and function, and also adds the ability to image scarring of the heart muscle. However, it is expensive and has technical

limitations. MUGA scanning uses radiotracer for assessing the pumping action. It is one of the most accurate and reproducible methods. However, this method doesn't give adequate information about heart muscle thickness or valve performance. Additional methods, such as serum B-natriuretic peptide (BNP) or noninvasive impedance cardiography, may be useful, but currently, there is the data to support their routine use is insufficient. Thus, although echocardiography may be less sensitive than MRI or MUGA scan, it has significant advantages of cost and convenience for DMD patients. It is recommended that MD patients should have cardiac investigations (Echo and ECG) before any surgery, every 2 years to age 10 and annually after age 10.

The relatives of patients with MD who are carriers of the defective gene are at increased risk of cardiac abnormalities including ECG changes and DCM. Hence, it is recommended that all carriers should have an echo and ECG at diagnosis or after the age of 16 years and at least every 5 years thereafter, or more frequently in patients with abnormalities on investigation.

How can cardiac complications be treated?

Stage of the disease and treatments:

Pre-symptomatic stage: In this stage, the disease process has begun, but no overt signs or symptoms are evident to the host. The following medications may be prescribed in this stage:

- ACE inhibitors: Angiotensin converting enzyme (ACE) inhibitors like Captopril, Enalapril, Ramipril and Lisinopril are heart medications that dilate (widen or relax) the blood vessels to improve the amount of blood pumped by the heart. They do so by preventing an enzyme in the body from producing angiotension II, a substance that affects the body's cardiovascular system by narrowing the blood vessels and releasing blood pressure raising hormones. Large studies have shown that Ramipril and enalapril decrease symptoms and improve survival even in those who do not have any symptoms. Therefore, it is suggested to start all patients on these medications by 9 years of age even if cardiac function is normal or nearly normal. Their side effects include cough and swelling.
- ARBs: Angiotensin receptor blockers or ARBs like Losartan block the action of angiotensin II by preventing it from binding to its receptors in the blood vessels. As a result, the vessels dilate and blood pressure is reduced, making it easier for the heart to pump blood.
- Beta blockers: Beta-blockers work by blocking the effects of epinephrine (adrenaline) and slowing the heart's rate, thereby decreasing the heart's demand for oxygen. Long-term use of beta-blockers helps manage heart failure. E.g. Carvedilol.
- Spironolactone: This drug is utilized to lower blood pressure and also to treat edema (fluid retention) caused by heart failure.

Symptomatic stage: Symptoms of the disease start to develop at this stage. The medications prescribed during this stage are listed below:

- *Direct effect:*
  - **Medications:** ACE inhibitors, beta blockers, spironolactone, Furosemide (used to treat edema and swelling) and Digoxin (used to lower heart rate), anti-arrhythmia drugs (amiodarone, etc).
  - **Devices:**

    Pacemakers: A pacemaker (see Figure 8.5) is used to treat arrhythmias. It is a small device which can be placed in the chest or abdomen to help control abnormal heart rhythms. This device uses electrical pulses to prompt the heart to beat at a normal rate.

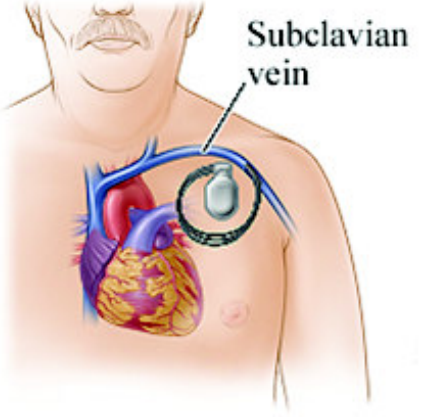

Figure 8.5: Depiction of an implanted pacemaker.

Defibrillators: A defibrillator (see Figure 8.6) is an electronic device which gives an electric shock to the heart. This helps re-establish normal contraction rhythms in a heart having arrhythmias or during cardiac arrest. In recent years, small portable defibrillators called automated external defibrillators (AEDs) have been developed. Defibrillation is an integral part of effective cardiovascular care.

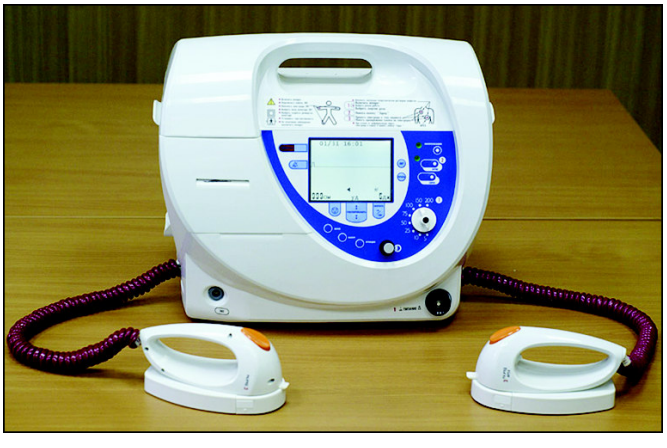

Figure 8.6: Defibrillator

- *Indirect effect:*
  - **Scoliosis surgery:** Scoliosis is the medical term for curvature of the spine. In MD patients, the muscles around the spine may also get weakened resulting in scoliosis. If the scoliosis is too severe, the rib cage is deformed, resulting in pressure to the heart. A number of surgeries have been developed to overcome the effects of progressive scoliosis. During the surgery, the spine is straightened out as much as possible and metal rods are placed on either side of the spine to keep the spine straight. These metal rods prevent the spine from curving again. However, these are major procedures and pose a multitude of risks like hemorrhage, infections, spinal cord damage, anesthetic problems, etc. They also require special post-operative care. Hence, this procedure is recommended only for patients who experience major difficulties.
  - **Pain medication:** Analgesics may be prescribed to reduce pain associated with cardiac problems. These are prescribed with caution as certain pain relievers may increase the risk of heart attacks. Hence, it is always important to speak to your doctor for the right medication for your child.

Cardiac Involvement in BMD

BMD patients experience worse cardiomyopathy as compared to DMD patients as their skeletal myopathy occurs later and progresses more slowly. Research suggests that up to 70% BMD patients have left ventricular dysfunction on echocardiography. As BMD patients have less skeletal muscle weakness, they have the ability to perform more strenuous exercises even with dystrophin-deficient cardiac muscles, which results in earlier manifestations of cardiac disease. Like DMD patients, individuals with BMD also present with cardiac problems like DCM and arrhythmias. Hence, medications prescribed for cardiac management is also similar to those prescribed for DMD patients (discussed above).

Cardiac Involvement in EDMD

Cardiac manifestations are common among EDMD patients and usually become evident in the third decade as muscle weakness progresses, although cardiac manifestations have also been reported in young adults without muscle weakness. The normal cardiac muscles are gradually replaced by fibrous and adipose tissue, a process that usually starts in the atria (leading to atrial arrhythmias), often involves the atrioventricular node (leading to conduction abnormalities sometimes requiring pacemaker implantation), and eventually affects the ventricles (causing progressive dilatation and heart failure). Hence, careful follow-up of these patients is mandatory as cardiac dysfunction poses a high risk of sudden death. Also, since sudden death may be the presenting symptom in this disease, cardiac screening of relatives (including female carriers with X-linked EDMD) is usually recommended. Medications prescribed for cardiac management in EDMD patients is the same as those prescribed for DMD, as discussed above.

Cardiac Involvement in LGMD

In LGMD, the subtypes mostly associated with cardiac involvement are LGMD2C to LGMD2F and LGMD1B. Type LGMD1B cardiac disease manifestations (atrioventricular block, sudden death, atrial paralysis, atrial fibrillation/flutter, and dilated cardiomyopathy) tend to occur later compared with EDMD. Medications prescribed for cardiac management in LGMD patients is the same as those prescribed for DMD, as discussed above.

Cardiac Involvement in Myotonic dystrophy

Atrioventricular and intraventricular conduction defects are common in both DM1 and DM2. Infrahisian block (a blockage located at the distal or outer part of the electrical conduction system of the heart) is likely an important cause of sudden death in these patients. As in many other types of MD, cardiac arrhythmias may occur early in the disease course, that is, in the absence of severe neuromuscular impairment. Structural heart disease is also frequently observed in DM, with left ventricular dilatation or hypertrophy observed in ˜20% of patients and left ventricular systolic dysfunction in 14%. However, clinical heart failure is less common (about 2%). Medications prescribed for cardiac management in myotonic dystrophy patients is the same as those prescribed for DMD, as discussed above.

The importance of cardio-protective vitamins and supplements

- **Coenzyme Q10 (CoQ10)**

  CoQ10 also known as ubiquinone is a vitamin-like molecule present primarily in the mitochondria of most cells. It is known for its effective antioxidant properties which help to reduce the damage caused by excessive oxidative radicals and calcium overload in dystrophic muscles. A recent study published in the European Jorunal of Heart Failure is one of the most robust studies on the benefits of CoQ10 in heart failure patients. This ten year study conclusively showed that CoQ10 supplementation significantly improves survival for even the most severe heart failure patients while radically reducing incidences of hospitalization.

- **Ubiquinol (Active form of CoQ10)**

  In the body, CoQ10 is present in three states; fully oxidized (ubiquinone), partially reduced (semiquinone) and fully reduced (electron-rich, ubiquinol). The ubiquinone must first be converted into ubiquinol within the body for optimum functionality. Hence, using ubiquinol which is the body-ready version of CoQ10 may prove to be have quicker and better results for patients with cardiac involvement.

- **Vitamin C**

  Vitamin C is a water-soluble vitamin which is essential for growth and repair of tissues in all parts of the body. It plays an important role in healing wounds, and for repairing and maintaining bones and teeth. It is also an antioxidant. Research

of scientific studies suggests that vitamin C may help in protecting arteries against damage. Its antioxidant properties have shown to slow down the progression of artherosclerosis (hardening of the arteries). It is also known the lower the risk of high blood pressure. Hence, vitamin C supplements should also be prescribed to MD patients.

- **Vitamin E**

  Vitamin E is the collective name for a group of fat soluble compounds with distinctive antioxidant properties. In addition to this, vitamin E is also involved in immune function. Studies analyzing the effects of vitamin E on heart disease suggest that a low level of vitamin E in the blood is more than twice predictive of heart attack than either high cholesterol or high blood pressure. Hence, vitamin E supplementation is also usually prescribed for patients with cardiac involvement.

Keypoints

- A cardiologist should be an integral part of the health care team for MD patients.
- Early symptoms of cardiac problems are shortness of breath on exertion, easy fatigability, palpitations, swelling of feet and shortness of breath on lying down.
- Early detection of cardiac involvement can be done by ECG and echo.
- In DMD two yearly ECGs and echo is recommended till the age of 10 years and yearly thereafter. In other muscular dystrophies, screening for cardiac function should be done at diagnosis and at regular intervals.
- Cardio-protective medications should be initiated as early as possible to prevent or delay cardiac complications.
- ACE inhibitors/ARBs, spironolactone, beta blockers have shown cardio-protective effects.
- Heart failure or anti-arrhythmic medications, pacemaker or defibrillator are available options to treat cardiac problems and improve quality of life.
- Before any surgical procedures or anesthesia or sedation, cardiac evaluation must be done to prevent complications.

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9.

Respiratory Management

Respiratory system involvement and complications are mainly seen during the advanced stages or Early and Late ambulatory stages of muscular dystrophy. In muscular dystrophy the respiratory muscles undergo weakness and lead to respiratory difficulty and in advance cases respiratory insufficiency. Respiratory insufficiency due to weakness or infection is most often the complication in the terminal stages and therefore respiratory management is of utmost importance.

Clinical symptoms:

- Sometimes there are specific symptoms but otherwise symptoms are subtle and indirect. Symptoms suggestive of respiratory insufficiency are fatigue, lethargy, poor appetite, weight loss and impaired concentration.
- If the diaphragm (Primary muscle for breathing) (Fig 9.1) undergoes weakness, symptoms like orthopnoea (difficulty of breathing of lying down), breathlessness when bending over and breathless when walking in the water with above waist

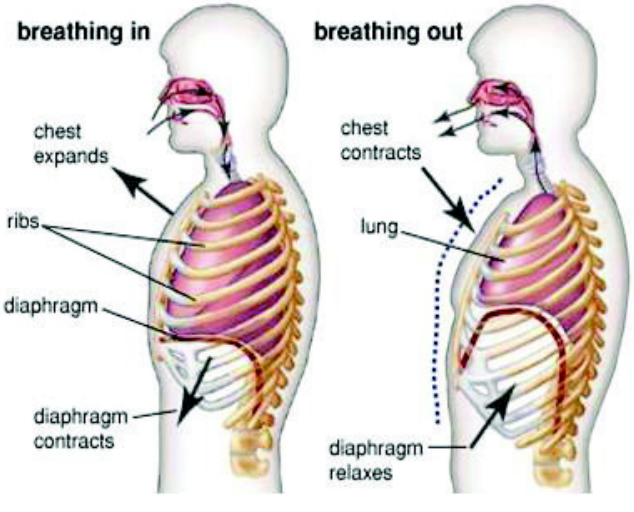


Figure 9.1 Location and action of Diaphragm - Primary muscle of breathing

immersion. It also causes paradoxical breathing pattern (Fig 9.2) characterized by inverse movement of abdominal wall. This means the abdominal wall moves inwards while breathing in, caving the stomach and moves outwards while breathing out, ballooning the stomach.

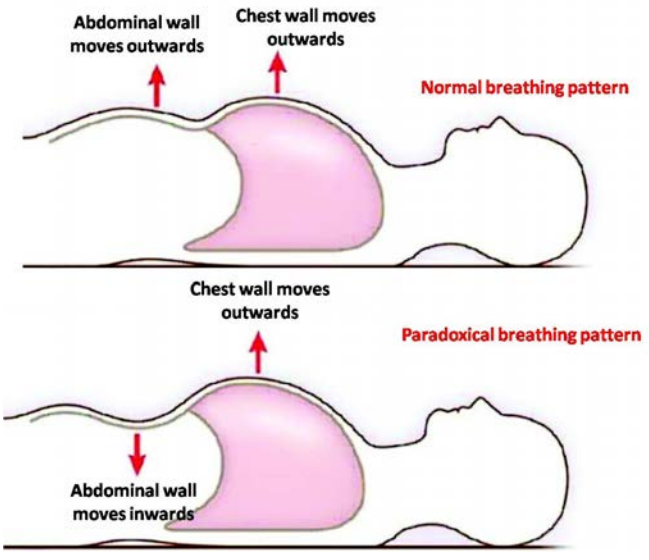


Figure 9.2: Paradoxical movement of abdominal wall

- If the muscles of upper airway are weak, difficulty may be experienced in swallowing and speaking clearly and fast.
- Upper airway weakness may cause the walls of the airway to collapse on itself while sleeping leading to complete or incomplete, temporary obstruction of air flow. This condition is known as obstructive sleep apnoea and the symptoms like snoring, episodes of sudden breathlessness at night and excessive sleepiness during daytime may be present. If obstruction is incomplete the individual is breathing sub normally which leads over accumulation of carbon dioxide in the body causing symptoms like early morning headaches, inability to concentrate and drowsiness.
- Recurrent chest infections may be a sign of insufficient cough. Insufficient cough could be due to weakness of muscles that help breath in (inspiratory muscles), breath out (expiratory muscles) or the muscles that close the food tract while breathing (glottis muscles)
- Individuals with respiratory muscle weakness usually show rapid and shallow brathing and excess use of neck muscles while breathing.

Common Investigations:

After a thorough physical assessment, clinical observation of the breathing technique, snuffing, coughing and breathing pattern after physical activities, a clinician may ask investigative tests to understand the chemical and biological effects of the altered respiration.

Pulmonary function test:

The test is very simple and non-invasive. It is a voluntary test and therefore administered without any anesthesia.

Before the procedure:

- Certain medicines may hinder the outcome of the test and therefore it is important that you inform your doctor of all the medicines you are currently taking.
- Inform your doctor if you have fever, cough or flu like symptoms.
- Inform your doctor if you have asthma.
- No additional preparation like fasting etc. is required.
- If you are a smoker do not smoke for 48hrs before testing.
- Empty your bowel and bladder before the test

Procedure of the test:

- You will be asked to remove all the jewelry, restrictive clothing if any and dentures.
- You will be given a nose clip to put on
- You may be sitting or standing while performing the test
- You will be given a clean sterile mouthpiece and asked to seal it with your lips while performing various breathing maneuvers.

After the procedure

- You may feel mild faintness or light-headedness due to forced expirations and inhalations performed.

Interpretation of the test

- The test gives information of the capacity of lungs to breath in, effectiveness and force of breathing out and many other respiratory parameters.

Arterial blood gas analysis (ABG):

The test is performed with a simple blood draw and tells about the concentration of various gases like oxygen and carbon dioxide in the blood. ABG picks up the CO2 retention which is an early sign of respiratory muscle weakness. It will help the doctor to decide whether the patient needs any assistive device like Bi-PAP for breathing. ABG can give information about low oxygen levels in the blood which may be the cause of breathlessness or early fatigue.

Management of respiratory impairment:

Pre-symptomatic, early ambulatory and late ambulatory stage

In these stages respiratory muscle weakness is not very evident. Very rarely patients

exhibit symptoms of respiratory impairment, however it is important to prevent these complications and delay the impairment.

Prevention of chest complications can be achieved by the following measures:

- Maintaining good oral and dental hygiene.
- Encouraging proper positioning during sitting and sleeping to prevent spinal deformities like scoliosis and kyphosis.
- Taking regular vaccination by which respiratory illness can be prevented like BCG, DPT, measles, hemophilus, pneumococcal diseases and yearly influenza vaccine.
- Being attentive and aware of other co-existing problems like asthma or any allergies as they target the lungs.
- Avoiding obesity as it becomes an additional strain on weak muscles. Many patients of muscular dystrophy are already at risk of obesity due to lack of movement and physical activity.
- Avoiding lying down especially immediately after meals.
- Early initiation of antibiotics if suffering from any flu or fever.
- Encouraging more physical activity if the person is able to walk, but without any exertion or fatigue.
- Carrying out deep breathing exercises, Incentive spirometer should be used to strenghthen chest muscles and nebulization if required, moving shoulder and upper trunk muscles, as they can facilitate chest movement.

In addition to these some assistive techniques as mentioned below may be prescribed by your physiotherapists or physician

Nebulization (Figure 9.3): A technique of administering medication by spraying it into the respiratory tract. Oxygen may or may not be used to assist in carrying the medication into the lungs. It can be done at home also with proper understanding of the apparatus.

Fig. 9.3 : Nebulizer

Incentive spirometer (Figure 9.4): it is a small portable device which helps to keep the lungs clear. It helps to strengthen the chest muscles. It is important that wheelchair bound patients use spirometer to maintain their respiratory functions for as long as possible.

Fig. 9.4 : Incentive spirometer

Early non-ambulatory and late non-ambulatory phase

Treating chest infections:

Recurrent chest infection is a common secondary complication of the neuromuscular diseases. To prevent recurrent chest infection maintaining regular hygiene and performing exercises that aid in deep breathing and clearing out the secretions is advised.

In an event of a chest infection consult your physician immediately -

How to recognize chest infection?

- Breathing difficulty
- Breathing by mouth
- Dryness of mouth
- Changes in the quality of voice
- Frequent sneezing and coughing
- Increased secreations with mild, moderate or high fever
- Chest pain
- Lethargy
- General body pain

Treatment of infections:

- Administering antibiotics under the prescription of physician
- Carrying out nebulization.

- Doing chest physiotherapy and coughing techniques to help keep lungs and airways clean.

Treating respiratory impairment

Respiratory impairment can be treated by providing ventilatory assistance.

Non-invasive ventilation

BiPAP *(Bi-level positive airway pressure)* (Figure 9.5)

Indications:

1. Breathlessness at night with disturbed sleep
2. Breathlessness on lying down
3. Low oxygen levels in the blood
4. CO2 retention in the lungs

Benefits of Bi-PAP

1. Supports breathing.
2. No surgical procedure is required, only nasal mask or a face mask is used
3. Cannot be used as a 24-hour support as it is uncomfortable.

Auto BiPAP:

It is a user friendly Bi PAP machine where the settings are pre set. (Figure 9.6)

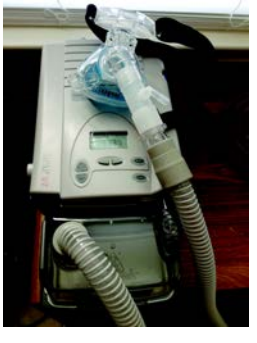


Fig. 9.5 : Bi-PAP

Fig. 9.6 : Automatic Bi-PAP

Non surgical breathing support:

1. Ventilator with mouth piece which can be transferred easily. It can also be attached to the wheelchair for day time support or may be a 24-hour support.
2. Among the many ventilators available some special ones worth mentioning are the Pulmonetic -LTV-950 ventilators (Figure 9.7) It is light-weight and comes with a 1 hour internal battery and a 4-10 hour external battery.
3. Ventilator with mouthpiece is ideal for patients who require it during day time and can manage without it for some time. It helps to improve energy levels.

Fig 9.7: Pulmonetic -LTV-950 ventilators

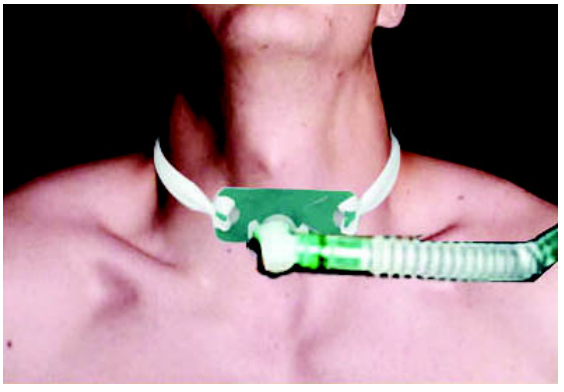


Fig 9.8: Tracheostomy

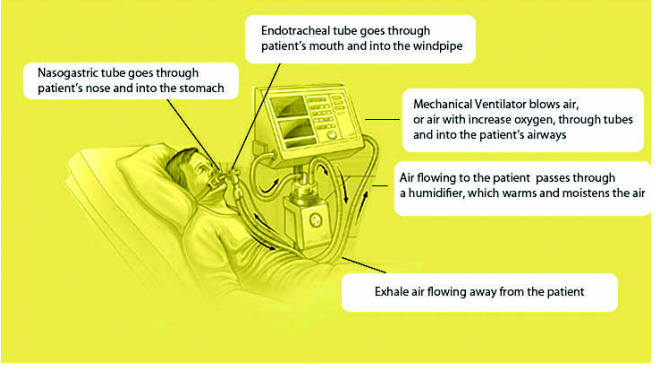


Fig 9.9 : Tracheostomy

Fig 9.10 : Volume Ventilator

Surgical intervention for breathing support:

This is required when the patient cannot breathe adequately or cannot be put on the above mentioned non surgical /non invasive devices.

1. During severe complication, patient may require hospitalization in the ICU (Intensive Care Unit).
2. When breathing difficulties increase, another surgical option that can help to reduce difficulty is tracheostomy (Figure 9.8 & 9)
3. Sometimes, the patient can be weaned off the ventilator (that means ventilator support can be removed) during hospital stay .This means that they can be managed without continuous ventilator support at home or with above mentioned devices or may have to be on 24 hours ventilator (Figure 9.10) support at home, but they can still lead a normal life.

4. Among the many ventilators that can be used at home for long term ventilation, a workhorse effective yet very inexpensive ventilator is the Newmon ventilator (Zephyr industries) that can be used 24/7 in any home for over one year. It had a 3 hours battery life and can be connected to car battery also. It needs hardly any maintenance. (Figure 9.11 & 12)

Example of Ventilator Management at home

Fig. 9.11 : Newmon Ventilator

Fig. 9.12 : Newmon Ventilator

Tracheostomy:

In this surgical procedure, a small hole is made below the neck, which is covered with a mesh and is connected directly to the windpipe. Before choosing this technique all the possible outcomes should be discussed with the surgeon. It can help in suctioning i.e. removal of cough with the help of tube (done by trained professional or can be done by parents with proper understanding of it). (Figure 9.13) Pulmonetic -LTV-950 ventilators Volume ventilator (Figure 9.14) is a device, which can be used during the night time because it is bigger than IPPB. This device reduces difficulty in breathing when the child is sleeping. Facemask or nasal mask is connected to airway. These devices can be used as and when needed, to improve ventilation.

Conclusion:

Early detection and intervention will help to prevent respiratory complications. A doctor's advice should be taken at the earliest signs of respiratory problems. Nowadays respiratory devices have helped patients with muscular dystrophy to breathe more comfortably. The devices are portable and easy to manage. Improved respiratory management can prolong the survival and improve the quality of life.

10.

Physiotherapy

Physiotherapy is a branch of rehabilitative therapies which makes use of physical modalities and exercises to treat various neuro-musculo-skeletal and cardiorespiratory disorders. It is a systematic and scientific approach towards understanding the science of body movements and facilitating them. Physiotherapists will help patients to achieve their maximum physical potential and improve their quality of life. In muscular dystrophy physiotherapy has two main roles to play preventive and restorative. One of the key areas of physiotherapy is to prevent the secondary musculoskeletal complications of the disease (contracture, tightness, postural deviations, scoliosis and others). Restorative functions of physiotherapy in muscular dystrophy are functional enhancement, correcting postural deviations and gait patterns and maintain the integrity of joints using various orthoses.

Aims of Physiotherapy

- To assess muscle strength, joint mobility, deformities and functional abilities.
- To determine the causes of deformities and prevent deformities.
- To suggest supportive physical aids when required.
- To correct the physical impairments to the best of the abilities of the patient.
- To educate the patients, parents/caregivers regarding the disease and its outcome.
- To guide the patients and parents regarding care and prevention of the deformities.
- To maintain independent walking as long as possible.
- To encourage daily exercises.
- To prevent frequent falls, fractures, pressure sores and stiff joints.
- To improve cardio-respiratory endurance of the patient.
- To motivate them to overcome complications and improve their quality of life.
- To plan an appropriate treatment program in co-ordination with other professionals of the rehabilitation team.

Basic principles of exercise prescription in muscular dystrophy

Exercise prescription in muscular dystrophy differs greatly as compared to exercise prescription in typically developing individuals. Muscular dystrophy is a primary muscular pathology with progressive degeneration. This degeneration is triggered even during the regular muscle contractions. However, not using these muscles does not preserve them longer. The muscles unless used appropriately undergo atrophy (reduction in the total number of muscle fibers) in addition to the dystrophic (reduction in the number of muscle fibers and replacement with fibrous non-contractile tissue) changes caused by the disease. Therefore regular low intensity graded and supervised exercise is required to be performed by individuals with muscular dystrophy. This exercise is prescribed on the basis of following principles.

1. Muscle plasticity

There are two types of muscles in our body, one type of muscle fibers are responsible for producing burst of strong contraction very quickly. These muscle fibers are more prone to damage during contraction. The other type of muscle fiber produces a slow contraction of smaller amplitude but can sustain it for a long time (Type I). These muscle fibers are less prone to damage during contraction (Type II). There is certain percentage of both types of fibers in any muscle of our body. Depending upon the function of the muscle, the proportion of fibers varies in different muscles of the body. This proportion also varies depending on how the muscles are trained. Although a muscle needs both type of fibers, with targeted training proportion of one type can be increased. This is called as muscle plasticity.

2. Regressive resistive exercises

For the treatment of individuals with muscular dystrophy regressive overload is used. Regressive overload means over a period of time resistance used to train the muscles is reduced. If the resistance is kept the same then the muscles will undergo more damage. Therefore it is reduced as there is progressive muscle weakness. Principle of overload means that the muscle should be stimulated to perform beyond its current capacity. This can be achieved using increased resistance provided to the muscle or higher number of repetitions with the same or lesser resistance. In muscular dystrophy higher repetitions are performed. Higher repetitions facilitate the growth of Type II fibers.

3. Facilitating concentric contractions and preventing eccentric contractions

Eccentric contractions are the contractions where the muscles shorten as they contract. These contractions are used to bring about movement in the body and are less damaging to the muscle. Eccentric (lengthening) contractions are the contractions where the muscle is contracting but lengthens while doing so. These are useful to control the speed and extent of the movement but bring about more damage to the muscles. Eccentric contraction of the muscles is unavoidable in day to day activities as these are the contractions that are required to control

any body movement performed against gravity. However the exercise training program should be designed to prevent such contractions and facilitate more of concentric (shortening) contractions. The main principle of training in muscular dystrophy is optimizing muscle strength and endurance.

4. Preventing disuse

Disuse is characterized by the difference between the physical activity that can be performed and the actual physical activities of the individual. It is the difference between the physical capabilities and physical performance. Due to the muscle weakness, increased effort to carry out an activity and fear of falls, individuals with muscular dystrophy are physically less active than others. This early decline in the physical activity speeds the process of muscle wasting and atrophy, thereby muscle weakness. This decline is physical activity must be prevented with the help of use of timely consistent tailored physical exercises.

5. Preventing Fibrosis

One of the most important principles in muscular dystrophy is to prevent fibrosis. Exercises aims at moving the joints through complete range, stretching the muscles as well as other tissues in the body are important in preventing the fibrosis. Active exercises also help prevent fibrosis in the muscles. A combination of regular moderate intensity active exercises within the limits of fatigue and passive stretching should be prescribed in muscular dystrophy.

Different types of exercises

For individuals with muscular dystrophy physiotherapists may use different types of exercises as follows

1. Muscle strengthening exercises

Exercises that make use of resistance bands, weights or individual's body weight to increase the strength of the muscles.

2. Muscle endurance exercises

Exercises that consist of minimal to moderate resistance but higher repetitions. These improve the capacity of the muscles to perform an activity for a longer time.

3. Cardio-respiratory endurance exercises

These are the exercises that are performed to improve the capacity of the heart to circulate blood and capacity of the lungs to improve oxygenation of the blood during increasing physical effort.

4. Stretching exercises

These are the exercises that are performed to improve the length of the muscles so that all the joints can be used through their complete range of motion. Regular

daily stretches help to maintain muscle length and keep joints mobile to prevent any deformities. Hold each stretch for 30 seconds and repeat 3-4 times. These stretches should be performed at least 5 times in a day. If the range is not complete, try to stretch it slowly and gently; just a little more each time. Do stretching in the opposite direction of the deformity or contracture, so that they help to put the joint into a more normal position. Do not use too much force and please stop stretching when it starts to hurt.

5. **Range of motion (ROM) exercises**

ROM exercises are regularly repeated exercises that straighten or bend one or more joints of the body and move them in all the directions that a joint normally moves. The main purpose of these exercises is to keep the joints flexible. They can help prevent joint stiffness, contractures, and deformities. ROM exercises should be done at least 2 times a day. While exercising, if the person gets tired or if he gets cramps, he should be given rest and decrease the number of repetitions. The person may be able to perform these exercises independently in the earlier phases. But as weakness progresses assistance may be required.

Depending on how the exercises are performed they are divided in 3 types:

1. **Active:**

where the person performs the exercise on his or her own (Stage I, II and III)

2. **Active assisted:**

where the person performs the exercise with some help from other (Stage II partially, Stage III and Stage IV)

3. **Passive:**

where the exercise is entirely done by someone else (Stage IV and V)

Depending upon who performs the stretch they are divided into two types

1. **Assisted stretching:**

Assisted stretching is passive performed by a therapist or care giver.

2. **Self stretching:**

Self stretching is active performed by the patients themselves.

Physiological benefits of exercise

All of these exercises have different effects of different body systems as explained below

1. **Muscles and Bones**
    - Increased density of the bone minerals
    - Improved absorption of calcium and phosphate in the bones
    - Bone growth facilitation
    - Maintenance and replacement of lubricating fluid in the joints
    - Increased number of muscle fibers
    - Increased size of the muscle fibers
    - Muscle growth stimulation
    - Improved blood supply to the bones and the muscles
    - Reduced muscle fatigue

2. **Heart and lungs**
    - Increased blood pressure as immediate response exercises improving the blood circulation
    - Reduction in the blood pressure as a late response to exercises reducing the cardiac stress
    - Improved capacity of the heart to pump blood
    - Improved return of the blood from extremities to heart preventing stagnation of the blood in extremities
    - Improved capacity of the lungs to breath in the air
    - Improved oxygenation of the blood
    - Improved clearance of carbon dioxide from the blood
    - Ability to breath air out more forcefully

3. **Nervous system**
    - Improved blood supply to the brain
    - Improved memory and other complex cognitive functions
    - Stimulation to form new blood vessels
    - Antidepressant effects preventing depression, anxiety and other negative psychological responses

4. **Effects on Fibrosis:**
    - Reduction of fibrotic processes by up to 50% improving pliability, extensibility thereby contractile strength of the skeletal muscles; reducing the joint stiffness and cardiac muscle fibrosis.

5. **Blood vessels and blood circulation:**
    - Formation of new blood vessels
    - Improved connections and network of blood vessels

- Improved circulation to the deep muscles of the body, brain, lungs, liver and kidney
- Improved clearance of toxic waste substances from the blood

Physiotherapy management

Stage 1: Pre-symptomatic (0-4 years)

In the pre-symptomatic stage very rarely the muscles undergo weakness. The main aim of physiotherapy is to facilitate motor learning and strengthening muscles with endurance exercises to achieve greater muscle plasticity.

Type of Exercise:

1. Moderate intensity resisted muscle strengthening exercises
2. Moderate intensity cardiovascular endurance training exercises
3. Muscle endurance training exercises

Stage 2: Early ambulatory stage (4-8 years)

In the early ambulatory phase children are still able to walk and can carry out all the physical activities independently with difficulty or with support of external objects. Functional deficits are minimal and the compliance of patients and caregivers to exercise may be limited because of the same. However exercise in this phase is very important. Parents and care givers must make sure that they comply with the instructions and prescription of exercise as suggested by their rehabilitation professionals. Table1. Summarizes the muscles that undergo weakness, tightness and resulting postural compensations

Table 1. Table describing the muscles undergoing weakness, tightness and resultant postural compensations in Stage II

Muscles that undergo weakness	Muscles that undergo tightness	Postural compensations
Hip extensors	Tendoachilis (Calf muscles)	Increased arching of the back while standing and walking (lumbar lordosis)
Ankle dorsiflexors	Hip Flexors	Walking on toes
Hip abductors	Lower abdominals	Stabilizing the knee with hands while getting up from the chair and floor
Hip adductors		Unable to control descent while sitting down
Abdominal muscles		
Neck flexors		
Shoulder flexors		
Shoulder abductors		
Shoulder extensors and depressors		
Elbow extensors		

Goals of Physiotherapy:

1. To prolong independent walking as long as possible.
2. To maintain muscle strength.
3. To prevent frequent falls and fractures.
4. To prevent bed rest for long period of time.
5. To continue exercises (shown in chapter 5).

Type of exercises:

1. Active exercise with moderate resistance and higher repetitions
2. Active and passive stretching for the calves, abdominal muscles and hip flexors
3. Movement and postural corrective exercises
4. Moderate intensity cardiorespiratory endurance training exercises

Stretching exercises:

1. Calf stretching Passive

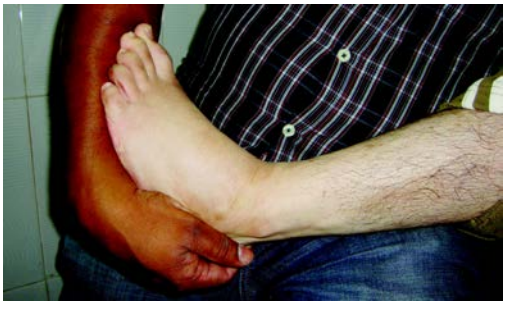


Fig. 10.1

Fig. 10.2

Place one hand under the knee and hold the heel in your other hand. Gently bend the ankle upward by pushing against the sole of the foot with the forearm.

2. Hip flexor stretching Passive

Fig. 10.3

Fig. 10.4

Alternatively to stretch both the hips joints together, ask the individual to lie on his/her tummy. Keep a below both the knees to lift knees above the pelvic height. With hip flexion tightness the buttocks will raise up. Push it down gently keeping the knees bent till gentle stretch is felt.

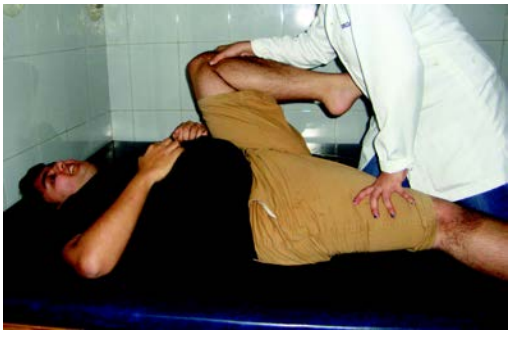


Fig. 10.5

Place one hand on one knee and with the other hand bend the hip and knee of the other leg as if trying to touch chest. Press down the knee of the other leg.

Fig. 10.6

Strengthening exercises:

Neck Exercises

1. Slowly turn the head to each side as far as possible without pain, hold and return to the center. (Figure 10.7 and Figure 10.8)
2. Tilt the head sideways on each side, so that the ear moves towards the shoulder; hold and return to centre. (Figure 10.9 and Figure 10.10)
3. Bend the head downwards, slowly taking it up to look at the ceiling. (Figure 10.11 and Figure 10.12)

Fig. 10.7

Fig. 10.8

Fig. 10.9

Fig. 10.10

Fig. 10.11

Fig. 10.12

Shoulder and Arm Exercises

1. Lift both hands straight in front and to the side, from your waist all the way over your head. (Figure 10.13 - 16)
2. Hold one arm straight out to the side at shoulder height, and then bring the arm in front of chest, keeping the elbow straight. Go just to the point where your arm starts to bend, then return to starting position. (Figure 10.17 & 18)

Fig. 10.13

Fig. 10.14

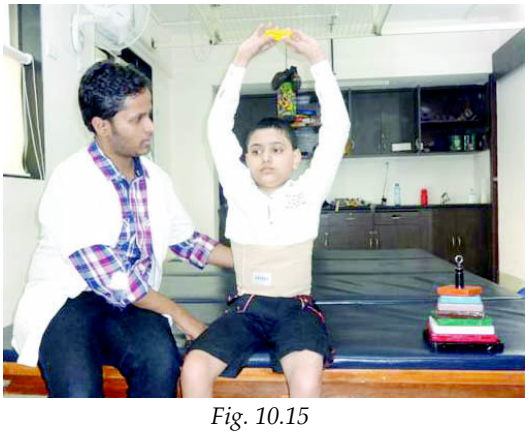


Fig. 10.15

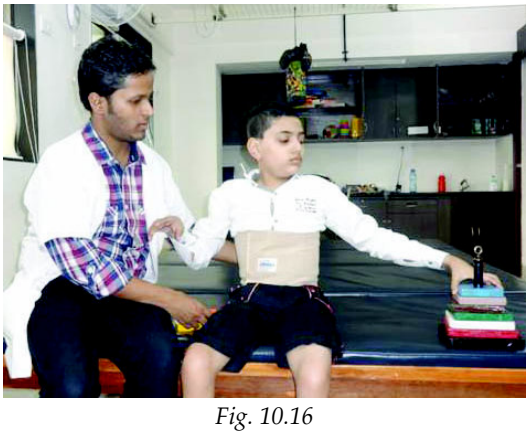


Fig. 10.16

Fig. 10.17

Fig. 10.18

3. Squeeze shoulder blades together in the back by taking shoulders back. Then relax and repeat. (Figure 10.19 & 20)

4. Bring both shoulders up towards your ears, then relax and repeat. (Figure 10.21)

Elbow and Forearm Exercises

1. Biceps: Hold the entire upper limb in a straight position. Then bend the elbow so that fingers touch the shoulder on the same side. Relax & return to starting position. (Figure 22)

Fig. 10.19

Fig. 10.20

Fig. 10.21a

Fig. 10.21b

Fig. 10.22

2. Triceps: Hold arm over head with elbow bent. Then straighten the elbow with fingers pointing to the ceiling. Relax & return to starting position.(Figure 10.23)

3. Forearm: Hold upper limb by side and elbow bent with palm facing the ground. Slowly turn forearm to face ceiling. Relax and return to starting position. (Figure 10.24 & 10.25)

Fig. 10.23a

Fig. 10.23b

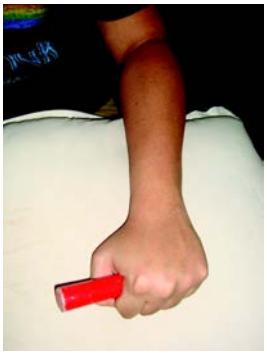


Fig. 10.24

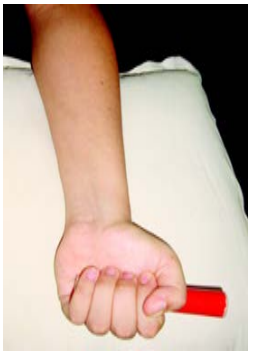


Fig. 10.25

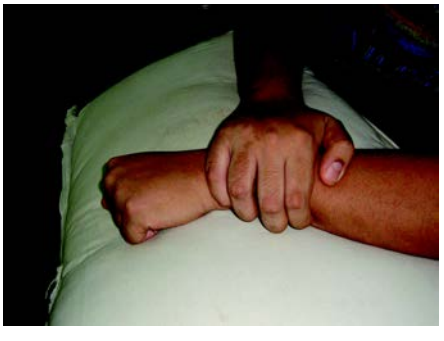


Fig. 10.26

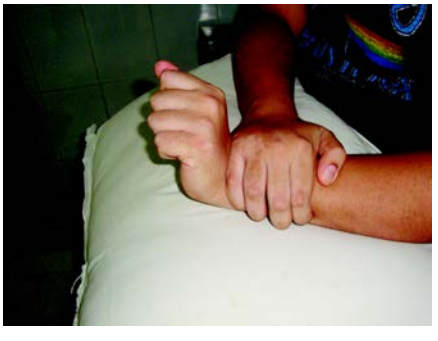


Fig. 10.27

Wrist and finger exercises

1. Hold wrist in neutral position with palm facing downwards. Then lift wrist up towards the ceiling. Relax and return to starting position. (Figures 10.26 & 10.27)

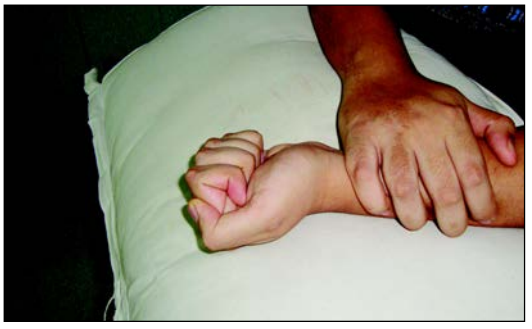


Fig. 10.28

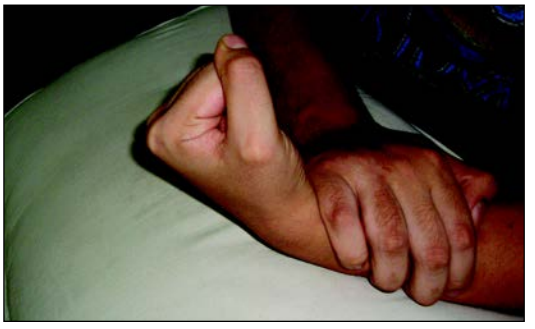


Fig. 10.29

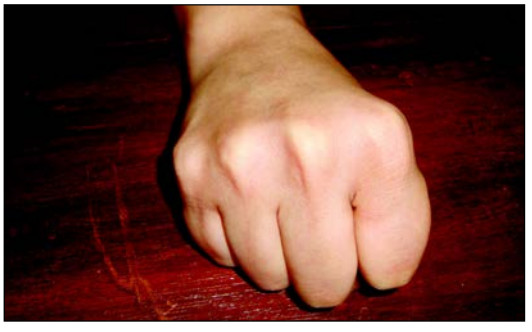


Fig. 10.30

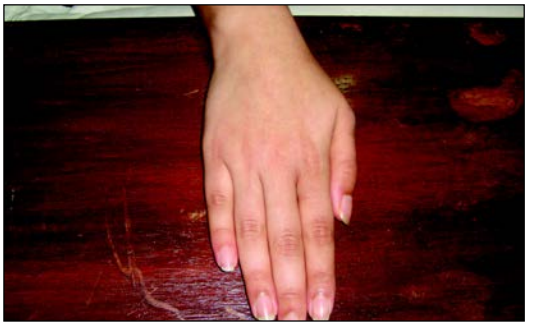


Fig. 10.31

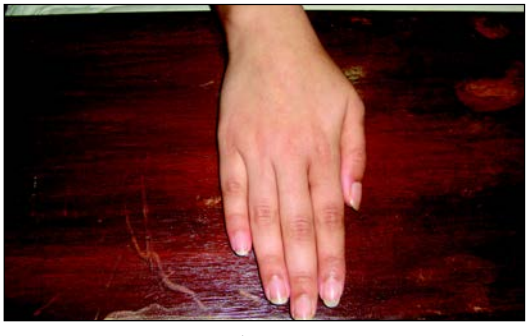


Fig. 10.32

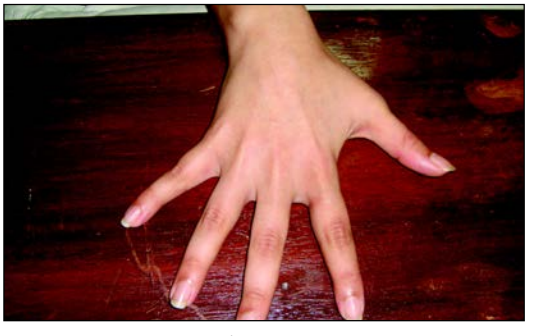


Fig. 10.33

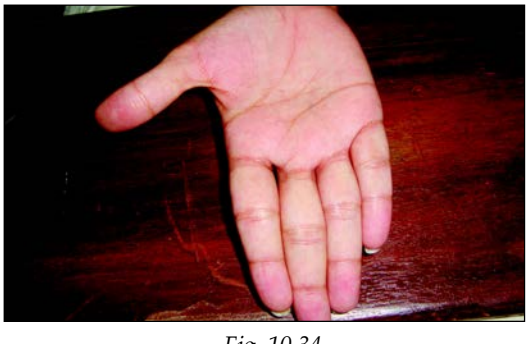


Fig. 10.34

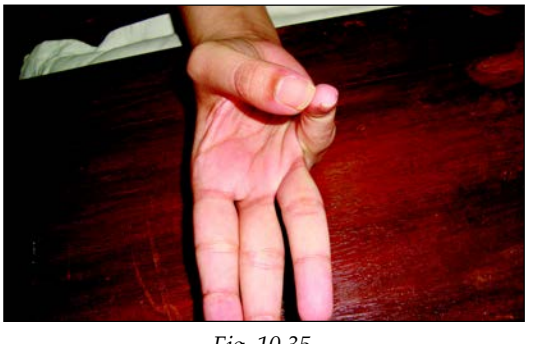
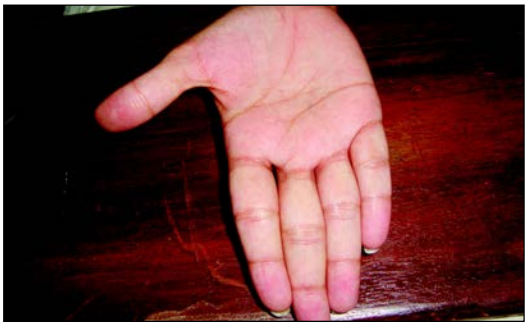


Fig. 10.35



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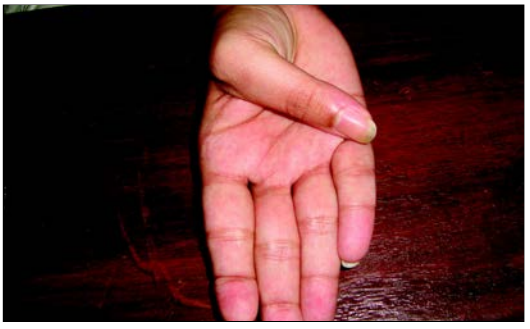


Fig. 10.37

2. Hold wrist in neutral position with palm facing the ceiling. Then raise wrist as if trying to touch forearm. Relax and return to starting position. (Figures 10.28 & 29)

Sitting with hand out in front on a pillow or table, the following exercises can be performed.

3. Opening and closing the hand. First make a tight fist. Then open and relax hand. (Figures 10.30 & 31)
4. Open hand and stretch the fingers as far apart as possible. Bring fingers together again. (Figures 10.32 & 33)
5. Counting on fingers. One at a time, bring each finger to touch the thumb. (Figures 10.34 & 35)
6. Thumb exercise. Move your thumb and place it across the palm. Move it out to the side again. (Figures 10.36 & 37)

Hip exercises

1. Lie on back with legs in a straight position. Slowly lift one leg without bending knee. Lift leg as much as possible. Then return to starting position. (Figure 10.38)
2. Lie on one side. Then lift the leg which is on top taking it sideways as much as possible without bending knee. Then return to starting position. (Figures 10.39)
3. Lie on stomach. Lift leg backwards as much as possible without bending knee. Then return to starting position. (Figures 10.40 & 41)
4. Sit in the chair or bed and lift up the legs with knee bent, mimicking the marching action in sitting (Figure 10.42)

Knee exercises

1. Sit with hip & knees in 90°. Straighten knee out in front without bending the back. Then return to starting position.(Figure 10.43)
2. Lie on stomach. Bend knee without lifting hip. Then return to starting position. (Figure 10.44)

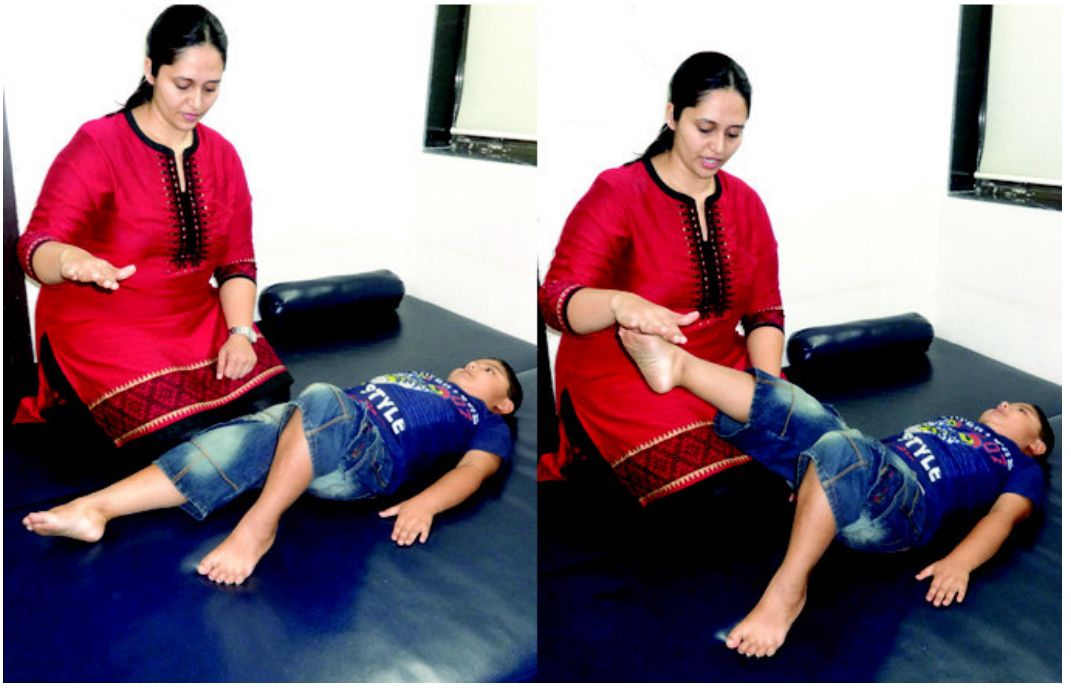


Fig. 10.38

Fig. 10.39

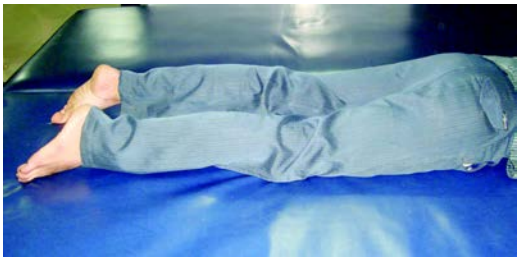


Fig. 10.40

Fig. 10.41

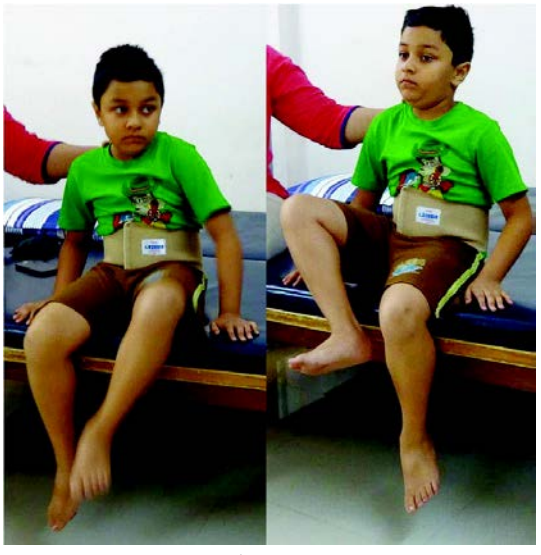


Fig. 10.42

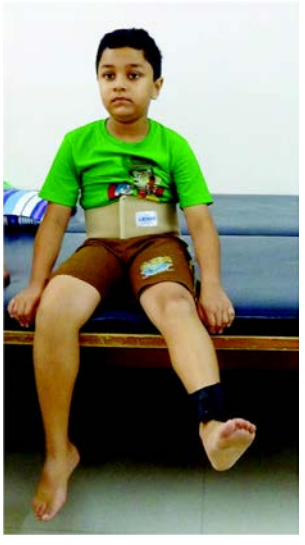


Fig. 10.43

Fig. 10.44

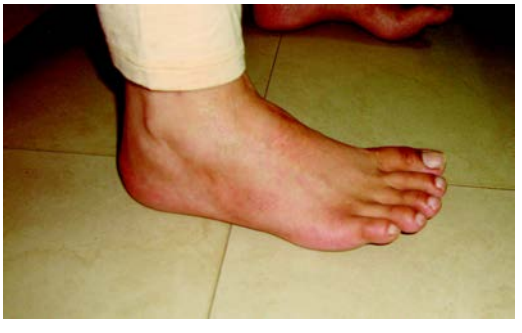


Fig. 10.45

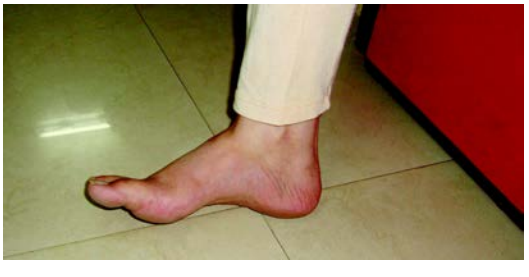


Fig. 10.46

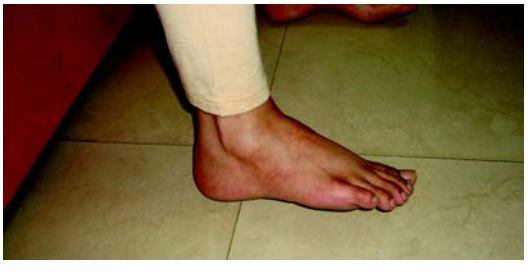


Fig. 10.47

Foot Exercises

1. Keep feet flat on the floor. Then slowly lift front of foot (heel touching floor) as if trying to point toes to the ceiling. Then lower them back. (Don't lift thighs off chair.) (Figure 10.45)
2. Keep heels on the floor. Then slowly turn foot inwards as if to check sole. Relax and return to start position.(Figure 10.46)
3. Keep heels on the floor. Then slowly turn foot outwards. Relax and return to start position. (figure 10.47)

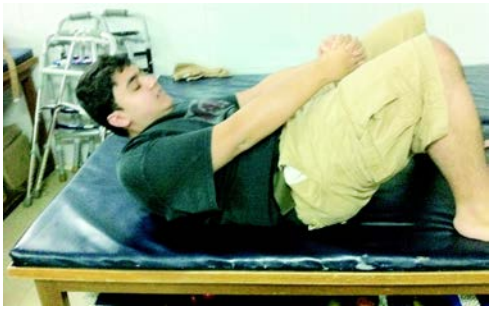


Fig. 10.48

Fig. 10.52

Fig. 10.49

Fig. 10.50

Fig. 10.51

Fig. 10.53

Trunk exercises

1. **Upper Abs:** Lie on back with hip & knees bent. Place hands across shoulders or on knee and attempt to come to sitting position. Return to starting position. (Figure 10.48)

   Although unlikely a child may need support while performing this exercise, in such a case gently hold on to both the arms as the child pulls himself up. (figure 10.49)

   Assisted exercise can also be performed on the vestibular ball. The child rests his back on the ball with head hanging down. The legs can be supported by the therapist if required. Holding both the arms, the child is then asked to sit up on the ball. (Figure 10.50)

2. **Lower abs:** Lie on back with hip & knees bent. Slowly bring knees to touch chest without the help of hands. Sometimes a child may need some assistance. (Figure 10.51)

3. **Bridging**: Lie on back with hip & knees bent. Lift hips up as much as possible. Then return to starting position. (Figure 10.52)

4. **Back extensors:** Lie on stomach. Raise head, neck & chest off the mat as much as possible. Then return to starting position. (This exercise can be performed on a flat bed or on a vestibular ball) (Figure 10.53)

Bed mobility exercises

1. **Rolling:** Starting position is for the child to rest on the back, it is essential to raise both arms overhead to facilitate clearance while rolling and prevents hands being trapped under the body while turning. (Figure 10.54)

2. **Crawling:** A child comes in a quadruped position bearing weight on both the arms and legs. He then slowly starts to move his alternate arm and leg forwards. (Figure 10.55)

3. **Kneeling:** The child sits with on his legs with hip and a knee flexed, and then stands up on the knees to achieve kneeling position. This can be performed without any support or with minimal arm support or with a support of a table. (Figure 10.56)

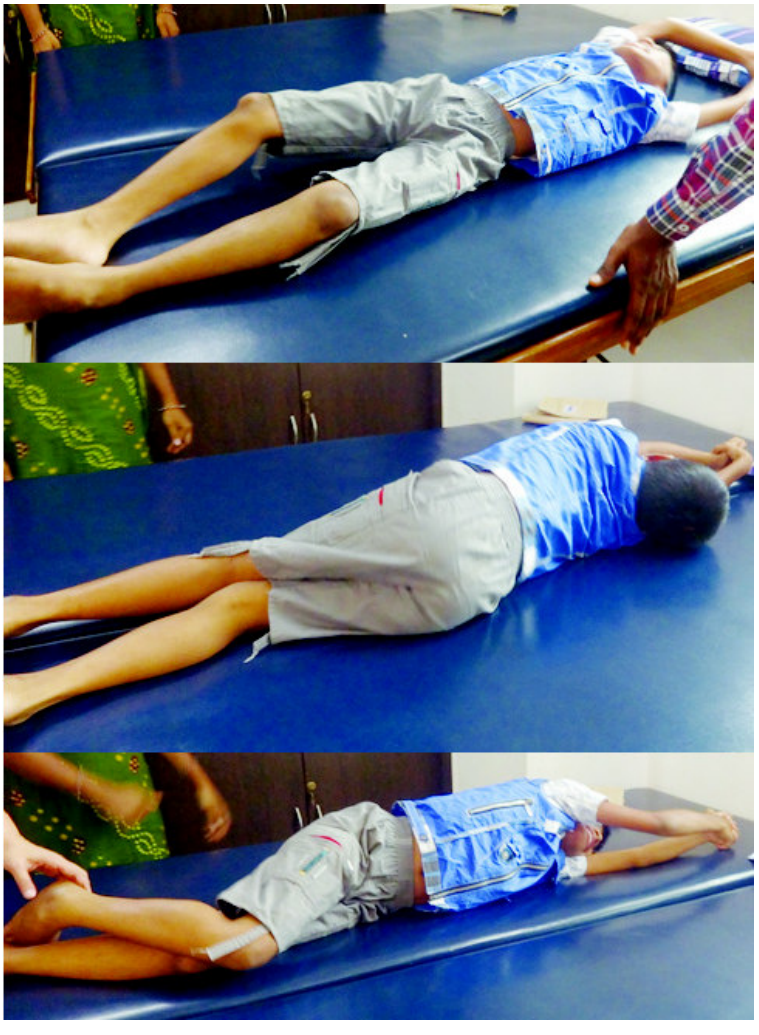


Fig. 10.54

Fig. 10.55

Fig. 10.56

Exercises co-activation of trunk and lower extremity muscles

1. Weigh bearing in All 4's (Figure 10.57)
2. Hip and Knee extension in All 4's (figure 10.58)
3. Cat and camel
4. Side sitting in crawling (Figure 10.59)

Fig. 10.57

Fig. 10.58

Fig. 10.59

Fig. 10.60

Fig. 10.61

Fig. 10.62

Fig. 10.63

Fig. 10.64

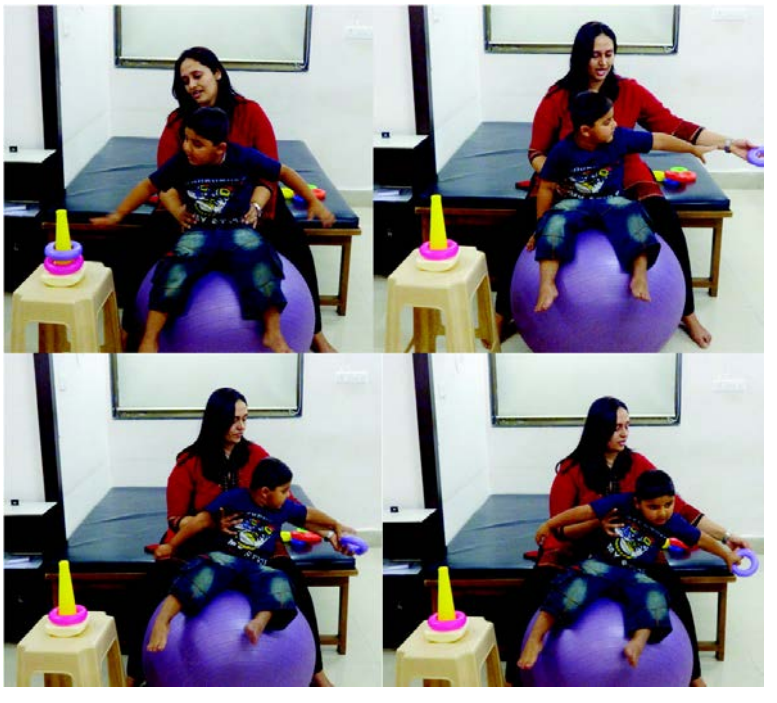


Fig. 10.65 & 10.66

Balance training

1. One leg standing (Figure 10.60)
2. Balance board exercises (Figure 10.61 - 10.64)
3. Vestibular ball exercises (Figure 10.65 & 10.66)

- **Stage 3: Late ambulatory phase**

In the late ambulatory phase the postural compensations are more enhanced and the tightness of the muscles may also accelerate. Children walk with severe arching of the back, waddling from side to side due to weakness of hip muscles and pronounced toe walking. The stability in standing and walking is very poor and they may fall even with a slightest push. Table 4 summarizes the muscle weakness, tightness and postural compensations in this phase.

Goals of Physiotherapy:

- To prevent any falls or fractures.
- To maintain walking with long leg calipers.
- To maintain muscle length.
- To prevent any chest infection.
- To conserve energy.
- To continue daily activities using special equipments like use of wheelchair for covering long distances for saving energy

Table 4: Table describing the muscles undergoing weakness, tightness and resultant postural compensations in Stage III

Muscles that undergo weakness	Muscles that undergo tightness	Postural compensations
Neck flexors	Tendoachilis (Calf muscles)	Severe arching of the back while standing and walking (lumbar lordosis)
Abdominals	Hip Flexors	Walking on toes and minimal waddling
Shoulder flexors	Lower abdominals	Stabilizing the knee with hands while getting up from the chair and floor
Shoulder abductors	Hamstrings	Unable to control descent while sitting down
Shoulder depressers	Ilio-tibial band	Foot turned inwards and downwards
Shoulder extensors		Slouched back while sitting
Elbow extensors		Walking with feet apart
Hip extensors spine		Minimal sideways curvature of the
Hip abductors		
Hip adductors		
Ankle dorsiflexors		
Ankle everters		
Knee extensors		

Type of exercise:

1. Active exercise with moderate resistance and higher repetitions (against gravity)
2. Gait retraining with splints
3. Active and passive stretching for the calves, abdominal muscles, hamstings, iliotibial band and hip flexors
4. Movement and postural corrections
5. Moderate intensity cardio-respiratory endurance training exercises

Stretching exercises:

1. Hamstrings stretching

   Passive (Fig. 10.67) (Fig. 10.68)
2. Iliotibial band stretching

Strengthening exercises:

In the late ambulatory phase the exercises as explained above should be continued. Some of these exercises may require assistance. Gait re-training is the key in this stage in.

Due to weakness of knee extensors, quadriceps, children tend to buckle in their knees while walking. This causes frequent falls and fear avoidance of walking. Therefore depending upon the weakness and tightness of the muscles, assistive devices like knee or ankle splints and modified footwear may be prescribed by your physiotherapist.

Some examples of the splints and shoes are:

1. Push knee splint: It is a simple splint that prevents knee from buckling and bending forward. (Figure 10.69)
2. High boots with posterior steel shanks: These are stiff boots that prevent in turning and down turning of the feet. (figure 10.70)
3. Below knee brace with an outer T-strap: If there is severe tightness of the muscles causing severe in turning of the feet which cannot be stretched to neutral position, then a special shoes with a an above ankle strap and outer strap at the level of ankle bones is prescribed. (Figure 10.71)
4. **Elbow splint:** Elbow splint is like push knee splint that prevents bucking of the elbow when putting weight on the arms. This can be used while performing bed exercises as well as walking. (Figure 10.72)

   For Neck, Shoulder, Elbow, Wrist and hand perform the active exercises as described earlier. Hip exercises can be performed using a suspension device in the gravity eliminated plane that provides assistance. In the late ambulatory phase muscles are still stronger than required for a movement in gravity eliminated plane. Your therapist may add resistance using therapeutic resistance bands.

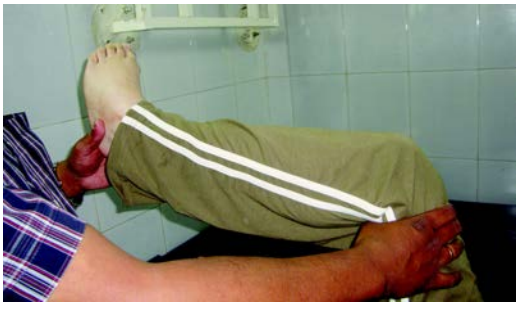


Fig. 10.67

Fig. 10.68

Fig. 10.69

Fig. 10.70

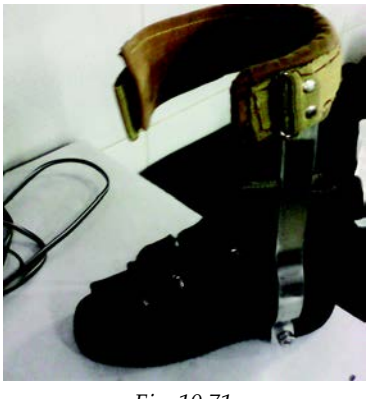


Fig. 10.71

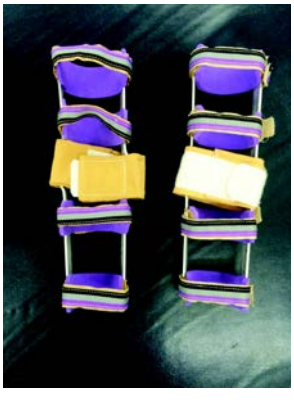


Fig. 10.72

Hip Exercises:

1. Child will lie on the bed with back rested, a push knee splint will be worn on the leg to prevent knee movements. The leg will then be suspended in an overhead suspension frame. The suspension hook should be tied straight above the center of the hip joint to be moved and the supporting sling will be under the heel . Then slowly ask the child to move the leg out and in (Figure 10.73-74).

   Resistance can be applied using the therapeutic resistance band in the direction opposite to the movement (Figure 10.75-76)

2. Child will lie on the bed with back rest now the suspension hook is right above the umbilicus and the supporting sling is attached to the spring. The child is then asked to press both the legs down together (Figure 10.77).

3. Child will lie on one side, the suspension hook right above the hip joint to be moved and the sling attached to a string. The sling will be supported at the ankle and the child will be asked to move the leg forward and backwards. A resistance band can be used in the direction opposite to the movement. (Figure 10.78 & 10.79)

Knee exercises:

1. The child will lie in bed with back rested, a pillow of different heights as deemed fit by the therapist will be places under the knee. The child will be asked to lift the heel up, assistance may be provided if required (Figure 10.80).

2. Alternative a child may be asked to turn to one side with a pillow between the two legs. He will then asked to bend and straighten the knee and the assistance will be provided as required (Figure 10.81).

3. The child will be lying on his tummy and will be asked to bend and straighten the knee (Figure 10.82).

Trunk exercises:

1. Upper abdominals: The children may develop neck flexor weakness during this stage. Because of the head drop behind while performing upper abdominal exercises as explained earlier. To prevent neck discomfort and injury, therapist will support the head while performing this exercise. (Figure 10.83)

2. Lower abdominals: Higher degree of assistance is required for this exercises as well which can be provided manually or by suspension exercises. The suspension hook will be straight above the umbilicus. The child will be asked to straighten the legs and then pull them towards the chest (Figure 10.84).

3. Assisted bridging: As the child is lying on the bed with knees bent, therapist will support the waist and ask the child to lift it as high as possible (figure 10.85).

4. Side twisting: As the child is resting on his back with both the knees bent therapist will ask the child to move both knees together to one side and then to the other side, to initiate a twisting movement of the body. Resistance can be applied with therapeutic resistance bands in the direction opposite to the movement (Figure 10.86).

5. Cat and Camel: The child comes in quadruped position from side lying and arches his back to look up followed by rounding the back to look down. This can be performed with elbow splints to prevent elbows from buckling (Figure 10.87).

Fig. 10.73

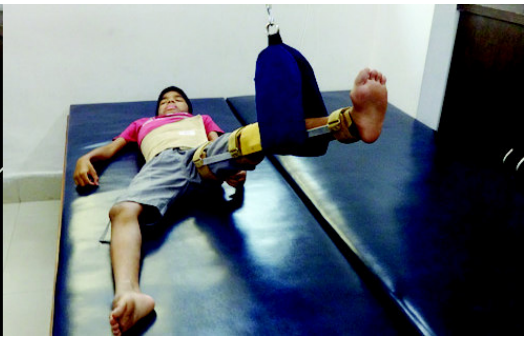


Fig. 10.74

Fig. 10.75

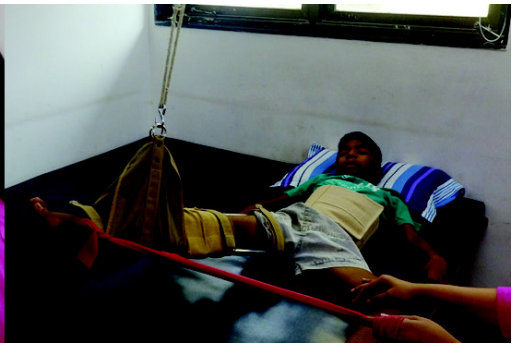


Fig. 10.76

Fig. 10.77

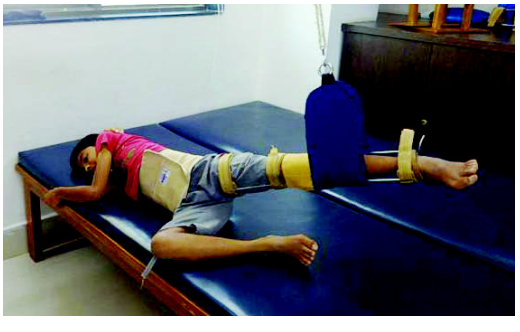


Fig. 10.78

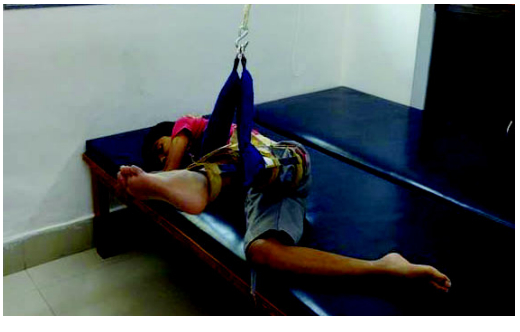


Fig. 10.79

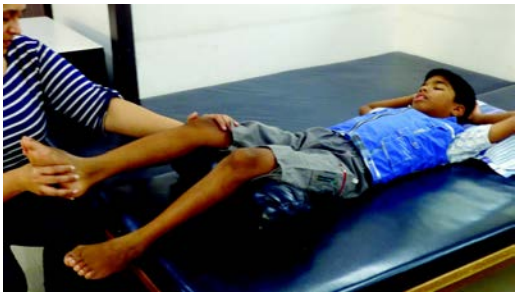


Fig. 10.80

Fig. 10.81

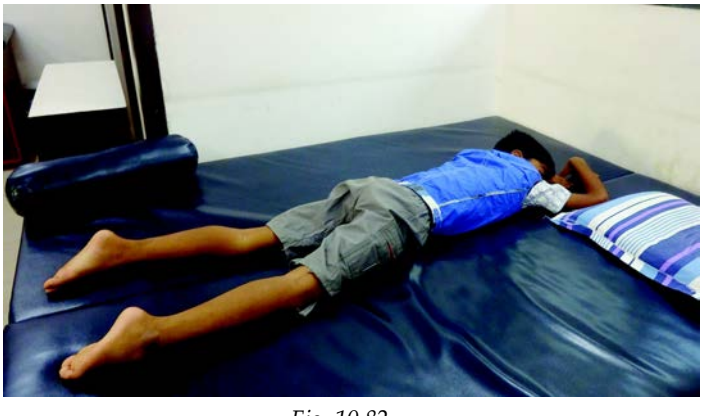


Fig. 10.82

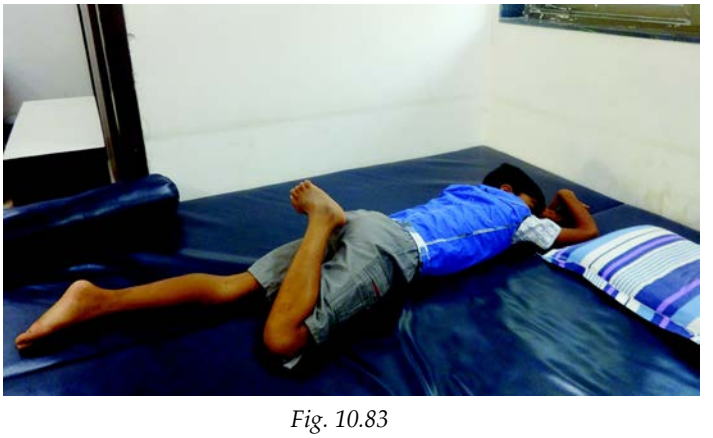


Fig. 10.83

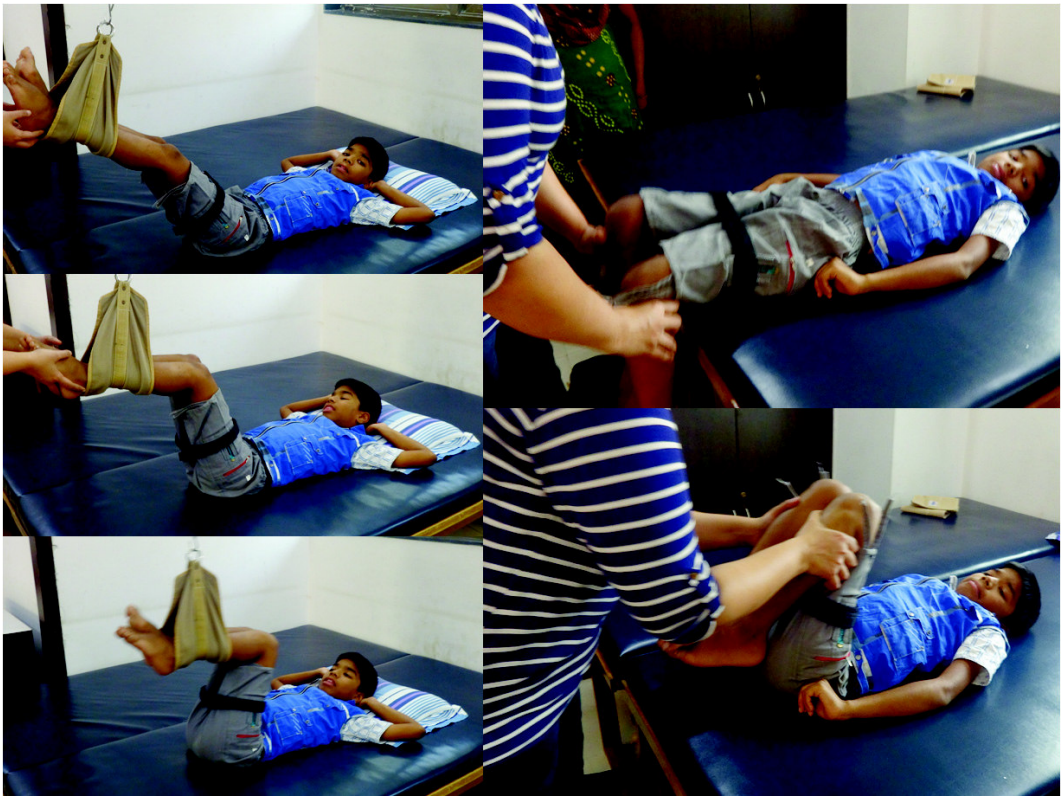


Fig. 10.84

Fig. 10.85

Fig. 10.86

Fig. 10.87

Fig. 10.88

Gait retraining

1. Child will be facilitated to stand wearing the push knee splints on one or both the legs and shoes as required (Figure 10.88).
2. Following this in the parallel bars various exercises like moving the leg forwards, backwards and sideways (Figure 10.89) will be performed.
3. Slowly from parallel bars the child will be facilitated to walk with the support of a walker, then minimal hand support and eventually without any support but with supervision (Figure 10.90 - 91).
4. Once the child is used to the wearing the splint the moving forward with it, balance training exercises will be performed. This includes but is not restricted to balance board exercises, reach out activities, perturbations, stability trained exercises etc.

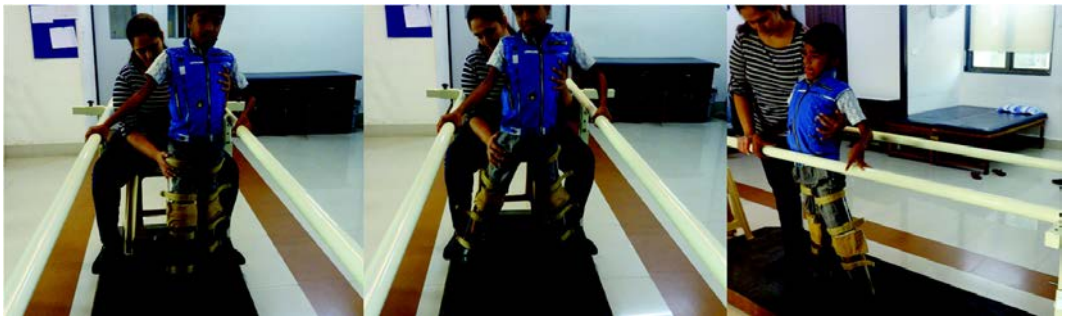


Fig. 10.89

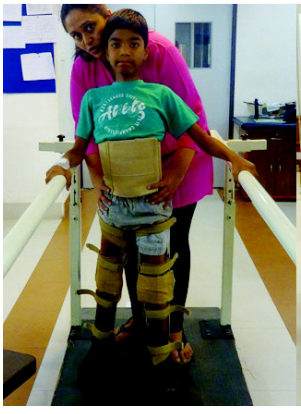


Fig. 10.90

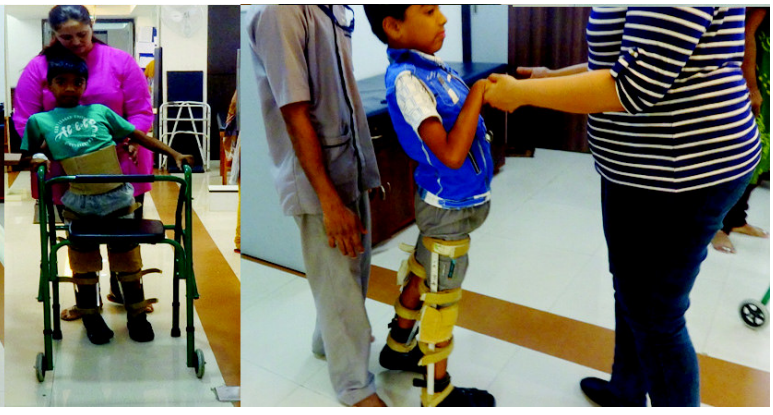


Fig. 10.91

Stage 4: Early Non-ambulatory stage

In the non-ambulatory stage most of the muscles of the big joints like shoulder and hips may show muscle strength below functional level i.e. inability to perform movements against gravity. The exercises in this stage are targeted at the maintenance of muscle strength. Exercises with mild resistance in gravity eliminate plane and active assisted exercises against gravity will be prescribed. Children also show presence of severe postural deviations and start developing scoliosis and spinal deviations. Therefore physiotherapists may prescribe spinal jacket to prevent further deterioration. Cardio-respiratory complications are prevalent in this stage, therefore attention needs to be given to the cardio-respiratory endurance training.

Goals:

- To prevent deterioration of muscle by exercising.
- To prevent contractures and deformities.
- Deep breathing exercises and use of incentive spirometer for improving chest volumes.
- To prevent scoliosis and if it develops, prescription of spinal jacket or spinal support.
- To assess requirement of assistive breathing such as Bi-Pap.
- To continue doing daily activities using special equipments like assistive devices.

Type of exercise:

1. Active assisted exercises with higher repetitions (against gravity)
2. Suspension exercises (in gravity eliminated plane) with moderate resistance and higher repetitions
3. Active and passive stretching for the calves, abdominal muscles, hamstings, iliotibial band, hip flexors, elbow flexors, pronators, and wrist and finger flexors.

4. Movement and postural corrections with supportive devices
5. Moderate intensity cardiorespiratory endurance training exercises

Table V: Showing Muscles that undergo weakness, tightness, Postural compensations

Muscles that undergo weakness	Muscles that undergo tightness	Postural compensations
Neck flexors	Tendoachilis (Calf muscles)	Severe arching of the back while standing and walking (lumbar lordosis)
Abdominals	Hip Flexors	Foot turned inwards and downwards
Shoulder flexors	Lower abdominals	Bent knee attitude / tightness / contracture
Shoulder abductors	Hamstrings	Legs fall outwards when lying straight on the back
Shoulder depressers	Ilio-tibial band	Hips are bent and rise up when an individual is lying facing down
Shoulder extensors	Pyriformis	Severe slouching while sitting
Elbow extensors	Elbow flexors	Prominent sideways curvature of the spine
Hip extensors	Pronators	Legs fall out in lying position with knees bent
Hip abductors	Wrist flexors	The alignment of shin bones and thighs is changed and shin bones are turned outwards
Hip adductors	Finger flexors	
Knee Extensors	Hip external rotators and abductors	
Ankle dorsiflexors		
Ankle everters		

Stretching exercises:

1. ***Elbow Flexors stretching:***

   Passive: Rest the arm of the patient on the pillow. The stretching can performed either in sitting or lying down. Gently straighten the elbow till a firm resistance is felt maintain. Maintain the position for 30 seconds.

2. ***Pronator stretching:***

   In the same position as hat of elbow stretching turn the arm to face the palm upwards, stretch till you feel a distinct resistance. Hold for 30 seconds.

3. ***Wrist and finger flexors stretching:***

   Rest the arm on pillow keeping the elbow and finger straight, push the wrist palm of the patient upwards. Hold for 30 seconds. If the muscles are very tight the same can be performed with fists closed.

Strengthening exercises

Trunk, hip and knee exercises are performed same as the previous stage but may require more support. The child may be unable to perform exercises against resistance and may only perform active movements.

Shoulder exercises:

1. As the child is resting on the back, the suspension hook is put right above the shoulder joint. Wrist is supported in the sling. The child then moves the arm away from the body and towards the body; if required the therapist may provide resistance to the movement using the therapeutic resistance band in the direction opposite to the movement. (Figure 10.93 and 10.94)
2. The child turns to one side with the same position of suspension hook and sling and moves the arm forward and backward. if required the therapist may provide resistance to the movement using the therapeutic resistance band in the direction opposite to the movement.

Elbow exercises:

1. The child is seated or lying on his back, two slings support the arm. One sling suspended on a hook straight above shoulder joint and placed under the arm. The sling supports the wrist. Child is then asked to move the forearm only to bend and straighten the elbow.

Wrist and finger exercises can still be performed actively by most of the children even in the late non-ambulatory stage. These exercises are the same as that showed in stage I.

Passive positioning:

The most important therapeutic component in this stage is passive positioning. As the children lose their walking ability, weight bearing on the lower extremity reduces which can enhance the process of thinning of bones and bone porosity. Porous bones become brittle and are at risk of fracturing with minimal trauma. Sometimes while lifting the child or transferring the child from one place to another the bones can suffer fracture (stress fracture). With use of steroids the bone density reduces and such bones are at a greater risk of fractures. Increased body weight is another contributing factor for such fractures. Therefore passive positioning and weight bearing is required to facilitate increase in the bone density.

Weight bearing on the lower extremities can be achieved in various positions like kneeling on the knees, quadruped and standing. All these positions can be achieved with varying degrees of support, with the help of vestibular ball while performing quadruped and kneeling (Figure 10.97). For standing suspended standing can be performed or a child can be support on standing board with the help chest, abdominal and knee straps (Figure 10.98).

Facial Exercises

As the muscles of the face and swallowing also undergo weakness in this stage, facial exercises for facial muscles, tongue execises are recommended (Figure 10.99 & 100)

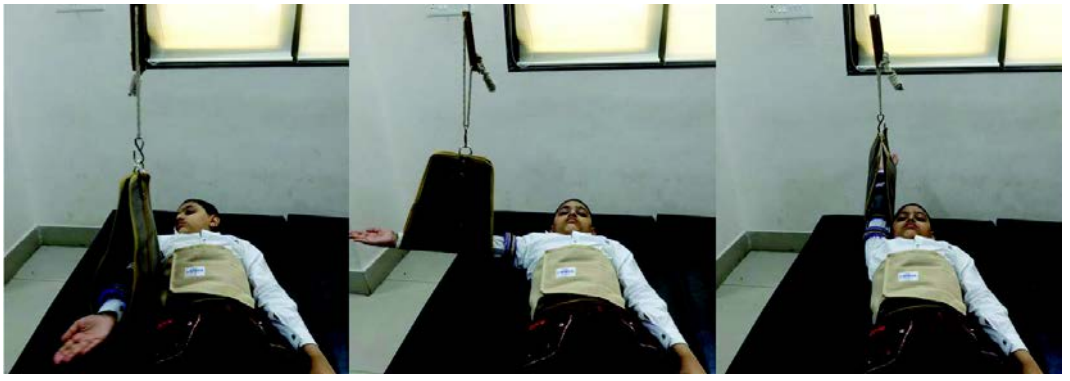


Fig. 10.93-94

Fig. 10.95-96

Fig. 10.97

Fig. 10.98

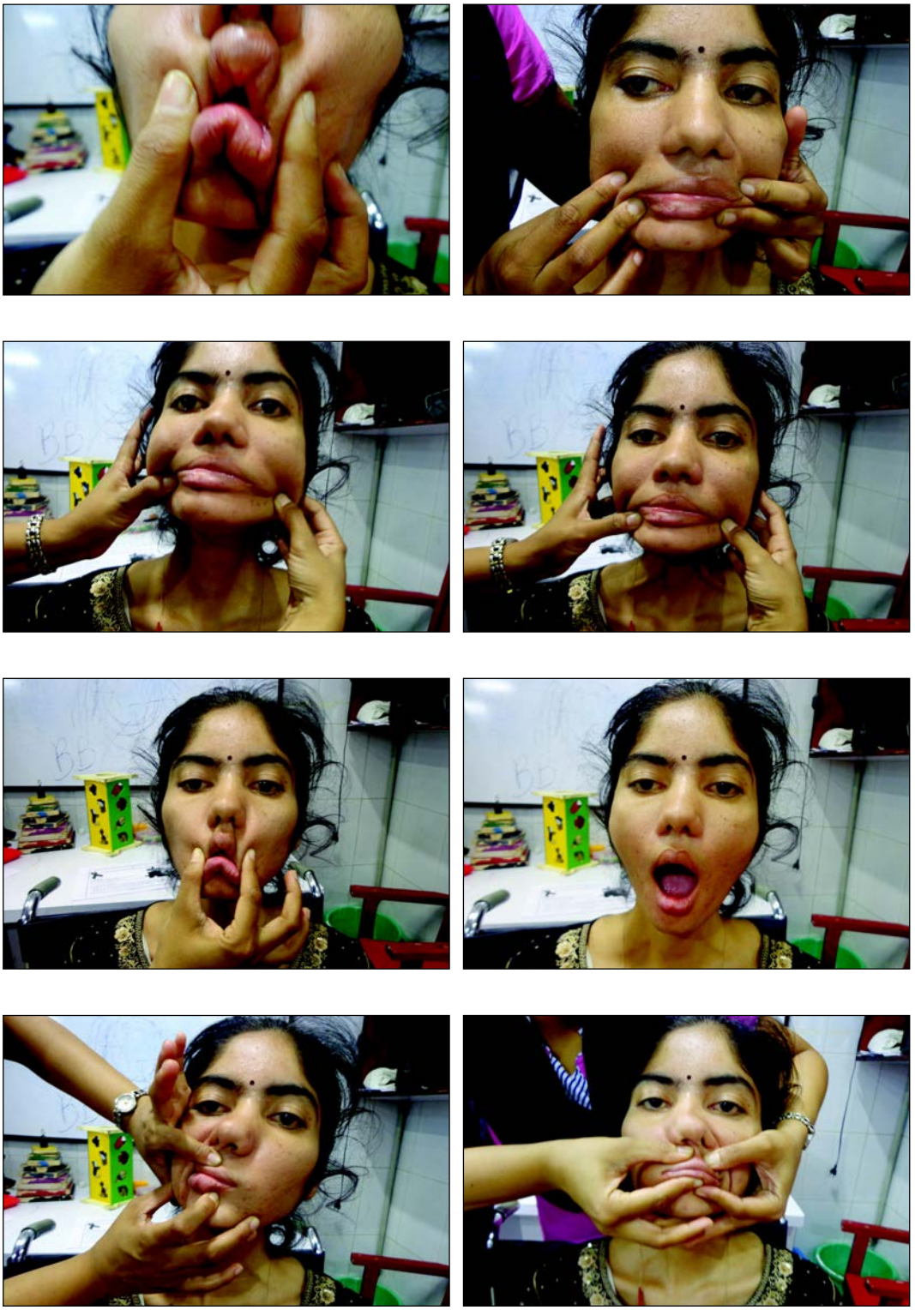


Fig. 10.99

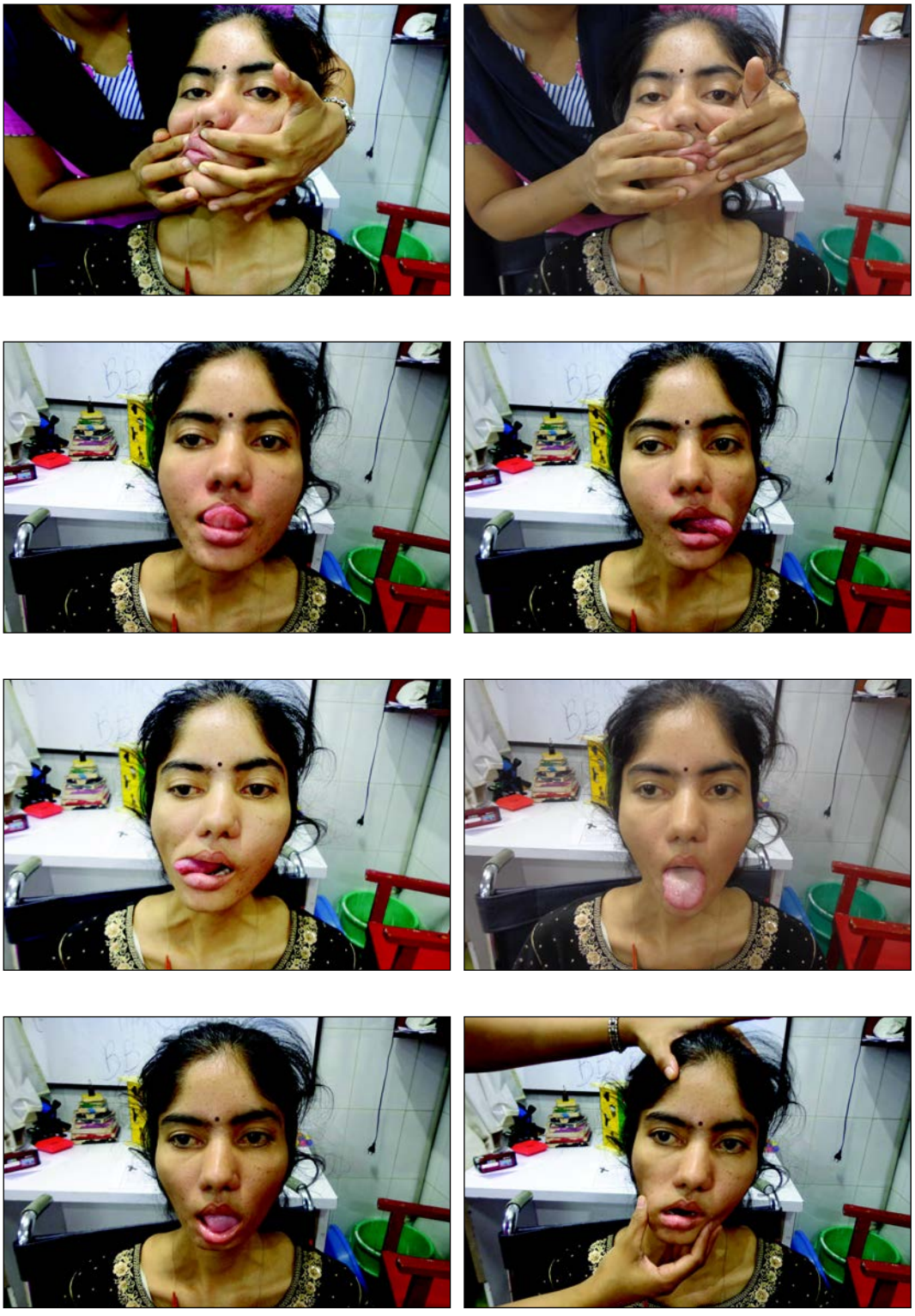


Fig. 10.100

Stage 5: Late non-ambulatory

In late ambulatory stage the physiotherapy care is more palliative. Most of the skeletal muscles have poor muscle strength and many joints may have undergone contractures.

Goals:

- To continue exercises to maintain muscle strength.
- To prevent worsening of the contractures and deformities.
- Deep breathing exercises and use of incentive spirometer for improving chest volume.
- Prescription of spinal jacket to improve posture and help in breathing.
- To assess requirement of assistive breathing such as BiPap.
- To continue doing daily activities using special equipment.
- To ensure proper to prevent pressure sores.
- To clear the chest of secretions.

Types of exercises:

1. Passive stretching
2. Passive positioning
3. Suspension exercises (Active assisted / passive)
4. Cardio-respiratory endurance
5. Secretion clearance exercises

It is of immense importance to perform regular physiotherapy exercises from early stages in muscular dystrophy to prevent rapid deterioration and maintain muscle function for as long as possible. Rehabilitation of muscular dystrophy is a multidisciplinary approach where the family members perform a very important role. Awareness of the family members towards rehabilitation ensures good and timely rehab for the patients. In later stages when the exercises cannot be performed actively passive exercises are required to be performed passively by the family members and caretakers.

11.

Aquatic therapy

Aquatic therapy is one of the most widely used rehabilitative techniques for muscular dystrophy. Aquatic therapy means making use of different physical and chemical properties of water to facilitate functional recovery, independence, prevent complications and slow down the damage to the muscles in individuals with muscular dystrophy. Aquatic therapy is defined by The Aquatic Therapy and Rehabilitation Institute as "The use of water and specifically designed activity by qualified personnel to aid in the restoration, extension, maintenance and quality of function for persons with acute, transient, or chronic disabilities, syndromes or diseases".

Benefits of aquatic therapy in Muscular dystrophy

- Reduce the work of the muscles thereby preventing accelerated muscle damage.
- It prevents the eccentric contractions of the muscles while performing various movements and therefore helps reduce the muscle damage.
- It improves the blood supply to the deeper muscles and helps to slow down the fibrotic processes.
- It provides a higher degree of freedom of movement which helps in boosting the morale, move the joints through their full range preventing secondary complications like muscle tightness, contractures and cardio-respiratory complications.
- It has a distinct physiological mood enhancing effect which may prevent negative emotional responses in individuals with muscular dystrophy.
- There is also improved blood supply to the brain improving the cognition in some cases of muscular dystrophy with co-morbid intellectual disability.
- In the later stages of the disease when the spinal deformities set in water environment provides freedom to unload and stretch the spine preventing some of the detrimental effects of the same.
- Aquatic therapy also improves respiratory capacity and cardiovascular endurance.

- Aquatic therapy and warm water exercises have pain reducing effect while stretching the muscle contractures, it also makes the muscles more pliable and easy to stretch.
- Increased blood supply, hydrostatic pressure of the water, improved endorphins and serotonin levels also helps to improve appetite and bowel movements. In the later stages of the disease it can prevent complications like severe constipation.
- Aquatic exercises help reduce sleep disturbances.

Properties of water

1. Buoyancy

Buoyancy is the upward push that water exerts on the immersed body. It is responsible for the weightlessness experienced in water. Deeper the immersion greater is the weightlessness. If the child is immersed till umbilical level then the effective weight on the legs is reduced by 50% and when immersed chest deep it is reduced by 75%.

Weightlessness is a very important phenomenon for therapeutic benefit. Weight bearing joints like ankle, knee and hip joints can be offloaded in water which helps reducing the stiffness of the muscles. Therapeutically this can be used to relieve the compressive forces on the joints and reduce the lengthening contractions (eccentric work) of the muscles. These lengthening contractions bring about accelerated muscle damage and therefore the exercises performed in water can give strength benefits without the harmful muscle contractions.

2. Hydrostatic Pressure

Is the pressure exerted by water and depends upon the density as well as the depth of immersion. The deeper we immerse the child the greater is the force. This is particularly helpful for reducing the swelling and providing passive relaxation through deep pressure. Hydrostatic pressure is also important to push the blood from the legs and thighs up increasing the blood returning to the heart. This also helps in increasing blood supply to the brain and therefore cognitive functions. The increased blood supply to heart is important for good cardiovascular health.

3. Density

Water is thicker or denser than the air. The density of water is more than the air and almost similar to human body. The density of water is important therapeutically as it is this quality of water that supports the child once immersed in water and also exerts an upward force. Because of the difference in the densities of various tissues in the body, a leaner child with lesser fat tissue will tend to sink more in the water whereas individuals with more fat tissue will tend to float.

4. Viscosity

Viscosity of water is the amount of friction generated with a movement in water. The friction is significantly higher in water than air which provides resistance to any movement of the body. This makes water an excellent strengthening tool. The

resistance provided by the water is dependent upon the speed of the movement and direction of the movements which are patient dependent. In painful conditions if the patients stops the movement the resistance drops to zero and therefore the strengthening activities can be performed within the limits of patient's tolerance.

These unique properties of water provide desirable environment for the individuals with muscular dystrophy. Immersion in water brings about beneficial effects in various body systems of a child with muscular dystrophy.

Beneficial effects of water immersion

Muscles and bone

Immersion in the water increases the blood returning to the heart and in turn the blood delivered to all the organs. Most of this blood is supplied to skin and muscle tissue. Blood supply to the deep muscles increases nearly threefold during chest level immersion. Improved blood supply helps slow down the pro-fibrotic processes in the muscles. In addition to this as the muscles don't have to perform lengthening contractions for movements in water, the damage to the muscles is minimized and therefore the fibrotic processes are further slowed down. Immersion offloads the joints facilitating relaxation of the muscles and smooth movements. The resistance provided by viscosity of water for any kind of the movement helps in stabilizing the tone and strengthening the muscles. Improved circulation helps improve flexibility and pliability of the muscles. Reduced fibrotic processes , improved pliability and strength of the muscles, prevents the secondary tightness and contractures.

Most of the individuals with muscular dystrophy develop osteopenia (reduced density of bones) or osteoporosis (brittle bones) in the later stage of the disease due to not bearing weight on their extremities. Most of the individuals are on regular steroids which cause osteoporosis after prolonged consumption. The bone density therefore is a concern. Aquatic exercise helps to increase the bone density.

Heart and lungs

Water exerts compressive pressure on the blood vessels and pumps up the blood from limbs to the heart. In individuals with muscular dystrophy because of inactivity, muscle weakness and secondary contractures and tightness the blood circulation is sluggish. This causes the blood to be pooled in the extremities and toxic waste to be accumulated. Immersion in water helps clear the toxic wastes. Improved blood pumping in the heart also provides heart with more blood to pump out improving the blood supply to the lungs and better oxygenation of the blood.

Compressive forces of the water provide resistance to the respiratory muscles (muscles required for breathing) and help strengthening these muscles. Exhalation or breathing out is passive rebound compression of the rib cage. In muscular dystrophy due to tightness of muscles and deformities there is incomplete exhalation of the air. Air is exhaled from only the upper parts of the lungs but accumulates in lower parts. Such accumulation could have various detrimental effects on the body. Immersion in water compresses the rib cage helping in better exhalation and lesser accumulation.

Brain and Nervous system

Increased blood supply to the brain leads to improvement in memory and other cognitive symptoms. The child is more attentive in the water. Water immersion facilitates stimulation of para-sympathetic nervous system which facilitates relaxation of the body and suppression of the sympathetic nervous system that is responsible for the responses of anxiety. Immersion in water therefore facilitates relaxation and further suppression of the fibrotic processes.

These beneficial effects of water immersion are used by for therapeutic benefit by aquatic professionals. It is important to understand that although immersion in water is beneficial, goal oriented and targeted exercises are required for optimum recovery and maintenance of the individuals with muscular dystrophy.

Aquatic exercises increase serum endorphin (hormone responsible for mood elevation) levels and levels of neurotransmitter serotonin which are responsible for reducing pain and controlling many functions like sleep, appetite but mainly mood. Aquatic exercises have a psychological mood elevating effect.

What to expect in an aquatic therapy session?

Aquatic therapy does not mean just swimming in water. Aquatic therapy includes purposeful therapeutic movements or exercises performed in order to achieve optimum benefits for the individuals with muscular dystrophy. There are various techniques in aquatic therapy. An exercises session will consist of a combination of these techniques and approaches like Halliwick therapy, Bad-Ragaz ring method, Clinical Ai-Chi, Aquatic exercises, Aqua aerobics and Passive relaxation or Watsu. Mostly in muscular dystrophy an exercise session will be conducted one - on - one by the therapist but group sessions may also be conducted to improve participation and peer interaction.

In the beginning the exercise session will emphasize on adaptation to water environment and being comfortable in water. Therapist may choose to engage the patient in various play activities on the surface of the water. This will be followed by respiratory and oromotor control in water where the child will slowly be introduced to under water environment facilitating better breath control. Various play activities like pushing the balloons, balls or other objects by blowing on them, making a well in the water, blowing bubbles in the water, flipping discs in the water by blowing on them may be used to improve the breath control.

Once the child is comfortable in water and has achieved good breathing control, various rigorous goal oriented activities will be performed during subsequent exercise sessions.

Stage I:

In the pre-symptomatic stage the goal of aquatic therapy is to train the muscles for various movements and strengthen them within the fatigue range. A combination of all the approaches as mentioned above can be used with emphasis of active movements. Individuals can be taught to swim during the pre-symptomatic stage. Stretching and

relaxation exercises may not be required and the therapist may perform these infrequently.

Stage II:

As the symptoms become evident strengthening of the specific muscles using above mentioned techniques will be undertaken. Also in the early ambulatory stage walking in the correct gait pattern will be facilitated in the water to prevent postural deviations. Stretching exercises will be performed more frequently. Cardiovascular and respiratory training will be undertaken.

Stage III:

In the late ambulatory stage aquatic exercises are important to facilitate appropriate gait patterns. Postural compensations can be prevented in water and therefore the muscles can be strengthened in a functional position. Stretching exercises will be performed regularly in this stage.

Stage IV:

In the early non ambulatory stage individuals may still be able to ambulate with or without support in water and therefore correct ambulatory patterns can be facilitated and physiological benefits of walking can be provided to the patient. This may also help in preventing or reducing the negative emotional responses and improve peer interaction. In this stage the main focus of aquatic therapy is on preventing secondary cardio-respiratory complications. The individuals can swim to improve the cardiovascular endurance. Specific respiratory exercises will be taught by the therapist. Apart from maintaining the healthy heart and lungs, aquatic therapy in this stage is important to facilitate peer interactions. It provides individuals with an activity to carry out as well as their peers and friends and provide an opportunity for equal participation.

Stage V:

In the late ambulatory stage if the secondary cardio-respiratory complications have already developed vertical immersion in water needs to be done with caution. The work of breathing increases by 60% during chest deep immersion and the individuals with compromised respiratory system may find it difficult to breathe. Also the work of heart increases during such immersion and therefore such immersion should be carried out strictly under the supervision of the therapist. Exercises with lesser degree of immersion can be performed without any risk. The mainstay of this stage is to maintain cardio-respiratory health, facilitate full range joint movements with passive or active but assisted exercises and stretch the contractures.

What precautions to take during and after an exercises session

- Consume plenty of water during the exercise session
- Make sure to empty the bladder and bowel of the child before immersion to prevent accidents in water and soiling

- If the child needs to sit on the edge, to enter and exit the pool then carry a mat on which child can sit to avoid aberrations and wounds
- Make sure that there is no open wound on the body

Is aquatic therapy an alternative to land based therapy?

No, aquatic therapy is not an alternative but a conjunct to it. Land based rehabilitation and aquatic rehabilitation needs to be performed together. Neither is alternative to the other. Although there are some advantages of aquatic rehabilitation as compared to the land based rehabilitation both are essential for optimum recovery.

Benefits of aquatic therapy over land based therapy

- There is less weight on the joints, the child is well supported and joints are not under stress like on land. Therefore aquatic therapy helps achieve the benefits of land based therapy without causing any harm to the joints.
- As the individuals are able to perform the tasks in water much easier than on land, their confidence and activity participation increases.
- Activities in water are more fun and interesting for the individuals therefore there is better engagement of the individuals in a session and better adherence to therapy than on land.
- For individuals with severe movement restriction on land. Aquatic environment provides some freedom for movement.
- The risk of fall significantly reduces in aquatic environment
- As the frequency for lengthening contractions in the water environment is much lesser than on land the damage to the muscles while exercising is lesser
- It improves blood circulation to the deeper muscles better than on land and improves pliability of the muscles.
- The fibrotic changes in the muscles are lesser than on land

Therefore aquatic therapy may be preferred for some activities and during some stages of the disease. It provides an excellent medium to train the individual and improve their motor impairments. It is fun and enjoyable ensuring long term adherence. It helps to maintain various cardio-respiratory health parameters. It is safe and very effective in improving the quality of life of individuals with muscular dystrophy. However aquatic therapy alone is not sufficient and must be incorporated in the multidisciplinary rehabilitation program including land based exercises.

12.

Occupational Therapy

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 carers are constantly changing. They need to assess and evaluate an individual's physical, psychological and social needs and focus on maximising 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 centred treatment goals. The initial step in management of an individual 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
- 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

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

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.

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 Range of motion 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 will decrease the severity of symptoms during episodes of colds or other pulmonary infections.

Game activities such as inflating balloons or using blow-bottles to maintain pulmonary function can easily be included in a home program. Night splints are helpful to slow the progression of contractures.

Play

In children, 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

In adults and children, 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. An individual in the early stages of muscular dystrophy will enjoy riding and it is a good exercise for helping them to maintain their balance .

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 upper limb function; these include reading and creative writing, painting, photography, graphic art and some crafts, such as model-making.

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

The progression of muscular dystrophy over time leads to loss of functions in personal care activicties thereby increasing dependency on the caregivers.

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 (Fig 12.1)
- rocker knife;
- cuffs with inserts for cutlery;
- Plate with a rim to contain the food when scooping; (Fig 12.2, 12.3)
- non-slip mats; (fig. 12.4)
- mechanical eating aids
- long straw for drinks(12.5)

Other alternatives such as elevating the plate height, and angled cutlery will minimize the amount of active arm, wrist and hand movement required (Fig. 12.6, 12.7). Mobile arm supports provides support to the forearm to facilitate eating and drinking.

Fig 12-1 : Two handled mug

Fig 12-2 : Plate Guard 1

Fig 12-3 : High rimmed eating untensil

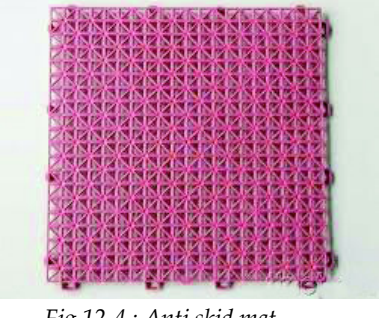


Fig 12-4 : Anti skid mat

Fig 12-5 : Straw holder

Fig 12-6 : Mobile arm support

Fig 12-7 : 'Arm thing'

Grooming

Consideration should be paid to the design features of items of equipment for shaving, (Fig. 12.8, 12.9, 12.10), combing hair such as long-handled brush/comb, (Fig. 12.11) and cleaning teeth, including weight and the type of grip (Fig. 12.12& 12.13). 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.

Fig 12-8: Foam based shaving cream

Fig 12-9 : Enlarged handle of toothbrush & razor

Fig 12-10 : Electric shaver

Fig 12-11 : Long handle comb

Fig 12-12 : Toothbrush

Fig 12-13 : Toothpaste dispensor

Fig 12-14 : Soap on a string

Fig 12-15 : Soap on mitt

Fig.12-16: Long handled body brush

Bathing

Bath board and shower aids such as hand held shower, non skid mats, bathing soaps on strings, (Fig. 12.14), hand mitt with pouch for soap,(Fig 12.15) soap dispensers, long hand scrubers or sponge (Fig. 12.16) 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 (fig 12.17) 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 (Fig. 12.18)can be made and various sorts of fastenings can be considered, such as Velcro and hooks. (Fig. 12.19 and 12.20)

Fig 12-17 : Velro clothing

Fig 12-18 : Zip puller

Fig 12-19 Dressing-aid-stick

Fig 12-20 : Velcro sandals

Fig 12-21 : Raised seat

Fig 12-22 Commode Chair

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 (12.21 and 12.22) 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 (12.23).

This type of support generally falls into two categories:

- support which wheels over the toilet (Fig. 12.24);
- frames which fix onto the toilet itself (Fig 12.25).

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 (College of Occupational Therapists, 2006b). Some of the common moving and handling equipment supplied by therapists are listed below:

- transfer boards; (Fig. 12.26)
- hoists and slings; (Fig. 12.27)
- sliding sheets; (Fig. 12.28)
- handling belts. (Fig. 12.29)

Raising the height of beds (Fig. 12.30) and chairs from the floor (Fig. 12.31) 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 diffi culties. 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

Fig 12-23 : Grab bars & railings

Fig 12-24 : Potty chair

Fig 12-25 : Raised seats 1

Fig 12.26 : Transfer boards

Fig 12.26 Transfer boards

Fig 12-27 : Hoists

Fig 12-28 : Sliding sheet

Fig 12-29 : Handling belt

Fig 12-30 : Blockls under bed

Fig 12-31 : Block raisers

Fig 12-32 : Hospital bed

Fig 12-33 : Matress overlays

positions that the young person will need. This is essential to minimise 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 (Fig. 12.32) Firm mattresses maybe used for easier shifting in bed. Mattress overlays made from foam, rubber, gels designed to be comfortable and encourage good blood circulation to the skin (Fig. 12.33).

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 for pressure relief to reduce the risk of contractures, deformities and pressure source. ; to maintain functional ability; and to maximise 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. Good postural support may also help to preserve chest and lung function 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.

Initially, only a manual wheelchair may be required for use. Basic requirements of a wheelchair include a firm seat and back, seating to support good posture, removable arm rests and swing-away footrests. Lap boards can be used to do table activities instead of moving to a chair (Fig. 12.34)

When the muscles of the arms become weaker, propelling a wheelchair may become difficult, in which case, using a wheelchair which is electronically operated may be a better option. When a person cannot sit for a long time in a straight position, a reclining back rest can also be thought about (12.35).

Wheelchairs are also available which move the person from a sitting position to fully supported standing position just at the press of a button. Gradually with time, a trunk strap and head & neck support will be also required (12.36).

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

Fig 12-34 : Manual wheelchair

Fig 12-35 : Eletronic wheelchair

Fig 12-36 : Sit to stand wheelchair

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 using motorized scooters or car modifications.

Scooters

A motorized scooter is helpful when walking long distances is difficult and tiring. Scooters can be used only by a person who is able to sit straight for a long period of time, has fair arm strength & fine motor control.

There are several options to choose from when buying a scooter: three- or fourwheeled models for balancing.

Some models are made of very light materials, designed to be dismantled for transporting, for example, in the boot of a car, boat, airplane or train (Fig. 12.37 &38)

Cars

Hand operated controls enable persons with muscular dystrophy to drive a car long after they stop walking.

The brakes, accelerator and the clutch are all controlled by hands. There are a variety of hand controls on the market but the best one should be decided along with the caregiver, patient & therapist.

Some cars also can also have ramps which allow the person to enter the car on the wheelchair (12.39&40).

Fig 12-37 : Scooters

Fig 12-38 : Modified mobikes for physically handicap

Fig 12-39 : Hand controls in car

Fig 12-40 : Ramps in cars

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 (Fig. 12.41, 42 & 43), word-recognition software and joystick (Fig. 44) 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.

Fig 12-41 : Touch pad keyboards

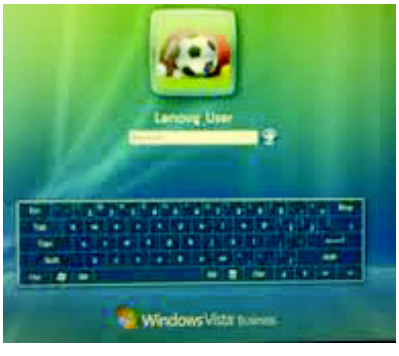


Fig 12-42 : On screen keyboard

Fig 12-43 : Touch screen mouse

Fig 12-44 : Finger touch pad joystick

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 carers. A few are listed below:

- ramps; (Fig. 12.45)
- bathroom alterations
- extensions;

- handrails; (12.46 & 12.47)
- door alterations; (12.48 & 12.49)
- hoists; (12.50)
- lifts. (Fig. 12.51)

Fig 12-46 : Hand rails

Fig 12-47 : Hand rails

Fig 12-48 : Sliding doors

Fig 12-49 : Remote operated doors

Fig 12-50 : Hoists

Fig 12-51 : Hoists

In the classroom

- Ideally, the classroom should be located on ground floor or the school should have the facility of a lift.
- Height of the chair and table should be adjusted to encourage independence for as long as possible and for ease in getting up.
- The child's chair should be near the door on the first bench for him to reach it easily.

- The child should be allowed to leave before others (10 mins before time) when leaving the classroom or remain until the last person leaves, to avoid rush in corridors.
- Photocopies of notes could be provided to the children instead of noting down.
- The child should be allowed to use a laptop computer to enable him to keep up with school work, as writing will become harder with time.
- Additional time should be given to complete class work & writing exam papers.
- As the weakness progresses, when the child becomes unable to write, exams should be taken in the form of orals instead of written or a writer should be provided.
- Sports period should be adapted for the muscular dystrophy kid, for e.g. playing with a ball, cricket and badminton in sitting. Later on, games like chess, carom or scrabble etc. can be given.
- The desk should have a locker facility in which a second copy of all the books can be kept instead of carrying a bag from home.
- The other kids at school can take turns with helping the child by giving support while walking, carrying books/bag for the next class or copying notes, etc.
- Additionally, all kids with Muscular Dystrophy should: Be given short breaks as needed. Be allowed to play physical games at their own pace.

At work

- Jobs which involve sitting activities like supervising, taking calls, teaching are more suitable vocations for muscular dystrophy affected persons.
- But jobs which require more of standing or travelling (especially using public transport), climbing stairs, bending are not advisable.
- Lifts should be used if available instead of climbing stairs
- Revolving chair could be used when the office is not wheelchair accessible. It helps in moving around independently or is easier when one needs to be pushed by someone else.
- For any other chair, a raised chair could be used with a table of suitable height.
- Computer could be used instead of writing.
- Special keyboard, mouse, etc for helps in energy saving.
- Shelves should be positioned at easily reachable levels e.g. (waist level).
- Grab bars or railings in toilets should be installed.
- Raised toilet seat should be used.

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 detioration
- 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:

- pencil grip (Fig. 12.52), angled writing boards (Fig. 12.53), 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.

Fig. 12.52 : Pencil grip

Figure 12.53 : Tilted writting boards modifications for writting

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.

Supporting elbows on the wash basin while brushing teeth. Below are some very simple adaptations which can be used to achieve the desired result:

- Dress/bathe/brush teeth by sitting instead of standing.
- When walking has stopped, the person can crawl while moving in the house.
- Bend from waist & neck while combing hair or eating when overhead activities are difficult (Fig. 12.54, 12.55&12.56)
- Bend on high level table/bed while doing upper body dressing/undressing.
- When washing hair, take support by sliding hands up the wall to reach the head.
- For eating, brushing or combing hair, support the elbow with the other hand or on a few books or pillows or a high table at shoulder level, to help in bringing the hand to the face.
- While wearing shoes, fold one leg and put it on the other so that putting shoes on the bent leg is easier.
- When chewing and swallowing muscles become weak, eat soft/mashed foods.

Fig 12-54 : Brushing

Fig 12-55 : Combing

Fig 12-56 : Eating

Fig 12-57 : Call Switch

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 carers 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: Late non-ambulatory

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 carer to their needs (Fig. 12.57).

Transfers: Moving and Handling

Moving and handling needs and the needs of the individual's and carers 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. 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. Carers 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.
- 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 carer'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 carers?
- 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 (Harpin, 2003) 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 carer 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 ofhis 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.

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.

13.

Speech Therapy

Introduction

Parents of DMD/BMD children have noticed that as their age increases and the muscle deterioration progresses, speech also seems to get affected. This in most cases is due to hypertrophy of the tongue muscles. Slowly, swallowing and respiratory problems also ensues. Hence, it is important to identify speech (respiratory/ voice), swallowing, language, and cognitive-linguistic difficulties at the earliest, so that timely intervention can be done.

An attempt has been made herein to present the clinical profiles seen in children and adults with Muscular Dystrophy and the intervention program as suited for that profile. The authors do not promise infallible profiles and their accurate intervention programs as there may be a lot of variability within the same level and same type of MD. Hence an attempt is made to give clinical profiles likely to be seen at each level along with suggestions for therapy at each level. This may hold true for only about 40% of persons with Duchenne MD and Becker MD.. Thus it is only meant to give basic guidelines to care givers and allied rehab professionals or even beginning ASLP professionals who would be working with children and adults with MD.

Attention should be paid to the following points and the level of difficulty should be noted:

- Did the child cry immediately after birth. • Did neck holding, turning, sitting, crawling, standing with support, walking, saying /ma/, /pa/, /ba/, /a/, /e/, /u/ and uttering meaningful first words occur as per age or was there any delay.
- Does the child have poor attention, thinking, reasoning [inquisitiveness].
- Is there any difficulty in moving the tongue adequately within the oral cavity, rolling on lips, touching palate, flapping to say /r/, lifting posterior to say /k/ or coughing, swallowing. Does the tongue appear thick and protrude out.
- Is there any difficulty in puffing cheeks, blowing, sucking, chewing, and biting?
- Do the lips remain wet always & need to be wiped periodically.

- Is breathing from the nose more laborious? Are there complaints of lack of stamina and breathlessness?
- Is there any difficulty in lifting things?
- Is there a voice change, more towards a nasal tone?
- Does the face lack expressions and appear mask like.
- Does the child complain about reading, writing [errors in spelling & identifying letters] and complex language abilities like creating a detailed story on any topic etc?
- Is the child's speech difficult for a listener to understand? Here are some simple exercises that can be done at home to reduce above mentioned

In case of those persons with other types of muscular dystrophy, at levels of early and advanced levels, the former may match with the first three levels (Levels I,II and III) and the latter with the Levels IV and V given for DMD and BMD. Hence no separate profiles have been given for the other types of MD. The concerned professional could match a particular profile with the ones given below and apply the therapy regimen given for the profile it matches best.

The classification followed is as given below:-

Level I Pre-symptomatic

Level II Early ambulatory

Level III Late Ambulatory

Level IV Early Non-ambulatory

Level V Late Non- ambulatory

LEVEL I- Pre-symptomatic

May not need any active therapy at this stage of the disease which may be in the period close to the diagnosis of the disease if it is identified earlier in the day.

Speech

There appears to be a slight change in finer aspects of motor development and behavior and hence speech being a very coordinated accuracy driven function may show some deviations.

Some may show less number of words per breath or run out of breath for last words of breath. In terms of voice and voice control, a person with Muscular Dystrophy (PMD) may not have a very wide pitch range and may occasionally have pitch breaks. There may be loudness fluctuations and especially after physical activity, their voice may sound very low and they have reduced loudness. Resonance may not be affected. Speech intelligibility may not be affected and occasionally there may be errors of articulation (pronunciation) such as cluster reduction eg Ice cream sounds like 'Ikkeem' or playtime sounds like 'peytime'. These errors too may not be noticed at single word production but in connected speech.

What may be noticed is the change in naturalness of speech where at times, again when they are physically fatigued, their speech may sound a bit sluggish or prolonged as though spoken with more effort and struggle than otherwise**.**

Management

An intensive therapy regimen is not indicated in children or adults with DMD/BMD at this level. A combination of oromotor strengthening exercises along with relaxation and breathing exercises would enhance their speech. These are given in detail at the management of Speech section at Level II.

Swallowing

Only if the child or adult with DMD/BMD, is eating in a hurry, eating mixed consistencies which also involves complex eating like hot soup which has vegetables and noodles apert from the thin liquid, or pani poori, he may have coughing due to entry of food particles into his airway. Or if he is fatigued he may not swallow in time and before the tongue moves posteriorly to guard the airway, food may trickle down in the airway leading to severe coughing. This may happen once in a week or a fortnight. This is not severe enough to cause weight loss but may lead to some discomfort when it happens. Sometimes a PMD may have food preferences such as based on previous experiences, he may avoid eating those foodstuffs where he had coughing or it took too much time to eat like pizza bread or naan / tandoori roti etc.

Management

The SLP/Swallowing therapist could guide these individuals to take some basic precautions, such as:-

- Slowing the pace while eating,
- Reducing the volume per bolus
- To take repeat swallows
- Pause between two mouthfuls
- To avoid having mixed consistencies
- To avoid distractions while eating
- To maintain good oral hygiene and rinse mouth prior to and after each meal

Language

The PMD at this stage is not commonly seen to have any language deficits. In children with MD if the onset is around 5 years, and the child is having delay due to other factors such as reduced speech and language stimulation due to experience deprivation or the child has autistic features or hearing impairment, then there may be a chance that the child may show language developmental delays and deficits.

Management

For children with MD associated with other disorders, the SLP should guide the parents to manage the problems holistically with the help of the entire team as required.

Occasionally the child may be able to name people and objects and animals, but may not be able to use the language in communication. Intensive speech and language stimulation and therapy may be indicated in such children. However, if there are no associated disorders, in children with DMD/BMD, there are no indications for language deficits and hence no indications for management.

Cognition

As mentioned above, unless associated with other disorders, a child with MD at this stage is not seen to have cognitive deficits.

LEVEL II Early Ambulatory

At this stage, the child or adult with MD may have deficits of a mild to moderate severity in more than one domain. Speech and swallowing may be more affected as if the distal (limb) weakness has affected normal mobility then functions requiring fine motor coordination of muscle groups would understandably be affected.

Speech

Respiration

Words per breath:- May be reduced due to short breath supply and weakness of respiratory muscles. This may improve with rest.

Phonation Duration:- May be reduced and this contributes to reduced words per breath, low intensity of voice and reduced intelligibility due to very soft spoken speech. However insight may be good and PMD may learn strategies to stop, pick up listener cues and speak louder to reach to their listener.

Management

- For breathing problem and unclear speech:
    1. Do deep breathing exercises. Inhale as much as possible from nose & exhale through mouth. This will help to relax neck, shoulder muscles.
    2. Do deep breathing followed by phonation of /a/, /e/, /u/ as much as possible.
    3. Mechanical Aids to help breathing: These devices are simple and portable, which give better ventilation to Duchenne muscular dystrophy children. One of the methods is called intermittent positive pressure breathing [IPPB]. This requires a mouthpiece, which is connected to airway. If facial muscles are weak then facemask can also be used. This improves breathing during the day as it can be easily placed under the wheelchair. But if introduced early then respiratory functions are preserved better. Volume ventilator is another device, which can be used during nighttime because it is bigger than IPPB. This device reduces the difficulty in breathing when the child is sleeping. Facemask or nasal mask is connected to the airway. These devices can be used as and when needed to improve ventilation.

4. In advanced stages of muscular dystrophy where breathing difficulties increase, another surgical option that can help reduce difficulty is tracheostomy. Here a small hole is made below the neck, which is covered with a mesh and is connected directly to the windpipe. Take proper consultation before choosing this option.

Phonation/ Voicing

- Pitch range:- May not be affected greatly but with fatigue PMD may have pitch breaks.
- Loudness:- End of utterances are characterised by reduced loudness which is due to reduced respiratory pressure than a problem of the vocal mechanism
- Quality/Timbre:- May not be affected but there may be the effortful speech or fatigue in muscles of speech which may affect the quality of voice. Voice being the so called 'thermometer to portray emotional well being' when the PMD is depressed or upset, the quality and timbre of voice will understandably be affected.

Management

A good breathing pattern would be the base for a good voice. Easy onset of voicing needs to be established and relaxed phonation is an important step. The SLP needs to focus on increasing the pitch range and loudness of voive which would also improve the overall quality of voice.

Resonance

Normal

Articulation

Sounds in isolation: Better at sounds and word level than at phrase and sentence level. Intelligibilty of speech may be affected at sentence and conversation level. Most words with clusters would be simplified and produced by omitting the cluster...eg gammar for grammar; Adi for Aditya

Management

Motor planning & programming may also be affected: This is different from muscle weakness. Because of planning and programming errors, the child appears clumsy, uncoordinated with poor eye hand coordination. For eg. Picking up a matchbox, taking out the matchstick and lighting it. This task needs signals from brain to hold the target, which is received by eyes and hands. Then the concerned body parts and muscles carry out the task. But if coordination between the muscles and body parts is inadequate, initiation of right body part is affected which results in uncoordinated eye hand movements. To reduce this difficulty, a verbal clue to carry out tasks and help in reaching the target can improve the difficulty.

Oral motor exercises:

- For poor lip closure: 1. Hold upper and lower lips together with little pressure and repeat 10 times in a day. 2. Ask the child to hold an ice-cream stick, whistle or spoon between the lips. 3. Ask him to close lips together by himself by using a labial seal with his fingers.
- For inadequate tongue movements: 1. Protrude tongue and elevate, 2. Move from left to right. 3. Roll on lips, on teeth, palate, cheeks from inside. 4. Try to lick candies, lollipops, and ice cream. 5. Try to remove food particle [dough, chocolate] from the palate with force. 6. Do back and forth movement of tongue on palate. 7. Try to cough as an exercise, say /k/ as an exercise. 8. Say /pa/, /ta/, /ka/ as fast as possible maintaining clarity, speech, loudness.
- For inadequate sucking: 1. Try to suck liquids from spoon. 2. Try to suck on lollipops, ice, tangy candies etc. 3. Suck on gauze piece dipped in honey, chocolate sauce etc.
- For inadequate blowing: 1. Blow whistles, soap bubbles, thermocol balls, bits of paper, candles etc. 2. Use respirometer [instrument to reinforce blowing & sucking].

Difficulties might occur in phonological processing: The child needs to recognize every letter and needs to associate it to its sound. This is done by the brain. The child may find it confusing to remember letter and sound. This problem again supports the problem with short-term verbal memory. Do not scold the child for making mistakes; rather give more practice with words along with pictures and letters. If not rehearsed regularly, the child would have problem. Practice sight words so that reading becomes easy. Consult a speech language pathologist for further detailed child oriented therapy.

Multi sensory approach: This involves integration of auditory, visual, tactile and kinesthetic approach. For eg: while teaching the child /p/ and /b/, the major difference between the two sounds is understood by listening because visually both look the same. Similarly for teaching /ka/ child can be explained it's the sound which can be produced by coughing hence child remembers the association with the action of coughing. When asked why is he coughing he hears the sound /ka/ once again and remembers it. Child will also know he has to produce /ka/ by lifting tongue from back and touching it to the roof of mouth. Kinesthetics means actually feeling the movement of tongue while producing the sound, like feeling how the tongue touches the roof of the mouth to produce /ka/ and with how much force tongue is pulled down back while saying /ka/.

Prosody

Overall the rate of speech would be slow and sluggish enough to attract attention to itself. The pauses in words may be awkward as when the PMD would run out of breath supply in the middle of a long word such as Borivli said as Boriv....ali with the pause taken to allow breathing.Intonation may not be markedly affected.

Speech Naturalness may begin to compromise from this level of severity onwards. However it should be borne in mind that the speech patterns in these individuals would be very variable. In some PMD at this level, voice may be a little low pitched, rate may be prolonged and speech sounds as if drawled and he may be at this level of difficulty for a long time with good intelligible speech.

Management

Speak slowly by prolonging the initial syllable post deep inhalation. . Exhale after every word. Ex. Count 1 to 10 slowly exhaling after every count. Practice omkar after deep inhalation. This will help to maintain good coordination between deep breathing, exhaling and speaking and reduce effort while speaking.

Swallowing

The clinical picture of swallowing may be as described above in Level I and in some PMD may be more severe. Delayed oral phase, difficulty to masticate food, control the bolus while mastication, difficulty to propel tongue posteriorly and inadvertent spillage of liquids into the airway, at this time leading to coughing may be signs in the oral preparatory phase of swallowing. Reflex may be triggered normally or may be a little delayed. If the PMD has pharyngeal weakness, there may be discoordination while swallowing leading to severe coughing for thin liquids such as water and milk. Overall, the PMD at this level would be comfortably managing on oral feeds.

Management

For difficulty in swallowing: 1. Reduce the size of the bolus. 2. Masticate slowly. 3. Push behind masticated bolus towards pharynx [throat] slowly. 4. Drink liquids slowly sipping and then pushing behind. Try chin tuck towards collar bone while swallowing. This will close airway passage and reduce aspirations. 5. If coughing starts, consult a speech language pathologist immediately.

Language

A PMD would at this level rarely manifest any language deficits but the use of language in a communicative context may be affected owing to the speech difficulties such as the person may not be able to sustain respiratory control long enough to complete the sentence and hence may not like to answer in class or describe an event amongst friends thus beginning to avoid speaking situations. He may participate less in conversations with people and take fewer turns and speak less when they talk.

Management

For delay in speech since childhood: 1. Talk as much as possible with the child so that the receptive vocabulary increases. 1. Talk as much as possible with the child so that the receptive vocabulary increases. 2. Use lots of pictures & actual objects to teach the child. 3. Talk slowly using open mouth approach at the level of child's eyes. 4. Speak loudly and let child observe your lip movements and tongue movements. 5. Encourage child's every attempt to communicate verbally. 6. Make it mandatory for child to use sounds to ask for his needs. Let him say / a/, /e/, /u/, pa/, /ma/, /ba/ etc whatever

possible. 7. Consult a speech language pathologist for detailed child oriented goal plan to improve his speech and language. • For difficulty in hearing: 1. Consult an audiologist. • For reduced expressions/ smile: 1. Massage the cheeks in circular motion and consult a speech language pathologist [speech therapist]. 2. Stretch the lips and hold smile. 3. Round the lip and hold.

Difficulties doing mathematics [Dyscalculia]: Remembering signs, relative values [greater than, lesser than], abstract or symbolic concepts like ten's place, hundred's place, money, fraction, etc. is difficult. Memorization of tables, automatic calculations are difficult. For this, give plenty of practical examples for additions, subtractions, greater than lesser than. Multiplications and division exercises need to be understood by the child first. Ex. 2x2=4 [here explain 2 comes 2 times i.e. twice] 2+2=4 [here 2 are added i.e. the original value is increased by 2] 2x3=6 [here 2 comes thrice 2+2+2, in multiplication the second value is the number of times the first value is added]. 2+3=5 [here 3 is added in first number i.e. 2, in addition, the second value itself is added in original value]. 2-2=0 [here again second value is decreased from first value. Remember always that the second value should be lesser than first value]. 4/2= 2 [Ask the child to make 4 balls and then ask him to make two parts ensuring both the parts have equal balls. This way, explain the concept of division. Do not go by the regular methods used in school because abstract thinking is difficult for children with dyscalculia. Learning tables will also be easier with the method mentioned above. Even though it is lengthier, it is more practical. Most of the reading, writing and mathematical errors go unnoticed because of more enlarged problem of muscle weakness.

Cognition

This would largely be within normal limits and a PMD at this level would even be continuing school, college or vocation at this stage.

Management

Other problems experienced, especially in Duchenne muscular dystrophy: 1. Poor short term verbal memory: Inability to retain new information in brain at a time. For this, try to use lots of pictures to introduce new information. Chunk it into small segments, so that remembering becomes easy. Try to associate it with the known information. eg. For remembering new address: use lots of pictures for landmarks.

Complex language processing might be difficult: This problem is not noticed easily as the child's day to day communication is not affected. But detailed description of any event or abstract reasoning might be difficult. This can be improved by giving topics to the child to construct 10 sentences. eg. Ask the child to do mind mapping. This increases thinking and reasoning abilities.

Mind mapping : Look at the illustration with a flow chart. One word is given to the child, say sun (centre) and it has five arrows where the child has to fill in words associated to sun e.g. solar energy, heat, plants need sunlight, sun is required to survive i.e. life. Again five words related to life; child has to mention words like oxygen, food, water, etc. This will improve association, reasoning and vocabulary as

well. This also helps in improving memory and retention.

Some of the Duchenne muscular dystrophy children might show signs and symptoms of autistic spectrum disorder. These may occur at milder level, but if tackled adequately and early, it can help the child in better language and social development. Use extensive language stimulation using multi sensory approach so that child learns fast. If child tries to remain aloof, don't ignore it regarding it as muscular weakness. Consult a speech language pathologist if any kind of delay or deviance is noticed in child's speech and language abilities.

LEVEL III Late Ambulatory

Speech

This group would be showing the similar clinical picture as seen in Level II however the severity would be more than that. One may see a moderately severe degree of difficulty in this group in all domains of speech and swallowing with lesser impact on language and cognition.

Respiration

There may be a breathless quality to speech with increase in weakness of the respiratory muscles however the primary modality used by an PMD for expression of one's thoughts would be through speech. There may be shortness of breath as the regulation of air supply for speech may be affected which requires excellent coordination of the ribcage muscles known as external and internal intercostals muscles apart from some action of the diaphragm. Hence words per breath would be reduced and the words spoken may be uttered in a soft voice with reduced intensity.

Management

The child or adult with MD may need guidance as to how to do steady breathing then to combine this with speech at phonation level then counting numbers and then slowly to introduce single words such as numbers and then days of week, months of the year and then go on to word completion tasks and so on to steadily increase the length of utterance while maintaining the breathing pattern.

Phonation

Again pitch range would be limited. Voice quality would be low pitched, soft, husky, hoarse and breathy (however not in all PMD) if associated with unilateral or bilateral vocal cord paresis. In persons with Oculopharyngeal dystrophy, the impact on voice would be much more.

Management

In case the PMD has hoarseness, the SLP can guide him into doing vocal adduction exercises wherein he places one palm over other while holding arms folded across chest and pressing palms tightly over one another says /a/ in a steady voice. Phonation is likely to improve if the vocal adduction is good.

In case there is weakness of the upper limbs of these individuals, they could be guided to push against the hand of the SLP placed on the forehead which again helps in bringing the vocal cords together. This exercise done regularly may improve voice quality. Care needs to be taken to give them adequate rest periods to avoid muscle fatigue.

Resonance

Normal

Articulation

Intelligibility of speech may be affected for phrases and sentences as well as for single words especially in case of proper nouns like own name or address or names of family members. So, if the names are unfamiliar and without any help from caregivers, it may severely affect intelligibility of speech. it would be difficult for strangers and people not in the PMD's inner circle to understand him.

Management

The exercise regimen given at Level II can be used more intensively for children and adults with MD at this stage.

Consonant exaggeration as given by Darley, Aronson and Brown (1969,1975) could be given wherein, the person is taught to highlight and exaggerate the production of each consonant in the word eg in the production of /Saturday/ the consonants /s/, /t/and /d/ are exaggerated. This is done with the intention to reduce speed and focus on speech sounds thus enhancing speech intelligibility.

Prosody

The rhythm and rate of speech would be compromised to a moderately severe degree and although the PMD may be communicating his thoughts and ideas through speech, speech would sound very disordered in all domains of speech. Rate of speech would be very slow and sluggish. Prolongations may be so long as to cause a break in the word. Eg 'M...yy...na..... me is...Ro ... han.'

This occurs as the speech muscle movements are very slowed down and by the time the PMD is completing the syllable, owing to prolongation, his breath supply is depleted and hence he has to begin again or complete the broken word in the next breath group. This severely affects the naturalness of speech. There is significant trade off in naturalness of speech in the PMD's attempt to preserve speech intelligibility. The PMD child or adult is likely to be very self-conscious of the awkward manner of their speech and may avoid speaking in new environs and to strangers and especially in group situations.

The PMD may have started using some adjuncts in speech on his own even without training. For example, he may use more gestures to support his speech or use exaggerated mouth movements to aid in clarity or if he sees confusion on the face of his listener, may offer to write or type a message or a significant word to clarify to his communication partner. A child with MD would look at his parent or therapist to ask for help if his communication partner is asking for repetitions.

Management

The exercises for fluency enhancement given at Level II may help if intensively followed. The speech efforts during therapy may be recorded and played back to show the desired speed and also the ease of production. This is encouraged to be followed even beyond therapy sessions and again, speech efforts need to be played back.

The techniques used by PMD which they may have developed on their own may be fine tuned in therapy sessions and if they are helpful, the person is encouraged to use it. Effective communication is to be emphasized by the SLP rather than precision of speech and intelligible speech is to be attempted even if speech may not sound natural.

Swallowing

As in case of speech, so too in the case of swallowing, the clinical profile would be a more severe form than seen in Level II.

In persons with Oculopharyngeal dystrophy(Level III), the impact on voice and swallowing would be much more than in other types of MD at same level.

Management

Intervention by a swallowing therapist would be imperative.

Some children may have been advised to be on parenteral methods of feeding such as Ryle's Tube(RT) feeds (Nasogastric tube feeds) or even on gastrostomy (PEG) feeds considering the chronic and severe and progressive nature of the swallowing and feeding disorder. Even if the child or adult with MD is able to tolerate oral feeds, it may be easier to have semisolids and soft solids. Liquids, both thin and thick, may well lead to coughing so it would be a good practice to have liquids through RT or PEG.

The PMD could be taken for swallowing therapy and initially rehabilitative strategies could be used and later compensatory strategies could be used. At all times care needs to be taken to check for airway safety and then therapeutic feeds could be tried. If the PMD could have them with least discomfort, the volume of the feed can be increased and the RT feeds could be complemented with oral feeds. A diet chart can be maintained by caregivers in terms of the nature of food given, the quantity and the reaction it triggered. This would enable the SLP as swallowing therapist and the dietician to decide if RT can be removed or at a later stage in therapy, whether RT needs to be replaced by a PEG for long term care.

Language

As explained in PMD at Level II, there may not be any language deficits in these children and adults with MD at an implicit level unless associated with any other disorder. Problems are faced in communication as explained earlier owing to severe difficulties in speech and owing to poor intelligibility of speech. They may take less turns in speaking, depend on caregivers and close family members to fill in for them when not able to be intelligible. Avoidance in speaking situations may be frequently

encountered or resorting to alternative means of communication may be seen. The load of conversational exchanges may be on their conversational partners and even if they are caring, the PMD may experience increasing amounts of frustration owing to their physical limitations as well as their communicative and feeding problems. From Level III to Level V, the quality of life (QOL) of these children and adults would be severely affected.

Management

The International Classification of Functioning, Disability and Impairment for Children and Youth (ICF-CY) gives very intensive considerations as to how these problems need to be looked at to reduce the barriers to communication, enhance the participation and reduce the environmental limitations for these children and adults with MD.

Cognition

Management

In Level III as well as in Levels IV and V, cognition may not be affected but the means to express it, that is speech, writing, signing, gestures, may be severely compromised and hence the PMD may not be able to express his thoughts, ideas effectively. In Levels IV and V, it may be difficult to express his basic needs even and only close family members who are the caregivers would be able to interpret from his body language, slight movements of eyes, hands, fingers, eyebrows and the like.

The SLP can work on planning AAC devices so that the barriers to participation and communication may be reduced.

LEVEL IV: Early Non-ambulatory

Speech

There may be a variability in the speech of persons at this level of functioning. Some may show the similar impact of the severity of their physical limitations on speech and some may not be so severely impaired in speech and communication. There will always be a range within which their complaints would fall. Persons with MD even if belonging to same type of MD may still manifest different clinical profiles. So, although at Level IV a person may manifest speech, swallowing, language profiles ranging from those described for Levels II, III, IV and V. As is said, there are no constants in biological disciplines and a caregiver or rehab professional would have to identify their PMD's respective profile from these and work towards intervention accordingly.

Management

Speech may be increasingly difficult at this level and at Level V, and if seen may be largely unintelligible. All processes of speech may be affected to a severe degree and the PMD may have been trained by now, to use Alternative and Augmentative Communication (AAC) devices. Communication may be limited to here and now, to express concrete ideas more related to physiological needs of the person. In view of communication intentions, the child or adult with MD, may only use communication

to regulate their environment for instrumental needs such as "Do this' 'Give me' ' Call my mother' etc.

Swallowing

Management

At this level of functioning as also at Level V, the child or adult with MD may have been placed on RT feeds or PEG feeds and may be having very little oral feeds in small amounts of safe consistencies. Or the PMD may be off oral feeds completely and only given hydration off and on to rinse the mouth or suck at wet gauze to maintain oral hygiene. Care needs to be taken that the PMD does not lose wait owing to swallowing and feeding issues.

Language

The profile for language may be as given in Level Iii and the person may be on AAC devices and facing severe limitations in using nonverbal means of communication as well.

Management

Communication oriented strategies need to be given whereas the speaker's role in producing intelligible speech is supplemented by efforts made to enhance the medium of communication such as to have better light on speaker's face, use of an amplifier to improve loudness and use better guessing strategies by conversational partners.

Cognition

Same as given in Level III

LEVEL V: Late Non-ambulatory

There may not be marked differences in the clinical profiles from Level IV and Level V except that in the latter the severity would be further affected. The functioning in all domains may be severely compromised.

Speech

Same as given in Level IV.

Management

Swallowing

Same as given in Level IV. Weight loss may be significant if the PMD has been on RT or PEG feeds for a prolonged period. Despite no oral feeds, the PMD is likely to have microaspiration of his own oral secretions which may eventually lead to aspiration pneumonia and may be one of the contributing factor in the mortality of these persons.

Some of these individuals may be on life support at this stage and may be on the ventilator frequently whenever they have severe respiratory difficulties.

Management

This would be similar to the management done for PMD at Level IV only the intensity of therapy regimen needs to be increased further to cater to the severity of the swallowing disorders. As in all persons with dysphagia, the focus would be primarily on airway safety and then on improving nutritional intake.

Language

Same as given in Level IV

Management

If the PMD is physiologically stable then may communicate with use of advanced AAC. Those with high tech devices such as seen in use by the illustrious Mr. Stephen Hawking, they could convey even complex thoughts and be a significant contributor to science and society.

Cognition

Same as given in Level IV and as explained above.

These are some of the guidelines that could be followed by rehab professionals and caregivers, family members and significant other persons (SOPs) of children and adults with MD. However it is by no means exhaustive. One may begin from here but may need to refer to more intensive treatment programmes. Also, this program in no way can replace the therapy given by the SLP and swallowing therapist. A treatment regimen would be more effective if the SLP could advise it and the therapy regimen could be carried out by the caregivers of the child/adult with Muscular Dystrophy.

14.

Psychological Management

Consideration of psychological aspects of the child is important to be taken into perspective, since it has an impact on the overall physical wellbeing of the child too. Cognitive and behavioral changes that happen need to be understood and handled accordingly.

What are the cognitive and behavioural changes or problems associated with muscular dystrophy at different ages?

Childhood:

Cognitive Changes:

During this period, the parents may notice language developmental issues like the child may have difficulty in expressing his/ her needs or may have difficulty in remembering a lot of information. This is especially seen in boys with Duchenne's muscular dystrophy because of which they are usually diagnosed as having learning disability especially dyslexia. Children with Duchenne muscular dystrophy may have problems with maintaining attention or concentrating, however these issues may be overlooked by their parents due to their physical condition.

Behavioural Changes:

Usually children at this age display problematic behaviour but children with muscular dystrophy display more impulsive behaviour and poor emotional control. Many of these children are on steroids, which usually have side effects that affect their behaviour. Some side-effects seen are that these children are more rigid, emotionally low and may not be cooperative. Eventually as their condition progresses, boys aged 8 to 10 years start having difficulty in adjusting as they stop walking and start using the wheelchair.

Teenage:

Cognitive Changes:

When young men with muscular dystrophy grow older their cognitive problems increase like difficulty in planning, organizing or completing tasks. As their educational level or work increases, their problems also increase.

Behavioural Changes:

Teenage or adolescence is normally known to be a difficult age, as at this point of time there are many hormonal and emotional changes in the body. Along with these, there could also be a possibility of having a limitation in the physical development. This may be a result of certain medical treatment for example: an individual may have small height or may have delayed puberty which could be an effect of puberty. This could make dealing with the changes of adolescence more difficult. Teenagers could have a difficult time adjusting as they might not get the freedom or independence since their condition will require more care and assistance as compared to others. As muscle weakness progresses, they are at risk of becoming more isolated or socially withdrawn. Parents should look for signs of chronic sadness, depression or anxiety.

Adults:

Cognitive Changes:

Adults with muscular dystrophy may adjust with their cognitive issues and may find out ways of dealing with them.

Behavioural Changes:

As individuals with muscular dystrophy progress from teenage to adult hood, they may undergo mood changes and emotional changes which would eventually lead to changes in their behaviour. Adults with Duchenne muscular dystrophy would be bed ridden and this would result in loss of independence. This would eventually lead to increased anger, irritability & frustration and may even show signs of depression.

Whereas, adults with limb girdle muscular dystrophy or Becker's muscular dystrophy would develop difficulty in functioning, which could lead to decreased socialization, low self esteem & self image. Also they would have multiple questions as to whether they should get married or if married, whether they should have children.

What is the importance of psychological assessment in muscular dystrophy?

A person with muscular dystrophy is at an increased risk of cognitive and emotional problems; hence early diagnosis and treatment is of great importance.

- Cognitive Assessments: Especially a DMD child with learning disabilities or autism should undergo testing for IQ, memory, attention span, problem solving, etc.
- Emotional and Behavioural Problems: A patient with muscular dystrophy should go to a psychologist for emotional status examination either every 6 months or annually. As many of the patients go into depression or suffer anxiety disorders, which may in turn worsen their physical condition.

Learning and Cognitive Skills in Muscular Dystrophy:

Intelligence is defined as "an individual's ability to adapt and constructively solve

problems in the environment" as mentioned by David Wechsler, a well known American psychologist.

Intelligence can be assessed by the means of an intelligence test. There are many intelligence tests available but an accurate IQ can be gained when the IQ test is for the Indian population, for e.g. Malin's Intelligence Scale for Indian Children (MISIC). This IQ test usually has 2 parts i.e. verbal sub-test and performance sub-test.

The verbal subtest includes questions regarding language, for e.g. how are the piano and guitar similar. Whereas performance sub-test assesses visual thinking and motor performance, for e.g. a subtest on block design, where you have to copy a block design. The time taken to conduct an IQ test is 30 minutes to 2 hours.

It is often seen that boys with Duchenne muscular dystrophy usually are at a higher risk of delays in walking, running and sitting. In a similar way, it is seen that the IQ of these children ranges from above average to below average. However, they are at an increased risk for having low IQ or some learning disability.

What is the cause of cognitive weakness?

Most probably there is a relation to brain functions. It is known that dystrophin is normally present in other tissues as well as muscle tissue, including the central nervous system. The lack of brain dystrophin might therefore play a role in the cognitive functioning of the boys. The dystrophin isoforms Dp427 - C and Dp427 - P would normally be distributed to the hippocampus and purkinje cells in the cerebellum respectively, contributing to greater post-synaptic density. The cerebellum and hippocampus are part of an integrated network that includes connections with the frontal brain regions. This altered postsynaptic plasticity may hinder efficient memory, automation and planning/organization.

Areas of Cognitive Weakness:

- Difficulty in finding words.
- Difficulty in short term memory.
- Difficulty in concentrating.
- Difficulty in switching from one activity to another.
- Difficulty in completing tasks.
- Difficulty in multi-tasking i.e. performing multiple tasks at the same time.

Brain Areas in which Dystrophin has been found:

Brain Area	Function of the Area
Hippocampus	Memory
Cerebellum	Automatization
Frontal Lobe	Planning & Organization

Research is still under process about the role of dystrophin in the brain.

Attention, Listening and Memory:

It is seen that patients with muscular dystrophy have problems remembering many things or assimilating information together, have difficulty in following directions or may not seem to listen. Also, there is a high chance for problems with the ability to focus on a task and with dividing the attention between many activities at a time. Their level of distraction may be high. Individuals with high IQ could also have difficulties dividing their attention.

Strategies to Improve attention, listening and memory problems:

- Sit close to the child and explain to him about the task or the problem to be solved to avoid him getting distracted.
- Break down the instructions and information into simple and specific statements.
- Check if the child has understood what he has been asked to do.
- If the child has difficulty dividing attention between many things at a time then give him one activity to complete at a time this would also help eliminate stress.
- If the child has an attention problem or has reading difficulty, then underline important points so that he does not miss out on important information.
- While teaching the child, use small time durations i.e. instead of a 1 hour long period use short 20 minute periods.
- Either make a to-do list or let your child himself make a list of activities which will help him remember the activities that he is supposed to complete.
- Arrange for extra time to be given to the child for him to complete an examination, as his physical condition might be a barrier or he might have concentration/memory problems.
- If the child is not able to write his examination because of weakness in his hand, arrange for someone else to write the exam for him.

Psychosocial Adjustment to Muscular Dystrophy:

Psychosocial adjustment means the way in which one adjusts to difficult and stressful events associated with muscular dystrophy.

Psychosocial Adjustment has six areas of functioning:

1. Relationship with friends.
2. Dependence on family members / caregivers.
3. Opposition to things or situation around.
4. Productivity.
5. Anxiety or depression.
6. Withdrawal.

Undergoing emotional and behavioral problems is a normal and a healthy way of socio-emotional development. However, research has shown that individuals with physical disability have an increased risk of developing behavioral and emotional

problems. This is usually one of the reasons why individuals with muscular dystrophy adapt to the consequences of behavioral and emotional problems. It is usually seen that individuals with muscular dystrophy become more capable of coping with their disability.

Learned Helplessness in Individuals with muscular dystrophy:

Learned Helplessness is when an individual thinks and feels that he or she has no control over the situation or whatever is happening to him or her. Learned helplessness can lead to many emotional reactions and behavioral problems.

For example:

Negative Chain: An individual with muscular dystrophy who is regularly undergoing physiotherapy, despite which he is deteriorating and is wheelchair bound feels sad and disappointed because he cannot walk independently.

Positive Chain: An individual with muscular dystrophy who can move around in his wheelchair feels that he is self-reliant and independent. He is still happy about the things that he can do by himself.

How to deal with emotional problems?

Everybody undergoes emotional problems but individuals with muscular dystrophy undergo a lot of stress and emotional changes. These changes are related to the different stressful situations arising because of their disease like hospitalization, being wheelchair bound, dependency, etc. Also when individuals take steroids, it could have side effects like mood swings and frequent changes in emotions.

Stages of acceptance:

Phase 1: Denial: "No not me"

Phase 2: Anger: "Why me, it's not fair"

Phase 3: Bargaining: "Yes me, but I still want to"

Phase 4: Depression: "I'm so sad, why bother with anything"

Phase 5: Acceptance: "I am going to have a worthwhile life"

Strategies to handle emotional problems:

- The first step to handling the emotional problems is to understand or give a name to the emotion that he or she is experiencing, for e.g. whether the person is experiencing anger, sadness or fear.
- It is important to make the individual feel that he is being heard. Hence, he should have support in the form of a good listener.
- It is very important to teach the person to express his emotions in a constructive manner.
- The individual could maintain a personal diary where he writes the thoughts & emotions that he is experiencing.

- If an individual with muscular dystrophy is having frequent mood changes which are having negative effects on his health and routine, he should consult a psychologist.

Temper Tantrums:

Temper tantrums are normal issues associated with the process of growing up. The issue of temper tantrums is usually seen in boys with Duchenne's muscular dystrophy. This is their way of drawing attention to themselves, be it positive or negative attention. Dealing with temper tantrums becomes a tricky situation. If you shout at the child for throwing a tantrum, it may lead to an increase in the tantrums, whereas if you show the child that you are okay with the tantrums then it would lead to encouragement of such a behaviour.

Strategies to handle temper tantrums:

- The best way to deal with this problem is to ignore when the child is throwing temper tantrums. However this technique cannot be always used.
- Time out: This does not mean punishing the child; it means that we are allowing the child to calm down.

For e.g.: we make the child sit in the corner of the room where there is no possible means of entertainment and where the child feels bored. He should be made to sit there for at least 5 to 10 minutes and he should be asked to think why he was given timeout. This would help him avoid being given a timeout in the future.

However, when temper tantrums worsen or may be out of your control then you should consider consulting a child psychologist.

When to consult a Psychologist?

- You feel helpless in dealing with the temper tantrums.
- It leads to stress and negative feelings within the family.
- You are not comfortable with the response after the temper tantrums.
- The child causes some sort of harm to himself.

Coping with Duchenne muscular dystrophy:

Usually it is seen that persons with muscular dystrophy accept their disorder and adapt to it quite well. However, many a times, due to stressful situations or inability to function socially or physically, they may undergo sadness, anger, frustration or guilt.

Strategies to Maximize Coping Skills:

- Be available and open to talk to the affected person.
- Try to identify the problems that the person is undergoing, which are stopping him from functioning up to his maximum potential.
- Allow the individual to be as independent as possible.

Quality of Life:

Quality of life is more important than the quantity of life. This is also true for individuals with muscular dystrophy as they have a whole life with possibilities ahead of them. Hence, it is important to understand that rather than aiming for the quantity of life we should aim to improve the quality of life.

Strategies to improve quality of life:

- Take each day as it comes rather than planning for the future.
- Help the individual find happiness in small things.
- Don't make them feel different or disabled. Treat the individual in the same way as others.
- Safety is very important, but that does not equate to binding him within the house. In fact, he should be given the opportunity to experience situations and activities like other people.
- Help him socialize and keep in touch with other people. Socializing is very important for his well-being.
- Help the individual develop a hobby which keeps him engaged and helps vent out his feelings and emotions.
- Help him develop a positive self-image and self-esteem.
- Let him be as independent as possible.
- Like other people go out and have vacations or small trips, even individuals with muscular dystrophy should be able to take short trips. Make proper arrangements keeping in mind their needs for e.g., a wheelchair accessible hotel.

Strategies for Caregivers:

Ways to manage aggressive & difficult behaviour:

- Develop a weekly routine for the patient, explain it to him and help him stick to it. Incorporate rewards for tasks well achieved, as children are usually noncompliant after exercising every day.
- Incorporate recreational activities in the time table as it is very important to have something to look forward to during the day. This helps to motivate the patient and does not let him get depressed about his condition. For example: Painting or playing board games with siblings or watching television.
- Explain the situation to the patient, if there are any changes made or if he is taken for some therapy that he denies to undergo, for example: If the patient does not want to exercise on a particular day, explain to him the situation, how doing so would have repercussions in the long run and set up a reward system if necessary.
- Try to keep calm when a child is misbehaving. Angry parents and teachers tend to escalate the situation. This would worsen the situation as the child would feel neglected and feel that nobody understands him.

- Focus on the positives: Strategies that only focus on punishment do not promote positive behaviours. Increase motivation, or change attitudes. Rewarding/ praising/encouraging good behaviour is more effective in the long run. Look for opportunities to say "yes" instead of "no." ("Yes, you can have a cookie, after you…").

Psychotherapy and drug interventions:

- Well-known techniques exist which help in various areas. These include training for parents to cope with bad behaviour and conflicts, individual or family therapy and behavioural interventions. Applied behaviour analysis may help with certain behavioural issues related to autism.
- Some children & adults may benefit from the use of prescribed medicines which help with emotional or behavioural problems. These medicines can be used under specialized supervision and monitoring for depression, aggression, obsessive compulsive disorder (OCD) or attention deficit hyperactivity disorder (ADHD), when these problems have been specifically diagnosed by a doctor.

15.

Diet And Nutrition

MD leads to loss of muscle function and wasting and progressive muscle weakness. As a result, the body replaces the muscle tissue with fat and connective tissue. Delayed growth, short stature, and increased fat mass are typical characteristics which impact the nutritional status.

Patients might be at risk of under nutrition/malnutrition commonly seen towards the end stage of the condition. They are also at a risk of being overweight/obese due to lack of physical activity, or as a side effect of steroids. In addition they also have deficiencies in calorie, protein, vitamin (water and fat soluble), mineral, and fluid.

As the condition progresses, access to a dietitian or nutritionist is needed to guide the patient to maintain good nutritional status to prevent both under nutrition/ malnutrition and being overweight/obese, and to provide a well-balanced, nutrient-complete diet. Dietitian will also be very important if tube feeding is required.

Diet / Nutritional Therapy

Why is Nutrition Therapy Important???

Nutritional therapy can aim in improving the overall quality of the life of the patient. Nutritional care in the early stages of the condition can prevent or rather delay onset of osteoporosis and other deficiencies like Calcium and Vitamin D. The body replaces the muscle tissue with fat and connective tissue. Altering the fat intake is therefore essential.

Research has 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).

A complete balanced diet keeping in mind the nutritional requirement and the current nutritional status of the patient is essential in muscular dystrophy.

The most common nutritional hazard in muscular dystrophy is related to weight gain. This is mainly due to lack of physical activity along with increased food intake.

It is a myth that by eating fewer meals a day, a person's weight can be controlled. Smaller frequent meals are advisable as it not only balances the food intake but also eases digestion. When food is eaten in smaller quantities it enables complete digestion of the food and slow release of the energy which helps in steady utilization by the body.

Nutritional Intervention is individualized according to the type and stage of MD.

Nutritional care for different stages:

Stages of MD	**Intervention**
Pre symptomatic and early ambulatory stage	Monitoring a normal weight gain for age
	Nutritional assessment for over/ underweight
Late ambulatory	Restriction in energy intake due to decreased physical activity
	Monitoring high protein needs
	Monitor for nutritional deficiencies especially Vitamin D and calcium and others
Early non ambulatory	Assess the nutritional intake.
	Treating constipation (infrequent or difficult bowel movements) by increasing the intake of fiber and fluid or usage of laxatives.
	Monitoring GERD (gastro esophageal reflux), to reduce acidity and heart burn.
	Monitoring for nutritional changes in specific disease state like heart complications and hypertension
	Supplementation of nutrients required as they are prone to osteoporosis and fractures, due to steroid intake
Late non ambulatory	Problems of dysphagia to be monitored due to poor oral intake, and the need to consider tube feeding.

Determining nutritional needs:

It is of utmost important to determine the nutritional needs of the patient with MD due to decreased physical activity, reduced caloric need, increased protein and antioxidant requirement due to muscle activity/protein catabolism and high oxidative stress. (Figure 16.2)

1) **Energy:** The energy requirement needs to be altered depending on the initial nutritional status and physical activity. Although it is difficult for the patient to target the ideal body weight (IBW), an average of plus or minus 5 kilograms can be permitted.

   A per day meal must be distributed in such a way that post afternoon; the choices of food must be light and easy to digest. The breakfast, mid morning, lunch must cover major calories of the total daily requirement as it can be utilized throughout the day.

2) **Proteins:** In normal muscle there is a delicate balance between muscle protein synthesis and protein degradation. It is believed that this balance is disturbed in muscular dystrophy (MD) by decreased muscle protein synthesis and/or increased muscle protein degradation, resulting in net catabolism. In an attempt to reduce or reverse this catabolism, a high protein diet is essential. High Biologically available protein sources needs to be consumed, for e.g., lean meat, egg whites, milk and its products, soybean, pulses and legumes and sprouts. For some, protein supplements are recommended to meet the higher protein requirements.

The following are the requirements of Energy and proteins as per age per day:

AGE/SEX		**IBW (kg)**	**ENERGY (kcal)**	**PROTEINS (gm)**
Infants	0 - 6 months	5.4	92/kcal/kg/d	1.16g/kg/d
	6 - 12 months	8.4	80 kcal/kg/d	1.69g/kg/d
Children	1 - 3 yrs	12.9	1060	16.7
	4 - 6 yrs	18	1350	20.1
	7 - 9 yrs	25.1	1690	29.5
Boys	10 - 12 yrs	34.3	2190	39.9
Girls	10 12 yrs	35	2010	40.4
Boys	13 - 15 yrs	47.6	2750	54.3
Girls	13 - 15 yrs	46.6	2330	51.9
Boys	16 - 17 yrs	55.4	3020	61.5
Girls	16 - 17 yrs	52	2440	55.5

3) **Fats:** Fat is essential in our diet as it forms a protective layer around our organs and aids in digestion of fat soluble vitamins like Vitamin A, D E and K. A person requires 4 Tsp of oil in a day. However, fat from ghee, butter, cheese, coconut is saturated and needs to be avoided. Omega 3 fatty acids, present in Fish/fish oil, flaxseeds and walnuts is an anti inflammatory. It helps in strengthening the cell wall and supports formation of new muscle cells to repair the injured muscle.

4) **Carbohydrates:** Carbohydrates are the energy givers of our daily diet. A balanced

diet includes a wide variety of cereals like jowar, bajra, ragi (nachni), poha, rawa or sooji, maize or makkai, wheat, wheat bran (with the outer husk), dalia are a few to name. Cereals are energy dense and also contain loads of fibre and micronutrients which are required by our body in small amounts. Cereals form the bulk of the staple Indian Diet. They also contribute towards the carbohydrate intake hence must be taken in lower amounts during the second half of the day as physical activity is restricted and may lead to weight gain.

5) **Fiber:** Low fiber foods tend to cause most trouble with constipation, such as highly processed snack and junk foods, fried foods, too much of red meat, ice cream and cheese. These foods are low in nutritional value and hence should be replaced with healthy alternatives like whole grain cereals, pulses, fruits and vegetables with skin and seeds like fenugreek seeds, pumpkin seeds, and sunflower seeds.

6) **Pre and Pro Biotic:** Make pre and pro biotic a regular part of the diet to help build healthy bacteria in the gut and help relieve constipation. E.g. yogurt (freshly prepared, 4 hourly set curd), yakult drink or commercially available supplements.

7) **Vitamins and Minerals:**

   a. Vitamin E and Selenium are antioxidant and anti inflammatory. It has been found to have protective effects in stress induced muscle injuries. Vitamin

E deficiency has been understood to lead to a nutritional myopathy. Rectification of deficiency, leads to muscle protection and amelioration of muscular dystrophy. It is hence essential to take Vitamin E supplements.

b. Calcium and Vitamin D, confined to a wheelchair, patients with MD inevitably develop bone weakening osteoporosis, although the process often begins before patient becomes wheelchair bound. Patients on steroids therapy have a declining bone health and are prone to fractures especially of legs and spine. Hence, Calcium and Vitamin D supplementation might be essential. Sources of calcium include, milk and its products, eggs, ragi, soyabean and its products and fortified foods. Vitamin D is generated within the body in response to adequate sunlight. Hence exposure to sunlight is essential.

c. Coenzyme Q10 (CoQ10), is a natural compound made by the body and found in most foods. It improves the use of oxygen at the cellular level, particularly in muscle tissue, and is being used as a treatment for muscular dystrophy.it has also been found to improve physical performance of patients with MD. Regular doses begin at 100 - 200 milligrams a day.

d. Magnesium, folate, Vitamin B6 and B12 are required for building muscles, bones and synthethis of cells.

e. Supplements, such as carnitine, creatine, amino acids (arginine), anti-inflammatory/anti-oxidants (fish oil, vitamin E, green-tea extract), and others, are being used by some parents and are endorsed by some practitioners. Antioxidants present in Green tea and vegetables and fruits, also aid in neutralizing the free radicals so as to cause less trauma of muscles. Glutamine is not recommended and food containing added MSG should be avoided.

A multivitamin supplement along with antioxidants and other necessary minerals is thus recommended.

For patients with problem in chewing and swallowing might require a placement of tube in situ to meet the nutritional requirements. It can provide either total or supplemental nutrition and can be used for short term or long term management.

It is vital to seek referral to dietician when tube feeds have been recommended.

Why is it important to maintain adequate weight?

i. To reduce the burden on weakened muscles

ii. To maintain mobility and flexibility of the body

iii. To maintain range of motion of the joints of the body

iv. To reduce the strain on respiratory muscles and delay onset of heart complications

v. To reduce the risk of scoliosis

vi. To reduce difficulty of transfers, especially for care takers if individual is immobile

vii. To reduce fatigue

viii. To minimize the effect on patient's ability to walk

Simple to follow instructions in case of muscular dystrophy

1. Small frequent meals must be consumed every 2 hourly.
2. A balanced meal includes all the nutrients required for the day.
3. Breakfast is the most important meal of the day.
4. Avoid too much carbohydrate rich foods in the second half of the day. All cereals are rich in carbs - rice, wheat, poha (rice flakes), rawa (semolina), maida (refined wheat flour), breads etc.
5. Plenty of protein rich foods to be consumed all throughout the day. All pulses, sprouts, soya bean, paneer (cottage cheese), nonvegetarian foods such as eggs, fish, chicken, lean meats, milk and milk products are good sources of proteins.
6. Additional supplements for omega 3 fattyacids can help a great deal after stem cell therapy. Some food sources of omega 3 fattyacids are almonds(badam), walnuts (akrod), olive oil, flaxseeds, eggs. These foods must be consumed on regular basis.
7. Including foods rich in znic and selenium also proves useful as patients are seen having a deficiency of the same.
8. Reduction in the total amount of fat ie: oil, butter, ghee, cheese, coconut, groundnuts, selected dryfruits like cashewnuts, kismish is required.
9. Simple sugars and sweets can add to a lot of calories in the daily diet hence must be avoided as far as possible.
10. Fresh vegetables and fruits not only add fiber to the diet but also lower in calories compared to carbohydrate rich foods or foods high in fat.
11. Whole cereals like jowar, bajra, ragi, oats must be encouraged as they have a higher fiber content.
12. Any fried food if desired must be eaten for breakfast in small amounts as it can be digested throughout the day.

13. Consumption of egg whites increases the protein intake as well as keeping the calories low.
14. Chicken and fish also can be included in the daily diet as long as the preparation does not involve too much of fat content.
15. Cooking methods such as boiling, grilling, steaming can help reduce oil and fat content in the foods.
16. Whole pulses and sprouts must be consumed on daily basis to increase the protein, fiber and micronutrients especially for vegetarian patients.
17. Green tea is found to be very rich in antioxidants that prevent the degeneration of the muscles hence must be consumed daily. It also aids in digestion and helps in weight loss. At least 2 to 3 cups of green tea must be consumed per day.
18. Make eating a pleasurable one for the patient.
19. Adding lot of colourful vegetables and fruits to the plate will make eating healthy foods an enjoyable one.
20. Choice of foods that the parents make is very essential as the child looks upon them.

How to manage constipation?

Constipation is one of the major concerns of the parents. Patients do not consume enough fiber and water in the daily diet hence leading to constipation. Excess water leads to frequent urination the fear of which forces them to consume less amounts of water. Drinking small amount of water at equal intervals of half hour to one hour can ease the situation. A glass of warm water early in the morning helps in bowel motion.

Precautions to take if the individual is on regular steroids

MD patients on steroids often have fluid and salt retention causing further puffiness and weight gain. Therefore the fluid and salt intake must be calculated accordingly. They also experience increased hunger pangs which must be controlled strictly.

Special considerations

- Small frequent meal needs to be consumed. Breakfast being the most important meal of the day.
- High protein diet is recommended.
- Avoid too much carbohydrate rich foods like refined flour (maida), bakery products, simple sugars, sweets,
- Avoid foods rich in Fats like, fried foods, cashew nuts, ghee, coconut, red meat, butter.
- Use cooking methods such as boiling, broiling, sautéing, pressure cooking, steaming, roasting, poaching, grilling.
- Consume lots of vegetables and fruits.

- Consume enough fluid to hydrate
- A balanced meal is essential. Everything in moderation is the key to good health. Quantity restriction is what one needs to pay attention at.

Menu Plan for Indians (Non Veg)

Nutritive Value: Energy: 1800 kcal
Protein: 65 gm

Meal Pattern	Food Group	Units	Sample Menu
Morning:	Milk	1/4 unit	Tea/Milk/coffee
Breakfast:	Cereal	2 units	Paratha, 1 no
	Milk	1/2 unit	Tea/Milk/coffee
	Fat	1 unit	For cooking, 1 tsp
	Lean meat	2 unit	Omlette, 1 (2 Egg Whites)
Mid Morning:	Fruit	1 unit	Apple
Lunch:			Soup, optional
	Cereal	3 units	Roti, 2 no
			Rice, 1/2 cup
	Vegetable	2 units	a) Cauliflower bhaji
			b) Tomato, carrot & radish slices
	Lean meat	3 units	Grill fish, 3 pc
	Fat	1 unit	For cooking, 1 tsp
Mid Afternoon:	Milk	1/4 unit	Tea/Milk/coffee
	Nuts	1 unit	2 no almonds, walnuts
Dinner:			Soup, optional
	Cereal	2 units	Roti, 1 no
			Rice, 1/2 cup
	Pulse	1 unit	Dal, med, 1 cup
	Vegetable	2 units	a) Palak bhaji
			b) Coleslaw salad (no mayo)
	Milk		
	Fat	1 unit	For cooking, 1 tsp
Bedtime:	Milk	1 unit	Hot milk, 1 cup
	Fruit	1 unit	Orange, 1 no

Menu Plan For Western Countries

Meal Pattern	Food Group	Units	Sample Menu
Morning:	Milk	1/4 unit	Tea/Milk/coffee
Breakfast:	Cereal	2 units	Oats porridge, 1 cup
	Milk	1/2 unit	Tea/Milk/coffee
	Fat	1 unit	For cooking, 1 tsp
	Lean meat	2 unit	Poached Egg, 1 (2 Egg Whites)
Mid Morning:	Fruit	1 unit	Apple
Lunch:			Soup, optional
	Cereal	3 units	Whole Wheat Pasta, 1 1/2 cup
	Vegetable	2 units	a) Mix B.Veg
			b) Tomato, carrot & radish slices
	Lean meat	3 units	Grill fish, 3 pc
	Fat	1 unit	For cooking, 1 tsp
Mid Afternoon:	Milk	1/4 unit	Tea/Milk/coffee
	Cereal	1 unit	Biscuits, 2 no.
	Nuts	1 unit	2 no almonds, walnuts
Dinner:			Soup, optional
	Cereal	2 units	Brown Rice, 1 cup
			Rice, 1/2 cup
	Pulse	1/2 unit	Beans stew, 1/2 cup
	Vegetable	2 units	a) Stir fry veg
			b) Coleslaw salad (no mayo)
	Lean Meat	1 unit	Grill Chic, 1 pc
	Fat	1 unit	For cooking, 1 tsp
Bedtime:	Milk	1 unit	Milk, 1 cup
	Fruit	1 unit	Orange, 1 no

16.

Cardio-respiratory Rehabilitation

Although muscular dystrophy is mainly a disease of the skeletal muscles, the pathology also has its effects on the breathing (respiratory) muscles and heart (cardiac) muscles. This causes direct impairment of the function of the lungs and heart (cardio-respiratory function). In addition to this due to increasing movement limitation and skeletal deformities there is indirect impairment of the cardio-respiratory function. Therefore early cardio-respiratory endurance training exercises are recommended in case of muscular dystrophy. These exercises have many beneficial effects on the respiratory system and cardiac system which prevent rapid deterioration and secondary complications. Cardio-respiratory endurance exercises are the exercises that are performed to improve the capacity of the heart to circulate blood and capacity of the lungs to improve oxygenation of the blood during increasing physical effort.

Benefits of cardio-respiratory endurance exercises

1. Heart and lungs

- Increased blood pressure as immediate response exercises improving the blood circulation
- Reduction in the blood pressure as a late response to exercises reducing the cardiac stress
- Improved capacity of the heart to pump blood
- Improved return of the blood from extremities to heart preventing stagnation of the blood in extremities
- Improved capacity of the lungs to breath in the air
- Improved oxygenation of the blood
- Improved clearance of carbon dioxide from the blood
- Ability to breath air out more forcefully
- Prevention of aspiration and secondary respiratory infection
- Improved ability to clear secretions by coughing, preventing secondary respiratory infection

2. Blood vessels and blood circulation

- Formation of new blood vessels
- Improved connections and network of blood vessels
- Improved circulation to the deep muscles of the body, brain, lungs, liver and kidney
- Improved clearance of toxic waste substances from the blood

Stage 1: Pre-symptomatic (0-4 years)

In the pre-symptomatic stage, cardio-respiratory endurance activities are performed in the day to day routine of the children. Therefore there are no specific exercises to be performed however the children must be allowed to carry out their daily and peer activities. They should be encouraged to engage in moderate play activities and shouldn't be prevented from doing so.

Stage 2: Early ambulatory stage (4-8 years)

Aim of cardio-respiratory endurance training:

- Improve baseline heart and lung function
- Prevent rapid deterioration
- Enhance breathing capacity

Cardiac endurance exercises:

In the early ambulatory phase the child can perform moderate intensity cardiovascular endurance training activities without damaging the muscles. The intensity of the exercises is decided by the therapist based on the heart rate and blood pressure response of the child to the exercise. Physiotherapist will first conduct a 6 minute walk test. In this test a child will be walking (running or jogging will be prevented) to cover maximum distance in 6 minutes. Heart rate, blood pressure, breathing rate and rate of perceived exertion will be measured before, during and after the test. Based on the distance covered the heart rate, blood pressure, breathing rate and perceived exertion response, exercise prescription will be given. The physiotherapist will observe the physical performance of the child in preliminary assessment sessions and record the response of the heart rate, blood pressure and breathing rate (respiratory rate) to determine which activities can be performed and for how long. A simple scale called Pictorial Children's Effort Rating Scale (PCERT) (Figure) will be used.

Most commonly moderate intensity exercises between 5 - 6 on PCERT scale will be prescribed for 30 - 40 mins, 5 times a week.

Based on the capabilities of the child, various activities that can be performed for cardiac endurance training are: Cycling, swimming, walking, running, arm cycling, aerobic exercises, dancing, rowing, training on elliptical and step exercises.

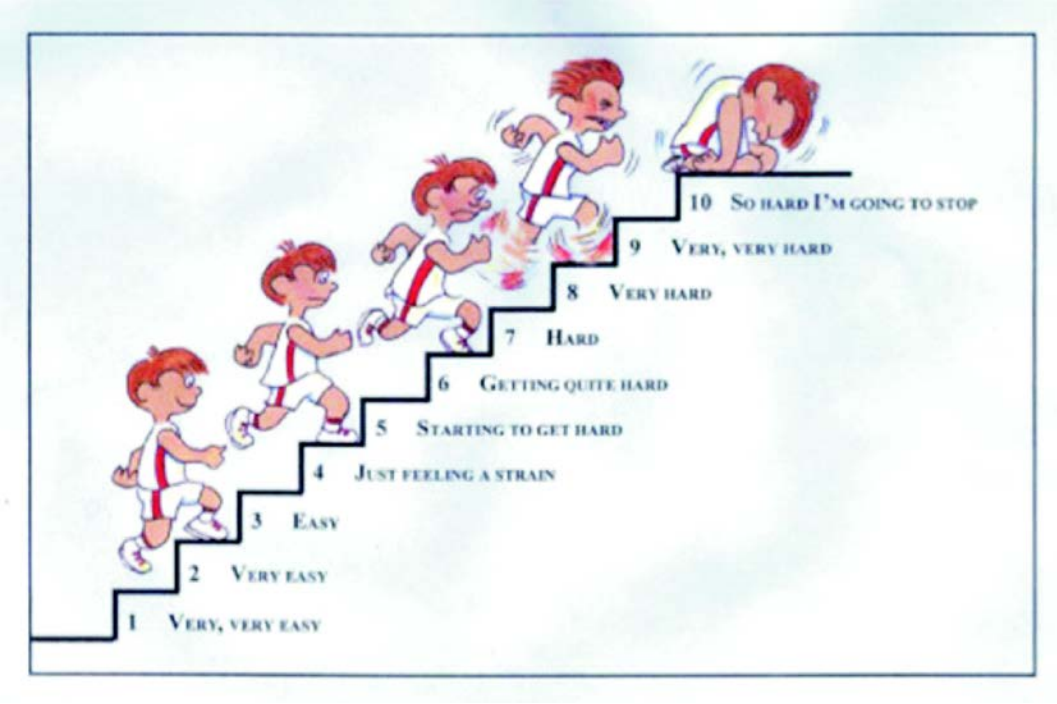


Figure 16.1 : Pictorial Perceived Exertion Scale for Effort Estimation and Effort production

Table 2: Borg scale of perceived exertion

Rating	Description
6	No Exertion
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very Hard
18	
19	Extremely hard
20	Maximum exertion

Respiratory endurance exercises:

Respiratory endurance training exercises during this stage include playful activities like blowing balloons, blowing candles, making bubbles in the thick paste to improve the expiratory muscle strength and endurance. To improve the inspiratory muscle strength and endurance, children can be encouraged to participate in playing instruments like mouth organ and flute and singing. They can also be encouraged to partake in the outdoor play activities or swimming. At this stage regular physical activity is important to maintain the respiratory endurance.

Stage 3: Late ambulatory phase (8-13 years)

Aim of cardio-respiratory endurance training:

- To prevent any chest infection.
- To facilitate secretion clearance
- To prevent heart related complications
- Enhance and maintain cardiac endurance required for physical function

Cardiac endurance exercises:

Some individuals may develop respiratory difficulty or cardiac complications in this phase. Depending upon the cardiorespiratory assessment the physiotherapist will prescribe the exercises. Most commonly moderate intensity exercises between 11 - 13 on Borg scale will be prescribed for 30 -40 mins, 5 times a week.

Exercises can include different activities, based on persons capabilities like; Cycling, swimming, walking, running, arm cycling, aerobic exercises, elliptical training

In addition to exercises your physician may refer you for an opinion from a cardiologist. As indicated medicines to prevent cardiac complications in the later stages may be started

Respiratory endurance exercises:

Respiratory exercises will be prescribed to improve the capacity of breathing in and out and to strengthen respiratory muscles like diaphragm and intercostals muscles. Performing these exercises from early stage can prevent rapid respiratory deterioration in later stages. These exercises will also help clear the airways better and therefore reduce the secondary respiratory complications in the later stages of the disease.

1. Pursed Lip Breathing

Technique:

Breath in through your nose with your nostrils opened up wide for about 2 seconds. Pout/pucker your lips as if you are blowing a candle and slowly breathe out through puckered lips. Make sure to breath out very slowly at least two to three times slower than breathing in.

Frequency:

Perform 10 to 20 breaths, 6 to 7 times /day

Benefits:

- Slows down breathing ensuring that the bad air is exhaled completely
- Because of the resistance provided by puckering lips airways remain open for a longer time and more of the stale and trapped air can be thrown out.
- Efficiency of breathing is reduced
- Respiratory endurance improves
- One can perform a physical activity for longer without getting breathless
- Uptake of oxygen and exhalation of carbon di-oxide is better

2. Diaphragmatic strengthening / Deep breathing exercises

Diaphragm is the most important muscle responsible for breathing. When it does not perform optimally muscles of shoulder and neck are used for breathing hindering their primary work of joint movement and stability. Therefore total muscle work responsible for breathing increases a lot and muscles get fatigues sooner. It is therefore important to strengthen the diaphragm and practice diaphragmatic breathing to improve breathing efficiency.

Technique:

Perform diaphragmatic breathing in a resting position either sitting or lying down. Relax your neck and shoulder muscles. Slowly breathe in air through your nose and hold for 2 seconds. Placing one hand on your chest and the other on your belly make sure that your belly moves outwards first as you breath in. Chest should follow your belly. Pucker your lips slightly as you breath and then gently press on your belly to maintain pressure over the diaphragm.

Frequency:

Perform 10 to 20 breaths, 6 to 7 times / day

Benefits:

- Improves efficiency of breathing
- Prevents rapid respiratory deterioration
- Air circulates in the deeper parts of the lungs
- Accessory muscles like neck and shoulder muscles are preserved
- Reduces breathlessness

3. Forced exhalation

Technique:

Perform this exercise after deep breathing exercise. To perform forced exhalation be seated on a chair or rested on the bed. Take a deep breath. As you breathe in make

sure your belly rises outwards. Hold the breath for 2 seconds and squeezing your stomach forcefully expel the air through pursed lips. In case any sputum is generated cough and throw it out. Repeat the forced breaths for 6 - 8 times and then perform deep breathing exercises for 3 -4 times.

Frequency:

6 - 8 Breaths of forced exhalation followed by 3 to 4 breaths of deep breathing, repeat the cycle 3 times; perform this morning and evening every day.

Benefits:

- Improves efficiency of breathing
- Facilitates deep inhalation
- Circulation of air in deeper parts of the lungs
- Uptake of oxygen and exhalation of carbon di-oxide is better
- Ensures that the bad air is exhaled completely
- Helps clear the secretions

4. Inspiratory Spirometry

Technique:

Sit in the chair with back supported. Hold the Incentive Spirometer in front of your straight up. Hold the mouthpiece in your mouth tightly and seal it with your lips. Breath in through your mouth slowly and as deep as possible. Breath out through your nose and wait for the piston to fall down to bottom. Repeat the same procedure 8 -10 times. Perform 2 -3 normal breaths. If any accumulated secretions loosen up cough and throw it out to clear your throat. Repeat 8 - 10 breaths with the spirometer.

Frequency:

Perform 3 cycles, 4 to 5 times / day

Benefits:

- Strengthens respiratory muscles
- Prevents rapid respiratory deterioration
- Improves efficiency of breathing
- Facilitates deep inhalation
- Circulation of air in deeper parts of the lungs
- Uptake of oxygen and exhalation of carbon di-oxide is better

Important considerations:

- A doctor should be consulted at least once in a year and forced vital capacity test should be done.
- Flu and pneumonia should be not considered lightly.
- Regular breathing exercises should be done under the supervision of a physical therapist.

- Proper antibiotics should be administered in case of any infection or any chest infection.
- If admitted for any surgeries, doctors should be informed not to give any inhaled anesthesia or succinylcholine. (This is very important and can be lifesaving)
- If any breathing machine is used, care should be taken to ensure that the apparatus is properly fitted and also timely sterilized.

Stage 4: Early Non-ambulatory stage (11-16 years)

Aim of cardio-respiratory endurance training:

- Facilitate deep breathing and improve lung capacity
- Manage secondary heart complications
- Prevent severe debility due to poor heart and lung function
- To prolong requirement of assistive breathing such as Bi-Pap.

Cardio-respiratory endurance training:

Due to increased incidence of cardio-respiratory complications in this phase, the exercises are aimed at maintenance of the cardio-respiratory function. Most commonly exercises of moderate intensity between 11 -13 on borg scale for 30 -40 mins, 5 times a week. However, it is important to monitor the response during this stage. In addition to exercises medical management of cardiac complications as explained in chapter 5 and Chapter 8 is essential.

Respiratory exercises:

Respiratory exercises in this phase are not only aimed at improving muscle strength but also improving the secretion clearance. Due to weakness of respiratory muscles, swallowing difficulty and limitations of positioning there are increased secretions and ineffective secretion clearance in this phase. In addition to the exercises as explained earlier following exercises should be performed for clearing secretions.

Huffing and coughing

Technique:

Take a deep breath. Make sure that your belly rises outwards as you breathe in. Hold your breath for 2 seconds. Open your mouth wide and forcefully breath out squeezing your belly. You may also apply some pressure on your belly with your hands. Huffing is different from forced exhalation. In huffing you open your mouth wide in forced expiration mouth is pursed. Perform 8 - 10 huffs, if any secretions are mobilized cough and spit it out. Perform more huffs, if more secretions are present or chest congestion is persistent. Make sure to perform deep breathing exercises after coughing.

Frequency:

Perform 2 to 3 cycles or till the secretions are cleared

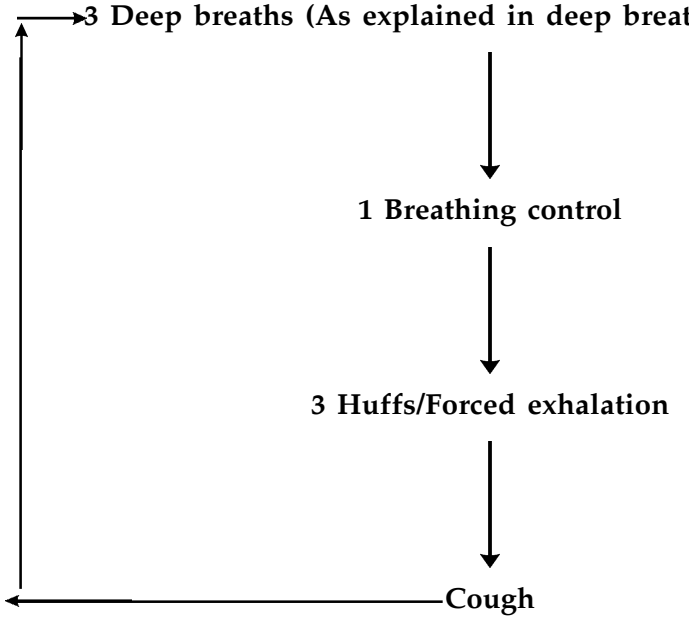
Benefits:

- Helps to mobilize secretions from the deeper regions in the lungs
- Airways are cleared
- Improved oxygenation of the blood
- Improved throwing out of the carbon dioxide
- Reduced risk of infections

Active cycle of breathing techniques

Technique:

Active cycle of breathing technique consists of various performing breathing control (deep breathing), huffing and coughing in a cyclic pattern. It helps for best mobilization and removal of the secretions. Breathing control is relaxed breathing mainly used to control the speed and depth a breath. During the ACBT technique a person performs



3 - 4 such cycles are repeated till the secretions are cleared out.

Frequency: 1 -2 cycles / day or as and when secretions accumulate

Benefits:

- Helps to mobilize secretions from the deeper regions in the lungs
- Airways are cleared

- Improved oxygenation of the blood
- Improved throwing out of the carbon dioxide
- Reduced risk of infections

Positional drainage

Technique:

Positional drainage includes positioning a patient in a position conducive for mobilization of secretions depending upon the lobe of the lungs involved. It will be suggested to you by your therapist after detailed respiratory assessment and auscultation. The positions are simple achieved using stack of pillows for support. After each position perform ACBT or Forced exhalation to clear secretions.

Frequency:

Each position should be maintained for 10 to 15 mins / twice a day

Benefits:

- Helps clear the lung secretions
- Passive relaxation
- Better oxygenation of the blood

Incentive spirometry

Deep breathing exercises

Diaphragmatic strengthening exercises

Pursed lip breathing

Forced exhalation

Stage 5: Late non-ambulatory (16 years and onwards)

Cardiac endurance exercises:

This is a maintenance phase. The cardiac exercises will consist of any activity the child can perform. It will mainly be the aquatic exercises as aquatic environment provides greater degree of freedom. The exercises should be performed for 30- 40 mins a day at the intensity of 9 -11 on Borg Scale.

Stop the exercises immediately in case of

- Rapid breathing
- Profuse sweating
- Chest pain
- Breathlessness
- Palpitations

In addition to the exercises in this stage the medical management of cardiac disorders is essential.

Respiratory exercises:

Focus of respiratory exercises will be on secretion clearance and maintenance of inspiratory capacity. Exercises to be continued in this phase are

Incentive spirometry

Active cycle of breathing technique

Positional drainage

Deep breathing exercises

Pursed lip breathing

In this stage in addition to these exercises assistive devices like Bi-Pap or artificial ventilator may be required for breathing. Care of these devices is very important. Maintaining aseptic conditions to minimize chances of infection is of utmost importance.

As the symptoms progress in this stage the children become more and more dependent on the artificial ventilation. They may require permanent ventilator support. Support for breathing can be provided by surgical and non-surgical means. This is explained in detail in chapter 9, Respiratory management. The main aim of cardiovascular rehabilitation at this stage is to mobilize and clear the secretions. This is achieved by a suctioning. Which can be performed by the nurse of physiotherapists.

Cardio-respiratory rehabilitation is a very important area in the management of muscular dystrophy and it should not be neglected. Parents and caregivers must make sure that adequate care and training is provided to improve cardiac and respiratory health and maintain it for a longer time with fewer complications.

For everything there is a season,
and a time for every matter under heaven:

A time to be born and a time to die;
A time to plant and a time to pluck what is planted;
A time to kill and a time to heal;
A time to breakdown and a time to build up;
A time to weep and a time to laugh;
A time to mourn and a time to dance;
A time to cast away stones and a time to gather stones together;
A time to embrace and a time to refrain from embracing;
A time to seek and a time to lose;
A time to keep and a time to cast away;
A time to rend and a time to sew;
A time to keep silence and a time to speak;
A time to love and a time to hate;
A time for war and a time for peace.

Ecclesiastes: Chapter 3, Verse 128

SECTION - III

Hollistic Approach in Muscular Dystrophy

17.

Yoga Therapy

योगस्थः कुरु कर्माणि सङ्गं त्यक्त्वा धनञ्जय।
सिद्ध्यसिद्ध्योः समो भूत्वा समत्वं योग उच्यते॥ ४८॥

(yoga-sthah kuru karmani sanyugam tyaktv? dhananjay
siddhy-asiddhyoh samo bhutvh samatvam yoga ucyate)

- Bhagavad Gita 2.48

Sri Swami Satchidananda, the late founder of Integral Yoga, believed that true and lasting happiness is our very own nature: what we seek is already found within. Integral yoga is a sweet and gentle style that, today, is taught throughout the world.

We might already have an idea of what Yoga is but to understand it better, we have to know what it has become as well as its roots and beginnings. A quick look at the history of Yoga will help us appreciate its rich tradition and it might help us incorporate Yoga into our lives.

Although Yoga is said to be as old as civilization, there is no physical evidence to support this claim. Earliest archaeological evidence of Yoga's existence could be found in stone seals which depict figures of Yoga Poses.

The American Institute of Vedic Studies which aims at researching the original Vedic Yoga also follows the teachings of Ganapati Muni, the chief disciple of the great South Indian sage Ramana Maharshi, and Ganapati's disciple, Daivarata Vaishvamitra, whom Maharishi Mahesh Yogi once brought to the West and called a great modern Rishi. This Yoga is also connected with the work of the great modern seer-poet Sri Aurobindo, who based his integral Yoga on a Vedic model, and Kapali Shastri, an important disciple not only of Sri Aurobindo but of Ganapati Muni.

Yoga is an ancient Indian mind body technique which is becoming increasingly popular throughout the world because of its several health benefits. Yoga is an integrated system of self culture which aims at harmonious development of body, mind and covers all aspects of human life that lead to physical well being, mental harmony

culminating into positive thinking, happiness and peace. Yoga envisages health in totality on the principle of healthy mind in a healthy body. Yoga is not merely a few postures (asanas) but a holistic life style which promotes physical, mental, emotional and spiritual well being. Although there are many types of yoga, Hatha Yoga is most commonly practiced. Core components of Hatha Yoga include stretching exercises and physical postures (Asanas), breath control (Pranayama) and concentration techniques (Meditation). Yoga is believed to help detoxify the body, mitigate chronic fatigue, enhance endurance, improve organ and immune functions.Beneficial effects of yoga have been reported in multiple chronic conditions including depression, stress, anxiety, menopausal symptoms, arthritis, low back pain, cancer, allergies, asthma, acid peptic disease, irritable bowel syndrome, migraine, metabolic syndrome, diabetes mellitus, cardiovascular diseases (CVD) etc. Yoga appears to be especially beneficial for primary and secondary prevention of CVD.

Therapeutic aspect of yoga is it includes the effective psychotherapy which brings harmony between body and mind. Yoga plays an important role in the prevention and cure of heart diseases, it can also alleviate the intensity of the cardiac disorders and revert it to stable condition. The heart has a direct relationship with the mind. The way to a healthy heart is through specific Asanas (postures), five bodily purifications, Pranayama (breathing exercises) and the art of meditation, which influences sympathetic parasympathetic and central nervous system. An enzymatic substance Dopamine-beta-hydroxylase (DBH) is secreted during meditation which reduces peripheral epinephrine activity in response to emotions and other stimuli also helps to reduce blood pressure and other cardiac disorders.

It has been shown that meditation acutely increases circulating level of melatonin which leads to the activation of pineal gland. Melatonin, being small and amphophilic, distributes throughout all tissue components and fluids. It can be found in greatest subcellular concentrations in mitochondria. Melatonin has been shown to protect healthy tissues from a wide range of offending agents like toxins, radiation, caloric, and metabolic insult through antioxidant and anti-apoptopic mechanisms in healthy tissues . Pranayama practice in the yoga schedule might have a role in reducing the oxidative stress. As an example, diaphragmatic breathing has been reported to reduce oxidative stress by decreasing cortisol that which inhibits enzymes responsible for the antioxidant activity of cells and by increasing melatonin, which is a strong antioxidant

Many published research studies indicate that patients who undergo yoga therapy show significant improvement in oxidative stress and inflammatory markers. Continued efforts should be made by researchers and clinicians to educate regarding the benefit of yoga therapy in order to improve TAOS, reduce MDA, RER, and inflammatory markers.

Yoga Therapy

As we have seen in this chapter, that management of debilitating and degenerative diseases like muscular dystrophy involves multifold aspects. It is generally a combination of conventional medical treatment with rehabilitation techniques. The

importance of rehabilitation techniques such as physiotherapy, occupational therapy and psychological rehabilitation cannot be over emphasized. All of the above therapies prove to be significant in managing the conditions arising out of the underlying neurodegenerative disease such as muscular dystrophy. But as with all forms of treatment, there is always room for improvement. This therapeutic gap can be filled by an ancient India wisdom for treatment of various conditions of the mind and body,namely Yoga Therapy.

As much as a fancy term Yoga is globally these days, its utility and impact in improving the well being of an individual is an established fact. Yoga is increasingly used by people all over the world to improve their physical fitness, as a stress reliever, to improve concentrations and lastly to enhance the spiritual experience. But the extrapolation of yoga therapy in the treatment of a myriad of diseases has only surfaced in recent times.

In order to truly gain the massive benefits from this ancient science, one needs to grasp the complete meaning of Yoga and the manner in which it heals both, the mind and the body.

The philosophy of yoga originated some 2000-3000 years ago, although according to Hindu texts its origin can be linked right to the beginning of mankind. It was Saint Patanjali who organized the science of yoga into a systematic practice and is rightly known as The Grammarian of Yoga. So what is Yoga? It is the union of mind and body,of conscious with the subconscious, of Jivatma with the Parmatma. It is a way of life. It is in effect the science of healthy living wherein one attains physical, intellectual, mental…

Yoga for Muscular Dystrophy

Inclusion of a therapeutic practice like yoga, in tandem with physiotherapy and occupational therapy can help mitigate the conditions of muscular dystrophy and greatly improve the quality of life. Yoga therapy uses asanas that involve stretching and relaxation of various muscles, in combination with deep breathing techniques to improve muscle tone and reduce pain. Research shows that the benefits of yoga for movement disorders include improved strength, flexibility, balance, overall fitness and quality of life.

Each individual has a different degree of muscular and neurological degeneration caused by the disease. Muscle spasms, atrophy and rigidity associated with this disorder often restricts balance and range of motion. Limits to balance and range of motion restrict the ability of individuals with movement disorders from practicing traditional yoga poses in a way that is beneficial to them. Yoga for movement disorders is marked by a practice that addresses the needs particular to people living with movement disorders. Yoga therapy needs to be customized according to the patient after studying his medical history in detail. Each asana has a specific purpose and helps specific areas of the body.

Thus not every asana can be prescribed to every patient in general. This is one of the main reasons that parents must help the individual suffering from muscular dystrophy

in practicing Yoga on a regular basis. Also, it is of absolute importance to consult a yoga expert to evaluate which asanas can be recommended to the individual, in order to facilitate his/her existing physiotherapy While physiotherapy is important to increase muscle strength, the entire exercise can be tiring and painful. But Yoga helps in reducing the physical and mental stress. Deep breathing techniques help in infusing more oxygen into the blood as opposed to regular shallow breathing. This improves blood circulation, strengthens the weakening muscles and helps in the removal of toxins that accumulate in the body. Yoga also addresses the mental and emotional damage caused by the illness. It helps to infuse positive energy into the individuals and thus help them to increase their inner strength to fight off depression & anxiety that characterize such illnesses. It inducts a surge of hope into the individuals.

We will illustrate here some of the simple yet powerful asanas that help in muscular dystrophy.

Pranayama

Prana means Life and Ayam means control. Pranayam means control of the inner force of human life. The breath we breathe in and out is regarded as Prana which means bioenergy that endows man with ultimate potential for self-development. It is the vital life force. But man must suitably control and channelize the prana or use it for right end. Yoga prescribes various practices of Pranayama or control of Prana popularly referred to as breathe control. The yogic breathing itself becomes a prayer, a satisfying spiritual experience in which one is aware of the living presence of God.

Benefits of Pranayama

1) Better blood circulation.
2) More oxygenation.
3) Longeveity i.e.full health life.
4) Mental concentration.
5) Increase in lung elasticity and capacity.
6) Purifies blood.
7) Emotional control.
8) Cheerfulness.
9) Prevention to diseases.

Pranayam can be performed in Sukhasana.

Sukhasana

Life is a series of activities. We conclude one activity only to start another. A preparedness kriya allows a person to be mentally prepared for an activity. Sukhansana is one of the many asanas which quieten the mind. This asana is named for preparedness or conditioning. But muscular dystrophy patients have to sit in a comfortable pose. If patients are not able to sit, they can do by laying down as well.

There are 3 types of Pranayama which we describe here:

Pranayama (I): Equalization of inhalation & exhalation

Technique: Sit firmly and comfortably. *Breathe in out for equal counts. *Breathe 10 times. (Fig. 17.1)

Fig. 17.1

Fig. 17.2

Benefits:

- Augments pleasant feelings throughout whole body.
- Helps to calm the mind.

Pranayam (II): Inter costal Breathing

Technique : Hands on the side of the chest,*Make chest rise up as you breathe in for 3 seconds and fall as you breathe out for 3 seconds. *Repeat 10 times. (Fig. 17.2)

Benefits:

- Activates the abdominal organs, provides a gentle massage, releases flatus and reduces fat in the abdominal region (best for muscular dystrophy because fat can be reduced).
- Helps in respiration and relaxation.
- Useful in insomnia.

Pranayama (III)

Technique: Sit in an asana for preparedness. *Use the little finger to block the other nostril. Breathe out from the open nostril. *Do same for the other nostril. *Repeat 10 times.

Benefits:

- Sedative effect on the tone and rhythm of the heart & brain.

Asanas for Muscular Dystrophy

1. Parvatasana (Fig. 17.3 and 17.4)

Technique: Sit in comfortable pose,

- Both the hand should be on both sides of the body.
- Inhale for 3 seconds, raise both the hands simultaneously upward and above the head, palms facing upward.
- Keep the elbows straight & join the palms.
- Pull the abdomen slightly inside. Hold breath. *Exhale for 3 seconds, bring the arms down.

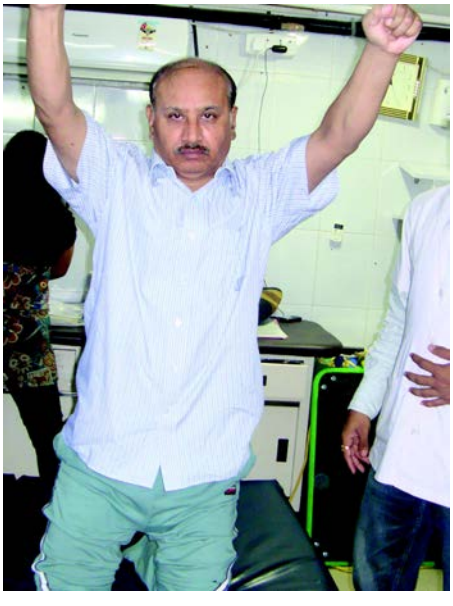


Fig. 17.3

Fig. 17.4

Benefits:

- Stretches all the abdominal and pelvic muscles.
- Loosens the hip joints.
- Helps to reduced the flatty and flabby abdomen.
- Improves the shape of body.(It is very beneficial for MD).

2. Yastikasana

Technique:

Lie on back legs fully extended and arms extended at the side.

- Be relaxed, inhale and raise arms above the head, rest them on the floor and stretch.

- Holding breath, slowly stretch the body at full length, the toes and fingers pointing outward, as if trying to reach out. (Any attempt at maximum stretching of the body should be only during retention of breath).
- Repeat 3 to 4 times with in-between pose.

Benefits:

- Corrects faulty posture.
- Tenses the usually relaxed abdominal and pelvic muscles.
- Offers relaxation, when maintaining a non-stretch, passive attitude.
- Removes spasm.

3. Stretching

In muscular dystrophy limbs are always weak, if one cannot to do the asanas properly, then patients have to stretch only to the extent they can. But stretching is compulsory for patients with MD. In Yoga, slow stretching is very beneficial. Patients need to do the stretching regularly.

A lot of yoga research, as it's currently constructed, focuses on the short term, with trials often lasting only 8 to 12 weeks. "Yoga is a powerful intervention, but a gradual one," explains Dr. Timothy McCall, a board-certified specialist in internal medicine, a longtime yogi, and the medical editor of Yoga Journal. "So examining it for that amount of time won't capture more than a fraction of what it can do."Still, McCall would rather see yoga studied than not. "Will studying yoga show the scope of what it's capable of? Not at all," he says. "But is it helpful? Absolutely. It allows us to make the case to skeptical physicians, policymakers, and others that yoga can be a promising treatment modality for people with specific health conditions."

योगस्थः कुरु कर्माणि सङ्गं त्यक्त्वा धनञ्जय।
सिद्ध्यसिद्ध्योः समो भूत्वा समत्वं योग उच्यते॥ ४८॥

(yoga-sthah kuru karmani sanyugam tyaktv? dhananjay
siddhy-asiddhyoh samo bhutvh samatvam yoga ucyate)

– Bhagavad Gita 2.48

18.

Vocational rehabilitation

Vocational rehabilitation includes vocational education and training. Vocational rehabilitation aims to reintegrate the individual with physical, mental and psychosocial impairments into the community and vocational activities suitable to their abilities.

Vocational Education: Vocational Education is defined as the field that aims to equip people with knowledge, know- how, various skills and / or competencies required in particular occupations or broadly on the labour market. It also involves developing expertise in a particular group of techniques.

Vocational training: Vocational Training is a centre based programme for individual with special needs that helps them develop and enhance their vocational skills and capabilities who are otherwise unable to access open employment and prepare them and give them a chance for employment. Vocational training in India is provided on a full-time as well as part-time basis. There are many private institutes in India which offer courses in vocational training and finishing, but most of them have not been recognized by the Government.

Various muscular dystrophy associations in the US are providing vocational training to muscular dystrophy patients. The Muscular Dystrophy Association (MDA), The Centre for Disease Control and Prevention (CDC), The United Parent Projects Muscular Dystrophy (UPPMD), The Cure CMD, The American Association on Health and Disability (AAHD) are some of the organizations committed in providing vocational education and training to children and adults with muscular dystrophy. These associations offer support and information to assist parents in preparing and advocating for the best education possible for their children. They also guide and advise young people with muscular dystrophy the information and opportunities related to transitioning to adulthood.

In muscular dystrophy patients the vocational rehabilitation is not only aimed at vocational activities but also at the educational activities as the limitations are observed right since childhood or teenages. Education plays a very important role in an individual's career. Education provides an opportunity to enhance quality of life, productivity and social relationships, and drives one to their best in mind and spirit.

Education is a tool to achieve employment in adulthood, it helps in overall growth of a person and understanding of the worldly processes and systems.

Muscular dystrophy causes children to have limited mobility, day to day activities and participation in the society. This leads to inabilities to move out of confined home areas, and learn and be a part of the society. Weakness, immobility, fatigue, learning disabilities, limited social interaction in these children impacts them within the school environment and limits their learning ability and performance. Thus, it is important to make the educational officials and professionals aware of their abilities, disabilities and needs.

Special Education

Special education is a form of instruction that is designed to meet the needs of students with disabilities, so that they can learn the same skills and information as other children in school. This process involves individually planned and systematically monitored arrangement of teaching procedures, adapted equipment and materials, accessible settings. These help learners with special needs achieve a higher level of personal self-sufficiency and success in school and their community, than that may be available if the students were only given access to a typical classroom education.

Principles of special education

i. Enabling the student to realize his or her potential as a unique individual through access to an appropriate broad and balanced curriculum;

ii. Enabling the student to function as independently as possible in society through the provision of such educational supports as is necessary to realize that potential;

iii. Enabling the student to continue learning in adult life.

When it comes to education of MD children, various special education strategies are being employed in almost all the nations and each and every city of the world which include strategies such as Inclusive education, Individual education programme, etc. Individual Education Plan (IEP) is a written plan prepared for a student which is additional to and different from the usual curriculum that is provided to every class, and is amended and updated as appropriate, depending on the individual needs of the student. The IEP contains key information including student's strengths and needs, student's current level of performance, targets, resources and personnel involved. The IEP must ensure that it is individualized and student-centered, inclusive, holistic, collaborative, accessible, and well implemented.

The Individuals with Disabilities Education Act (IDEA) provides the requirements for the planning of an IEP and the implementation of it. The Office of Special Education and Rehabilitative Services, U.S. Department of Education in July 2000 brought forward the guidelines for an IEP.

Apart from individually planned programme, various other strategies and modifications need to be made in school and classrooms such as:

Understanding with the parents:

- Parent/Student/Teacher Meeting - getting together with the child and his or her parents to best figure out the student's needs
- Working together with student, parents, counselors, etc. to promote student's well-being and offer full support

Educating other classmates and peers:

- Addressing muscular dystrophy in the classroom; educating other students about the disorder
- Seating student in an appropriate place in room so he/she can fully participate and doesn't feel out of the loop.
- Utilizing a 'Buddy system'
- Creating opportunities for inter-personal interaction through games, activities

Easy mobility and maneuvering through the school premises:

- Thought needs to be given to physical access and safety around the school building
- Making sure student has access to elevators and ramps
- Making enough space within the classroom for easy wheelchair maneuvering
- Scheduling washroom breaks or allow student to leave class a bit early to maneuver through the building

Prevention of fatigue and stress:

- Trying a variety of supplemental material that works best with the muscular dystrophy student to promote learning.
- Extending time for projects, assignments, and exams.
- Allowing extra time, if necessary, for the student to complete tasks.
- Reducing or eliminating physical exertion and stress by minimizing writing and allowing oral tests
- Scheduling periodic rest breaks

Provision of assistive devices:

- Utilizing different devices such as computers, light touch keyboard, speech recognition device, recorder, etc. to allow the student to keep pace with the rest of the class.
- Providing writing and grip aids
- Providing a page turner and a book holder

Provision of appropriate seating arrangements:

- Specialized seating may be utilized consulting with the occupational therapist.
- Ensuring that tables are suitable for a wheelchair.
- Table-type desks with adequate leg space need to be considered if the student has a wheelchair.
- The board in the classroom has to be lowered if the student is in a wheelchair.
- To facilitate students' reading, providing easels, portable reading racks or adjustable desks.

Involving the student in activities:

- Encouraging the student to be as active as possible to keep healthy muscles in condition as long as possible.
- Promoting the use of muscles whenever possible and appropriate.
- Adapting Physical Education activities in which the student can participate according to his/her abilities.

Continuous motivating and encouraging the student:

- Providing consistent encouragement and support for students.
- Encouraging active classroom participation to help boost self-confidence.
- Rewarding student for a job well done.
- Being cognizant of signs of depression or isolation since the student may feel less part of the class as the condition progresses; and dealing with them accordingly by contacting parents, talking with the student, counselor and other supports.

Apart from physical disabilities, children's psychosocial abilities should also be taken into consideration. Constant monitoring for any difficulties in language development, comprehension, short-term memory, learning problems, social immaturity, withdrawal or isolation from peers, anxiety, depression, frequent arguing and temper tantrums is essential. There is a risk of co-morbid neurobehavioral and neurodevelopmental disorders, including autism-spectrum disorders, attention deficit/hyperactivity disorder (ADHD), and obsessive-compulsive disorder in children with DMD. Therefore the emphasis in psychosocial management is prevention of problems and early intervention to enhance the child's learning and maximize the potential outcome and to detect presence of any co-morbid impairment.

Once the children grow past the age of receiving school education, many other questions need to be addressed like what after basic education? What about the child's career? Will he be able to work and earn his living on his own? What type of job will be suitable for him? What kind of training he requires to become a professional? These questions may be answered by an occupational therapist or a vocational counselor amongst the rehabilitation team, who evaluates the interests, abilities and

limitations of the child and matches that with requirement of various jobs profiles to provide a practical option for employability.

In adulthood employability of the muscular dystrophy patients needs to be assessed. Work is fundamental to our lives. It means much more than just a paycheck. It offers purpose and the opportunity to lead an independent, self-directed life for all people, including people with disabilities. MD patients require specific skill training and support for future employment. Thus, planning and working on vocation should start as early as possible to ensure that skills required for their choice of profession are learnt earlier to keep pace with the time. This could be called pre-vocation training. Such services could be provided by an occupational therapist and/or a placement counselor who would follow these steps to ultimately place the person successfully at a suitable job. Various options are available for these patients, however the step is vocational assessment.

Vocational Assessment

Vocational assessment includes assessing the strengths, interests, vocational needs and the readiness for open employment of these people. The counselor takes a history of their early life including schooling, learns about their medical status and prognosis, and considers how their disability would affect their ability to work.

Sheltered Employment

Sheltered employment provides a simulated work environment and pre-vocational skills training programme to equip people who have the potential and capability for open employment with the possible required skills. The counselor evaluates new career possibilities and looks upon what interests the persons with disabilities in terms of a realistic profession. Also he explores sources and means of funding, if they require training for acquiring specific skills.

Work evaluation systems are used by occupational therapists to develop work samples for job simulation. The TOWER System is one of the work evaluation systems and over the years has served as a model for the development of many work samples. The TOWER uses a realistic job setting to thoroughly evaluate clients for a particular specific job. The TOWER is also used for job analysis and to place and train disabled people on job.

Vocational Training

Vocational training, prepares the patients for job applications, interviews, provides training for a particular job (e.g. Telephone operator) and teaches them about professional skills and social conduct required at the job site.

Job Placement

Once they are ready for employment, job matching to their capabilities are found and offered.

Follow up

This does not stop here. The patient once employed is also followed up to ensure his safety and fulfillment of added needs at job site by making possible modifications and accommodations.

Thus, vocational training in case of muscular dystrophy patients should be a centre-based programme which would help the patients who are unable to access open employment, develop and enhance their vocational skills and capabilities, with the aim to promote their employability. Policies governing employment of disabled people should place equal opportunities and environment for muscular dystrophy patients after considering their abilities and disabilities, and connect their educational and vocation smoothly. Also by adapting the physical work environment, the social environment and the work requirements and guidelines, such individuals can maintain meaningful employment. This may not only impact the individual's perceived self-efficacy but also his or her financial well-being.

Since muscular dystrophies cause muscle weakness and fatigue, limited mobility, loss of skillful movements, jobs requiring limited activity, movement and working hours should be kept in options.

At workplace strategies for the management of some of the common symptoms and limitations experienced by patients with muscular dystrophy

Fatigue/Weakness:

- Reduce or eliminate physical exertion and workplace stress
- Lighter non-physical duties such as desk based positions
- Schedule periodic rest breaks away from the workstation
- Allow a flexible work schedule and leave time
- Allow work from home
- Implement ergonomic workstation design
- Allow longer breaks

Fine Motor Impairment:

- Provide alternative computer and telephone access
- Provide arm supports
- Provide writing and grip aids
- Provide a page turner and a book holder
- Provide a note taker
- Consider computer based technology to minimize the need for handwriting or typing. Examples include voice activated software programs to replace keyboard and mouse input which can transmit data directly to the computer.

Gross Motor:

- Provide a scooter or electric wheelchair if walking cannot be reduced
- Provide parking close to the work-site
- Ensure the workplace is wheelchair accessible including entryways, work areas, washroom and kitchen amenities
- Make sure materials and equipment are within reach range
- Move workstation close to other work areas, office equipment, and break rooms

Medical Treatment Allowances:

- Allow telephone calls during work hours to doctors and others for support
- Provide medical leaves
- Provide part time work or flexible work hours to accommodate medical appointments and treatment

Stress Intolerance:

- Develop strategies to deal with work problems before they arise
- Provide sensitivity training to coworkers
- Provide information on counseling and employee assistance program

A muscular dystrophy patient can, thus, be successfully employed and become a dependable worker, a part of the society, a responsible citizen of the nation, in spite of his disabilities.

19.

Care for Caregivers

As important is the psychological well-being of the patients with muscular dystrophy, it is equally important that the caregiver's physical and mental health be also taken care of. The caregivers, parents or the spouse of the patients undergo lot of psychological distress such as anxiety, depression, frustration and frequent anger outbursts which tend to affect their quality of life. It is therefore essential for the caregivers to learn effective coping mechanisms to deal with their own emotions and feelings.

It has been seen that if there is an illness in the family or a person needs day to day care at home, the frequency of feeling frustrated or getting angry tends to increase. This can lead to frequent conflicts in the family as well. Therefore, management of such negative emotions and feelings become crucial so that the family can take better care of the patients.

When a child or an individual gets diagnosed with MD, a whole spectrum of changes occur in the individual's as well as the caregiver's life. It is important that due considerations be given to the caregiver's health: physical and emotional. It is essential for the caregivers to identify and recognize the early signs of stress and take appropriate steps accordingly to minimize and rectify it at the right time. To help recover an individual or a child with MD, it is important that the caregiver be strong themselves. Caregivers usually help the individual with MD with: ADLs, Exercising, Moving from one place to another, Positioning, Wearing and taking off splints, Managing medication routines.

During the period of their role as a caregiver, some of the problems faced by the caregiver include: Increased financial stresses,Added physical stress to present work, Managing medication routines, Managing exercise program,Changes in life pattern, Social isolaton.

Signs of caregiver stress:

- Weight loss
- Getting easily overwhelmed and easily irritable

- Feeling fatigued throughout the day
- Losing interest in previously enjoyable and valued activities.

This chapter will focus on how to identify care-giver stress and how to manage it.

Anger Management

The first and foremost thing is to recognize the situations in which the person can get angry. The situations will differ for both the patient and the caregiver. Table 1. Summarizes these trigger points for patients and parents.

Table 1: Patient and Caregiver trigger points

Patient trigger points	**Caregiver trigger points**
Constant instructions	Disobedient Children
Inability to perform a task	Disagreement with spouse
Lack of results	Criticism from the family/patient
Disagreement with spouse/parent	Physical and mental exhaustion
Deviation from pre set plans, desires or ambition	Mistakes - Yours and others
Over sympathy	Financial worries
Dependence on Family	Physical pain/illness/
Restricted social life	Feelings of helplessness/ mood swings

Patient Trigger points:

- **Constant instructions** - If the patient is being instructed constantly throughout the day to exercise or is being told what to do and what not to do on a regular basis, this can make him angry.
- **Inability to perform** - If the patient is trying to perform a particular task and is unable to perform, for ex: trying to learn a new form of exercise, he will feel frustrated and angry.
- **Lack of results** - If he is exercising regularly but there is no improvement in his condition; this can make the patient feel de motivated and increase his levels of frustration.
- **Disagreement with caregiver** - If there is a disagreement with the family or parent in terms of their care giving then the patient can get angry and would not cooperate with the family.
- **Deviation from Pre set plans** - As every person has some pre set plans or desires and ambitions, any deviation from it can lead to feelings of helplessness and frustration.
- **Over sympathy** - Receiving help, concern and over sympathy from people around when not required can also lead to feelings of low self esteem and helplessness.

- **Dependence on family** - For every small activity, help is required - such as having a glass of water to drink or changing position while sleeping or getting the television remote. For such activities, when there is dependency on the family, the patient becomes frustrated and throws temper tantrums.
- **Restricted social life** - Due to physical limitations now, the patient cannot go out whenever he wants to and his social life becomes restricted. This leads to isolation, loneliness and depression.

Caregiver trigger points:

- **Disobedient Children** - When children do not follow the parent's instructions, the family can feel frustrated and lose motivation to work on the child.
- **Disagreement with spouse** - If there is disagreement between the patient and his/her spouse, there can be conflict.
- **Criticism from family** - If there is constant criticism of the caregiver from the patient or other family members, this can de motivate the caregiver from taking good care of the patient.
- **Physical and Mental Exhaustion** - Caring for someone with muscular dystrophy can lead to physical and mental exhaustion as well. In this process, there is often neglect on the part of the family to take care of their own health. As a result, the caretaker also starts experiencing health issues such as excessive backache, headache etc.
- **Mistakes** - Mistakes on the part of the patient or the caregiver himself, become intolerable and there is conflict.
- **Financial worries** - Not being able to bear the cost of treatment can also lead to feelings of excessive stress and frustration.
- **Mood swings** - There is constant mood swings experienced by the caregiver from depression to anxiety to anger outbursts.

Tips to manage or control anger:

1. **Take a deep breath** - Deep breathing releases tension and stress. It relaxes both the mind and the body as there is increased oxygen supply to the brain and brings down the heart rate to normal level.
2. **Counting backwards from 10 to 1** - The person can practice counting backwards from 10 to 1. This helps to distract the person from the situation for a while.
3. **Time Out** - The individual can take some time out from the situation and then come back to it and respond instead of react.
4. **Visualization** - The caretaker can practice the method of Creative Visualization or Mental Imagery. For ex; he/she can imagine of a scene which will make him feel calmer and relaxed.
5. **Positive self talk** - The caregiver can think of some affirmations or positive

dialogues which he can repeat to himself/herself at the time when he is getting extremely angry. For ex; 'I am a peaceful being', I am a loveful being'.

6. **Cognitive Restructuring** - This is a process of learning to identify irrational thoughts and then converting them to more positive and rational thoughts. For ex; "All or nothing thinking" - The spouse might think, that 'My husband NEVER listens to me' or the parent might think, that 'My child is ALWAYS very stubborn'. These thoughts can be then converted into more rational thoughts like - 'My husband does listen to me most of the time but he does have his own opinion regarding certain things and I respect that' or the parent can reframe the thought for his child by saying - 'My child is independent in his thinking and decision making'.
7. **Better Communication** - It is important to learn better communication skills. The individual can plan from beforehand what he or she wants to say in a more calm and assertive way without being aggressive.
8. **Humour** - Introducing some good humor into potentially difficult conversations can lighten the situation and uplift the mood. The simple act of laughing can go a long way to reduce anger.
9. **Practice Gratitude** - Keep a gratitude journal. The individual can note down one or more thing that he is grateful for on a daily basis. This can significantly increase the psychological well-being and life satisfaction of the caregiver.
10. **Forgiveness**

Apart from their psychosocial well being caregivers must also take care of their physical health.

Tips to help caregivers:

Caregivers should always remember that if they don't take care of themselves then they won't be able to look after the one they care for.

Below are some tips suggested for caregivers:-

1. Don't be over-protective. Encourage the person with muscular dystrophy to do daily activities by himself as much as possible.
2. Use adaptive devices or technology to make him more independent (e.g. use of a long handled scrubber for bathing) and reduce physical stress of the caregiver (e.g. use of hoists or lifts instead of lifting).
3. Talk to family or friends & take help, to get some relief from duties.
4. Exercise regularly to promote better sleep; reduce tension & depression and increase energy and alertness. (Refer to a physiotherapist or doctor first)
5. Call & keep in touch with family & friends even though it may be for few minutes in a day through telephone or social sites like Facebook.
6. Do things which are enjoyable like watching comedy movies/serials as laughter and joy can help reduce stress.

7. Indulge in hobbies/fun activities with the affected individual to strengthen emotional bonding.
8. Join a social or support group to meet people going through the same phase and share thoughts & ideas.
9. Use energy saving techniques (mentioned below) to reduce tiredness.
10. Refer to a physiotherapist or occupational therapist regarding proper handling and moving techniques, especially to protect ones back.
11. Seek professional help regarding the concerns felt & appropriate medical care whenever required without delay.

Energy Saving Techniques

The main aim behind energy saving is to reduce unnecessary energy expenditure in the body. The five major principles which can be used into daily activities are:-

1. Organize the day, activities & environment

- Plan the daily activity schedule, alternating with heavy and light tasks. Also eliminate unnecessary steps of a task when possible.
- Gather and arrange supplies or tools for daily activities before start.
- Plan to do the heaviest work when feeling most energetic.
- Organize environment to reduce excessive carrying, bending & reaching.
- Avoid or reduce tasks that aren't very important or seek assistance to utilize energy for more liked tasks.

2. Use energy saving tools/equipment

- Use of electric appliances to save energy E.g. electric shaver, washing machines, microwave oven etc.
- Use assistive devices such as long handled reaches, to minimize the need to bend over to pick up objects from the floor.

Fig. 19.1 : Microwave Oven

Fig. 19.2 : Automatic Washing Machine

Fig. 19.3 : Trolley

- Use equipment which is easy to hold e.g. spoons, brushes/ combs with built up/enlarged handles.
- Replace existing heavy items with lighter ones; for example, use plastic plates & cups rather than china & glass.

3. Work with adequate rest breaks

- Take enough rest on completing a task and before moving onto the next one.
- Always rest before getting exhausted.

4. Avoid tiring and faulty postures

- Sit down for doing activities whenever possible. Avoid tasks that require

Fig. 19.4 : Wrong way of bending to pick up

Fig. 19.5 : Right way of bending to pick up

prolonged standing, squatting or stooping.

- Avoid raising your arms too high above shoulder level.
- Slide objects instead of lifting them.

5. *Use of proper body mechanics*
   - Keep your body straight while performing a task, poor posture consumes
   - more energy.
   - Avoid rotating the trunk while bending.
   - While lifting/placing heavy objects from/on lower surfaces, bend from knees instead of the back.
   - Keep your arms straight and close to your body while carrying objects, thus dividing the load equally between both arms at the same time.
   - Support your elbows on a table or a firm surface while performing a task to avoid positions that make you tired, e.g. during brushing, reading etc.
   - Push instead of pulling objects.

A small real life learning incident from Dr. Alok Sharma:

In January 2001 there was a devastating earthquake in the Kutch area of India. I was leader of one of the medical teams that was flown in by the Air force and we set up a medical camp in a village which was severely affected. Almost all the houses in this village had collapsed and half the people were dead. We used to do surgery there on a bullock cart. But before we and the army reached the villagers there without any help from the outside had managed a significant amount of relief work already. Once in the night as we sat by the fireside (there was no electricity), I asked the villagers how come they had organized their own relief work so effectively before we arrived. They told us something that changed the way we looked at life. They told us that immediately after the earthquake the village elders got all the people who were still alive together and gave them just one advice and suggestion. They told the villagers. "Lets not look at or think about what we have already lost. Let's focus on what is still left and try to make the best of that". These simple words were so inspirational. There was no family in the village who had not lost someone. But instead of grieving about their loss each and every one of the people there started working to salvage what and who was still left. Each one was given specific duties irrespective of what and whom they had lost. Instead of grieving about their losses these people were now working to helping those who were still alive. There is a big lesson we all, especially the family caregivers, have to learn from this incident. In our patients instead of being upset about what the patients cannot do we need to focus on what they still can do and work towards enhancing that aspect therefore improving the qualities of their lives to the best possible manner despite the disease and disability that they have.

20.

Assissted Living

Asssisted living facility is a housing facility for people with disabilities, these facilities include supervision or assistance with ADL's, co-ordination of services with outside health care providers. For patients with Muscular Dystrophy in whom the condition progresses over a period of time, these individuals need round the clock care and assistance. Assisted living bridges the gap between independent living and nursing homes. Assisted living facilities are beneficial for patients with muscular dystrophy as they are designed keeping in mind the abilities and challenges of these patients. This facilitates maximum independence and the patient may be self sufficient with these facilities.

Assisted Living has emerged as an alternative care facility based on the concept of offering continued care for people with chronic illness to promote independence and dignity. It may be feasible for MD patients who may not require a 24 hr medical care with adaptation at home and work place, keeping in different disabilities and needs of an individual. For individuals diagnosed and living with MD, it is essential to have an accessible home and workplace environment including school and maintenance of general fitness. An occupational therapist will assess and survey to identify the barriers and potential barriers; and to devise strategies and implement solutions to promote maximum accessibility and safety.

Living in Home:

Architectural Barriers and Restrictions :

Barriers are obstacles that limit the accessibility of an individual with disabilities to do the things that most of us take for granted such as working, taking public transit, and going shopping. Architectural barriers are required to be taken care to improve the accessibility at home eg: narrower hallways and doorways restrict the accessibility of a individual using a walker, w/c or an electric scooter, light switch and power point relocation.

A United Nations initiative for barrier free environment with access to all has published guidelines for the architectural considerations. It is a design manual for accessibility for the disabled and can be accessed online at

http://www.un.org/esa/socdev/enable/designm/index.html

In an outdoor environment there could be many architectural barriers like street furniture, traffic signs, direction signs, street plans, bollards, plants, trees, shop awnings and advertising signs, etc. Care should be taken to keep these out of the path of the travel. There are other essentials like singes, garbage bins, electricity poles, bicycle stands, roadworks etc. these are non-movable obstacles and so should be placed in such a way that a clear path will be available for passage of the wheelchair.

Home Safety:

Home accessibility is an important aspect for an individual passing through the various stages of the disease because the condition changes throughout the course. As individuals with MD have difficulties negotiating stairs and ambulating indoors and outdoors along with a tendency for frequent falls; hence, simple basic changes like repositioning the furniture , removing rugs, eliminating clutter repositioning electrical cords and so on, can be considered.

Important aspects of home architecture:

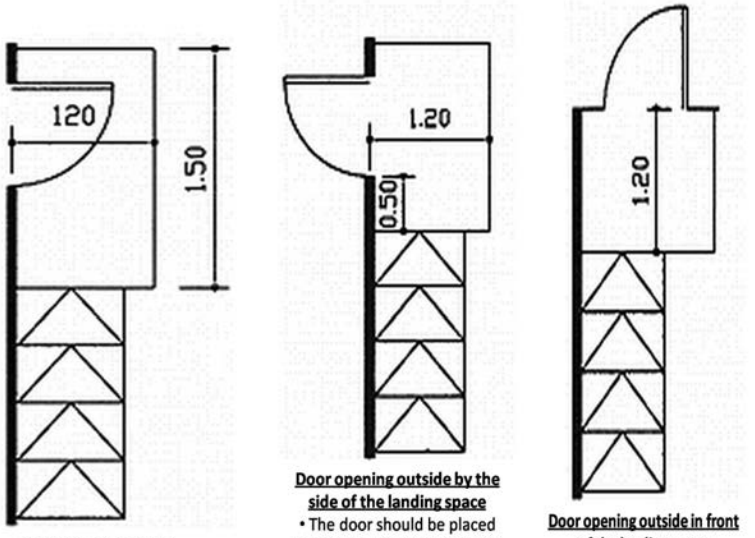
Entrances:

- Entrances must be wide enough, with a clear passage after the entrance to allow free movement of the wheelchair.
- Entrances should be easily identifiable.

The UN guidelines suggest following standards for the entrances.

New constructions can comply with following suggestions

Figure 20.1 shows the recommended dimensions for the landings and entrances with doors opening inward and outwards



Door opening outside

•The length of the landing should 1.5 mts
•The breadth of the landing should be 1.2 mts

Door opening outside by the side of the landing space

• The door should be placed atleast 0.5 mts away from the flight of stairs
• Length of the landing should be 1.2 mts

Door opening outside in front of the landing space

• Length of the landing till the door should be 1.2mts

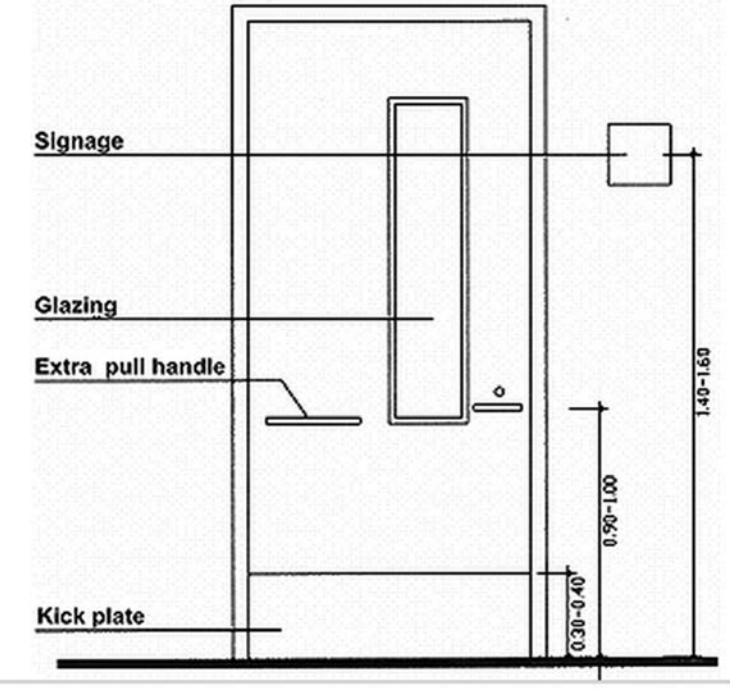
In addition to these structural recommendations it is recommended that

- There are no thresholds on the floor
- No jute mats outside entrance
- The flooring is of non-slip material
- There are no obstacles in the path
- The entrance door should be of different color than that of the surrounding walls for easy identification

Doors:

- Doors should be wide enough, placed appropriately to allow for a single motion passage of the wheelchair with minimal contours and maneuvering.
- Doors must have a handle and extra pull handle and proper sign.
- If the door is automatic it should remain open for a longer time than usual to allow for passage of the wheelchair completely.
- Front opening doors, automatic sliding doors are suitable for wheelchair friendly access however revolving doors should be avoided.
- In narrow spaces sliding doors may be useful.
- For self sliding doors pull handles should be placed at the lower level and should protrude out for easier grip sitting in the wheelchair.

Figure 20.2 shows the architectural recommendations for the doors



Front opening door

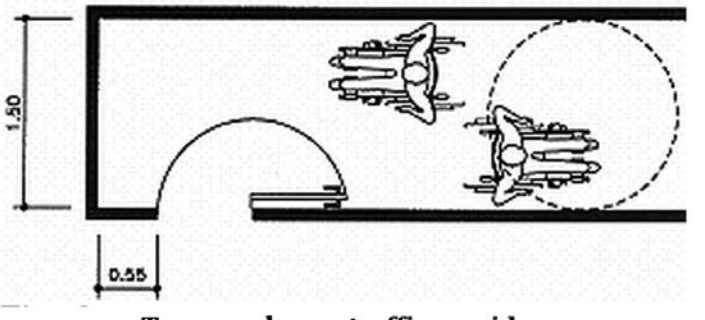
Corridors:

- Corridors should be wide and there should be straight length of the corridor available with minimal turns.
- If there are doors opening into the corridors then the corridors should be wider to allow free passage of the wheelchair with doors open.
- For any given corridor there should be a free passage space of 0.9 mts must be available.
- Sharp angulated turns should be avoided. Corridors should not be too long but long enough to prevent turning very frequently.

While designing and modifying the corridors following must be taken into consideration

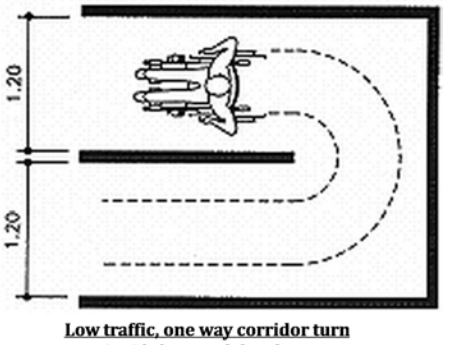
- The traffic in the corridor
- One way or two way corridor
- Number of turns
- Essential obstacles like doors opening in the corridor, drinking water, seating arrangements etc.

Figure 20.3, 4 & 5 illustrate the structural considerations for the corridors.



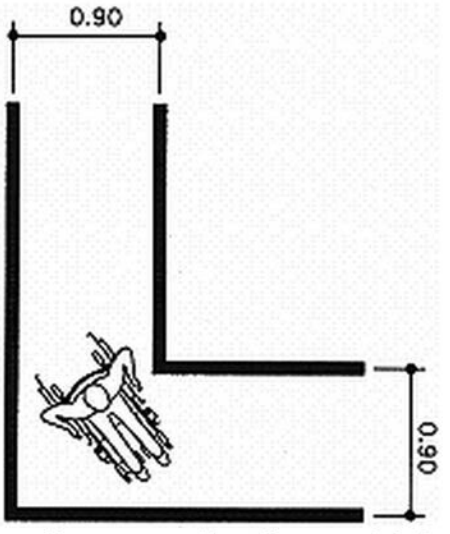
Two way, heavy traffic corridor

- The corridor length should be 1.5 mts
- The door placement should be a tleast 0.55 mts away from the end of the corridor



Low traffic, one way corridor turn

- Avoid sharp andulated turns
- A U shaped turn is recommended
- Length of the corridor must be 1.2 mts



Low traffic, one way corridor with passage of single wheelchair at a time

•The length of the corridor at entrance should be 0.9 mts

•The length of the corridor at the exit should be minimum 0.6 mts

Stairs:

- Staircases should not be too steep
- The height of steps should be uniform, in case of variation of the height it should be highlighted.
- There should be grab bars on either side of the stairs.
- Staircase should be wide enough to allow for two people stand side by side
- Spiral staircases are not recommended
- There should be appropriate landing (at least 1.2 mts along the entire width of the staircase) at the end of the flight of stairs, marked by tactile markings
- The width should be 0.9 mts for one way traffic and 1.5 mts for two way traffic
- Flooring should non-slippary
- The grab rails should be continuous even around the circumference of the landing, if the staircase if wider than 3 mts an intermediate hand rail should be present and it should be at the height between 0.9 mts to 1.4 mts.
- For every staircase an alternate elevator, ramp or lift should be available.

Railings and Handrails:

- All the hazardous areas, corners, open areas with a risk of slipping must have railings.
- Handrails should not obstruct the path of travel

- The height of the handrails should be between 0.85 to 0.95 mts above the finished floor levels
- For the benefit of wheelchair users a second handrail at the height of 0.70 and 0.75 mts should be places
- Railings should mounted on the wall with proper support structures to withstand heavy load
- At the end the railings should bend and blend into wall rather than leaving them open ended

Bathroom Modifications:

Solutions to bathroom accessibility can range from adding innovative or usage of portable equipment to work with the existing bathroom. Bath chairs including free standing or wall mounted benches enable a person to use a bathtub without sitting on the tub floor. This would mean less effort to exit the tub, since the chair usually sits at the same height thus eliminating the need for transferring from the low heighted bathtub floor. Use of reachers for retrieving items off the floor or from higher places instead of bending over or reaching. For individuals who do not use a bath tub, usage of strategies can be advocated such as sitting on a stool while bathing and use of a hand held shower. Low cost modifications like use of plastic non skid chairs as bath chairs can also be used. There could be several modifications made to the bathroom and toilets Figures 20.6 - 9 suggest the simple modifications.

Minor modifications include small, low-cost aids and equipment to improve accessibility.

Figure 20.6: Bath chairs

Figure 20.7: Bath tubs

Figure 20.8: Soap on Rope

Figure 20.9: Non skid floor mats

Structural recommendation for the bathrooms

- Insufficient space inside the rest room is the most common problem
- Rest rooms must have sufficient space at the entrance and inside to maneuver the wheelchair
- The access to the restroom should ideally be parallel to the toilet seat. Diagonal approach can be given while modifying the existing space however perpendicular approach should not be used (Figure 20.10)

Flooring:

Some types of flooring may not hold up under the weight of the power wheelchair. In muscular dystrophy there is increased tendency and risk for falls due to uneven surfaces hence it is important to work on the flooring at home and work place. Flooring changes like installation of nonskid mats can be considered. Changing or modifying

Fig 20-6 : Bath Chair

Fig 20-7 : Bath Tub Modification

Fig 20-8 : Soap on rope

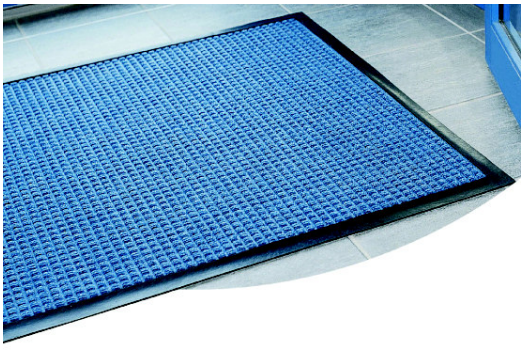
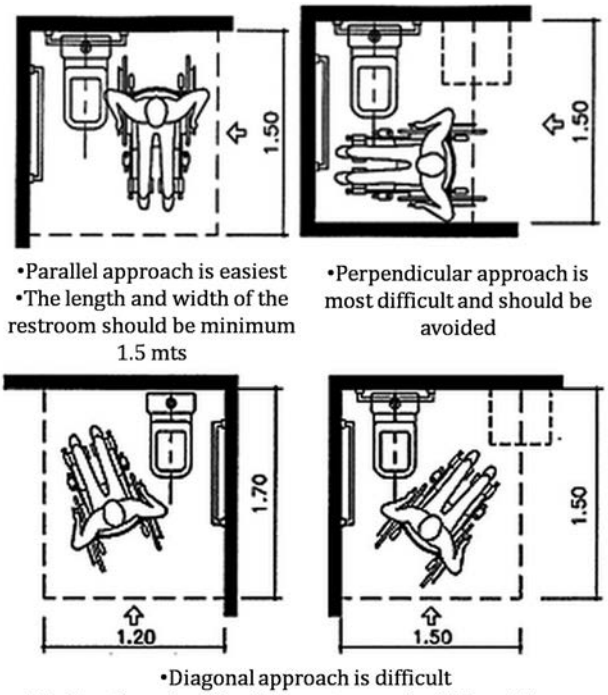


Fig 20-9 : Antiskid mats



•Parallel approach is easiest
•The length and width of the restroom should be minimum 1.5 mts

•Perpendicular approach is most difficult and should be avoided

•Diagonal approach is difficult
•The length and width of the restroom should be minimum 1.5 – 1.7 mts

Fig 20-10

walking surfaces is the next level of preventing slip and trips. Recoating or replacing floors, installing mats, pressure-sensitive abrasive strips or abrasive-filled paint-on coating and metal or synthetic decking can further improve safety and reduce risk of falling. In addition, resilient, non-slippery flooring prevents or reduces foot fatigue and contributes to slip prevention measures.

Fall Prevention techniques:

You can reduce the risk of slipping on wet flooring by:

- taking your time and paying attention to the floor surface and floor height
- adjusting your stride to a pace that is suitable for the walking surface and the tasks you are doing
- walking with a slightly broader BOS
- making wide turns at corners

You can reduce the risk of tripping by:

- keeping walking areas clear from clutter or obstructions
- keeping flooring in good conditon
- always using installed light sources that provide sufficient light for your tasks
- using a flashlight if you enter a dark room where there is no light
- ensuring that things you are carrying or pushing do not prevent you from seeing any obstructions, spills, etc.
- Both slips and trips result from some a kind of unintended or unexpected change in the contact between the feet and the ground or walking surface. This shows that good housekeeping, quality of walking surfaces (flooring), selection of proper footwear, and appropriate pace of walking are critical for preventing fall accidents.

In the work place:

Ergonomically designed work station:

Ergonomically designed workstation takes into consideration the height and width modifications required for wheelchair access and any other modifications that are required to accommodate assistive and external devices used.

Ergonomically designed chairs

Some salient features are chairs with adjustable arm, back and footrest and chairs with adjustable height. The back support should be with contour to accommodate the spinal curvature. For individuals with spinal deformities chairs could be custom made to provide support.

Assistive Technology:

Assistive technology includes any piece of equipment or device that helps to increase the independence of a disabled person. While assistive technology is not new, it is an ever changing and growing type of technology. Assistive technology has helped to enormously increase the ability of disabled people to lead more independent lives. Assistive technology devices enable disabled people to do all sorts of tasks such as turning on lights and appliances and opening doors while in a wheelchair, speak through synthetic speech systems.

Types of Assistive Technology:

Personal Emergency Response Systems (PERS) use electronic sensors that are connected to alarm systems to help individuals with impaired mobility who want to stay at home and be independent. PERS include such items as fall detectors for those prone to falls, and various pressure and motion sensors . Many systems can be customized for the user's particular risks.

Accessible computer input technology reduces the strain of sitting at a desk with a keyboard and amouse. There are various ergonomic accessories such as footrests, arm supports, and adjustable furniture to ensure the correct posture. There are also chorded keyboards that have a handful of keys (one per finger per hand) to type chords which produce different keys and letters. There are also many sophisticated accessible computer input products that can replace normal functioning computer parts. These include joysticks, touchpads, foot mice, speech recognition software, and even eye trackers.

Access and environmental controls are devices that allow someone increased control of things in their environment. These controls include things like remote controls, special keyboards and mice, switches, ramps, and signs.

Augmentative communication can support a person who cannot talk, or whose speech is not easily understood. There are many types of communication software and computers, picture boards, and voice output communication devices available for those with respiratory difficulties and who are fitted with a tracheostomy device. Also students can undergo professional training in information technology using special computer equipment.

The present is the only time when we can work and achieve, gain and gather. In the past we can now do nothing. In the future again we can accomplish nothing. In the 'dead' moments of the past and in the 'unborn' moments of the future we can never act. These 'living' moments are the only fields to be hammered at and wherein are all the glories of life, all the gains in existence.

Time never stops. It is fleeting. The now is the only auspicious occasion to initiate our new plans. Delays are dangerous, useless and barren. Today is the only day to attempt any great and worthy purpose. Opportunities come to all of us. The diligent catch hold of it. The foolish let it pass. Therefore us be smart and awake to recognize our opportunity to serve and while it is within our reach let us seize it and make it yield to us the results we demand.

What we have is a gift from God. But what we do with that is our own gift to God. Make your life a total gift to God.

- Swami Chinmayananda

SECTION - IV

Recent Advances in the Management of DMD

21.

Newer Drug Therapies

Research in the last two decades has given scientists a better insight into the functioning of muscles and the underlying cause of muscular dystrophy (MD). The last ten years have seen a significant rise in the number of clinical trials and a variety of therapies are now in the pipeline. These trials are being conducted to explore the possibilities of various newer drugs, along with modifications in the indications for use of older drugs. The status of some of these drugs is listed below as of the date of publication of this book. (Some of the newer research drugs are mentioned here with their initials, followed by a number. These are not the actual names of the drugs, but are used as references by researchers during the trials. The descriptions below include a brief outline about each drug, along with trial study numbers and study titles.)

Ataluren (Translarna) for treatment of nmDMD

Ataluren (Translarna) has created a history by being the first drug approved for treatment of nonsense mutation DMD (nmDMD). An estimated 13% of DMD cases occur due to a nonsense mutation. Ataluren allows to read through premature nonsense stop signals on mRNA and produce a full-length, functional dystrophin protein. Thus, ataluren has the potential to treat muscular dystrophies in which nonsense mutation is the cause of the disease. Ataluren has also demonstrated activity in various nonsense mutation cells in various animal based studies. (Fig. 20.1)

The positive potential of Ataluren is based on the results of a 174-patient Phase 2b double-blind placebo controlled study which showed that nmDMD patients treated with Ataluren (40 mg/kg daily) walked farther distance in six minute walk test (6MWT) than patients on placebo. The results also showed a slower rate of decline in ambulation and the drug was safe and well tolerated.

The U.S. Food and Drug Administration (US FDA), has granted orphan drug designation to ataluren for the treatment of nmDMD. Ataluren, under the trade name Translarna is permitted for conditional marketing authorization in the European Union for the treatment of five years and older ambulatory nmDMD patients. The European Medicines Agency (EMA), has also designated ataluren as an orphan medicinal product.

For more details, please visit http://www.ptcbio.com

Also refer to Gene therapy chapter.

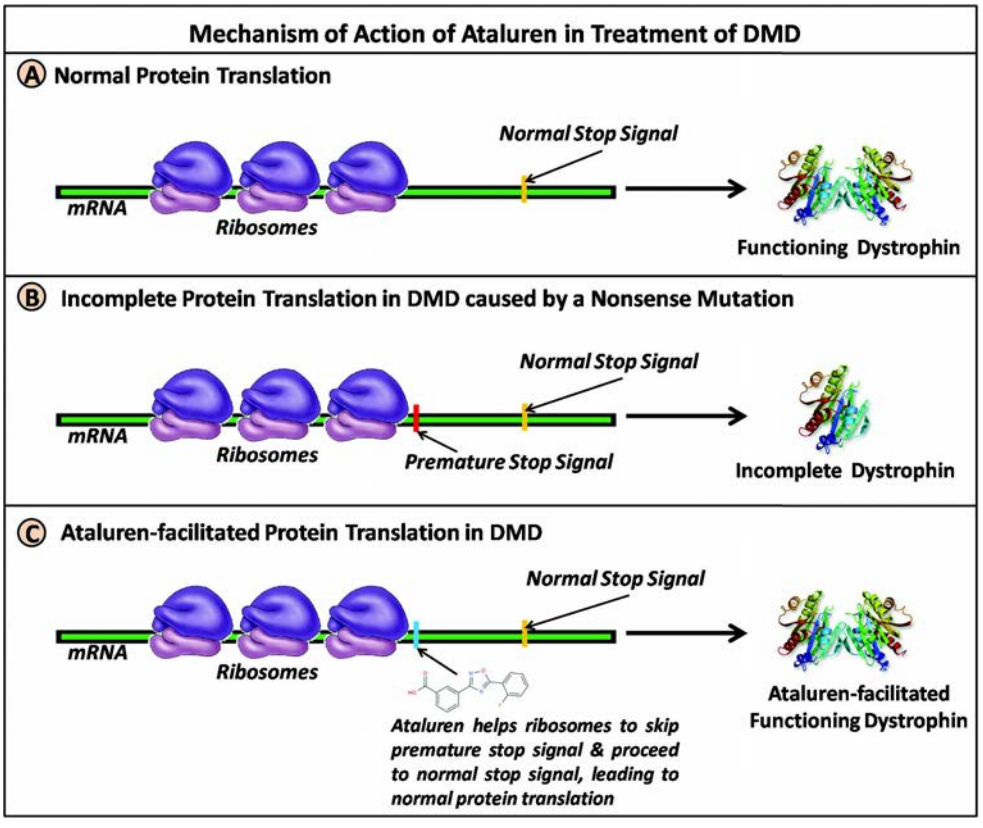


Fig 21-1 Mechanism of Action of Ataluren

Tadalafil for DMD & BMD (Trial study numbers - NCT01865084 [DMD], NCT01070511 [BMD])

(a) A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Tadalafil for Duchenne Muscular Dystrophy

(b) Functional Muscle Ischemia and PDE5A Inhibition in Becker Muscular Dystrophy

Tadalafil (brand name Cialis) is a muscle relaxant that is commonly prescribed to treat erectile dysfunction. However, previous research in MD mice models has shown that tadalafil may reduce symptoms of MD by improving blood flow to diseased muscles, leading to less fatigue after exercise. The drug is currently in Phase 3 of trails and is actively recruiting participants to establish if it can slow the decline in walking ability of boys with DMD. This trial, which is being conducted by Eli Lilly and Company, also aims to assess the safety and side effects of the drug. The results so far suggest that the drug successfully improved blood flow to the weakened muscles of the DMD boys. Another similar trial was carried out to test the effectiveness of tadalafil in BMD patients. This study has completed phase 4 of trials. The results of

this study show that a single dose of the drug improved blood flow to exercising forearm muscles in men with BMD. Based on these successful results, a larger and longer clinical trial is now being planned. For more information, please visit: www.clinicaltrials.gov and www.mda.org.

HT-100 for DMD (Trial study numbers - NCT01847573 & NCT01978366)

(a) A Phase 1b Open Label, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of HT-100 in Patients with Duchenne Muscular Dystrophy

(b) An Open Label Extension Study of HT-100 in Patients with Duchenne Muscular Dystrophy Who Have Completed Protocol HALO-DMD-01

HT-100, also known as halofuginone, is an oral small molecule drug developed by Akashi Therapeutics, Inc. (formerly HALO Therapeutics). Previous research in experimental animal models of MD has established that this drug possesses anti-fibrotic (fibrosis is the conversion of muscle into non-elastic fibers like strands/strings/tissue), anti-inflammatory and muscle regenerative effects. These findings are now being applied to develop a treatment for DMD patients. The drug is currently being tested in two studies; one study is a phase 1b/2a study of the drug to assess its safety, tolerability and mechanism in DMD patients, while the other is an open label extension of the first. Preliminary clinical data from these studies have so far revealed promising signs of biological activity along with a favorable safety profile. If these trials are successful, HT-100 may help patients in improving their heart and respiratory muscles. Various research groups are also attempting to identify the role of this drug for treating other debilitating disorders like dysferlinopathies. For further information, please visit: www.akashirx.com and www.clinicaltrials.com.

SMT C1100 (Trial study number - NCT02056808)

SMT C1100 - A Phase 1b, Open-label, Single and Multiple Oral Dose, Safety, Tolerability and Pharmacokinetic Study in Pediatric Patients With Duchenne Muscular Dystrophy

Utrophin is the functional equivalent to dystrophin and is continually expressed at specialized sites in normal mature muscles fibers. Thus, dystrophin can be replaced by increasing utrophin levels. Studies in mice models have shown that utrophin replacement has the potential to "cure" dystrophin deficient mice (mdx mice). SMT C1100 is an oral small molecule that modulates utrophin by increasing compensatory utrophin levels. This molecule has the ability to reduce central nucleated fibers and serum creatine kinase (CK) levels in mdx mice, and to protect against muscle damage from forced exercise. Phase Ib trials in a cohort of DMD boys demonstrated tolerability and reduction in serum enzyme levels of CK, aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Research on SMT C1100 is being conducted by Summit Plc, UK. For further information, please visit: www.summitplc.com and www.clinicaltrials.gov.

Oxandrolone

Oxandrolone is an anabolic steroid. The meaning of anabolic is a chemical that

promotes cell growth. Anabolic steroids are hormones or chemicals that mimic the action of male hormone 'testosterone'. One of the useful effects of Oxandrolone in MD is presumed to be its ability to increase the protein content in the skeletal muscles. There is some published literature that reviews the effect of Oxandrolone in the treatment of DMD. A pilot study of 10 patients conducted by G. Fenichel et al. 1997, suggests that oxandrolone may help increase the strength of the muscles within 3 months. The findings were preliminary but suggestive of benefits of oxandrolone similar to that of prednisolone, in the treatment of DMD. In 2001, G. Fenichel et al. conducted a 6-month, randomized, double-blind, placebo-controlled trial to test the effects of oxandrolone in the treatment of DMD. They measured the changes in the qualitative (manual) muscle testing(MMT) and quantitative muscle testing (QMT) after 6 months of administration of the drug. There was no statistically significant change in the MMT however QMT showed statistically significant improvement. There were no adverse effects observed during the trial period. Orr R. et al in 2004 conducted review of trials evaluating benefits of oxandrolone in the treatment of sarcopenia, neuromuscular disorders and catabolic disorders and found that many trials reported several benefits like enhanced body composition, improved muscle strength and composition and faster recovery from the catabolic injury. The review also reported adverse effects like temporary elevations in transaminase levels and reduced levels of high density lipoprotein cholesterol level; which may be suggestive of some adverse cardiac effect. The authors therefore cautioned the use of Oxandrolone. It is still an experiemental drug, however it shows promise in the treatment of DMD.

Eplerenone for DMD (Trial study number - NCT01521546)

Early Treatment With Aldosterone Antagonism Attenuates Cardiomyopathy in Duchenne Muscular Dystrophy

Eplerenone is an aldosterone antagonist, a diuretic that helps the body get rid of excessive fluid (tissue swelling) while retaining sufficient potassium levels. It blocks the buildup of fibrotic material and scarring that over time can turn cardiac muscles into non-functioning fatty tissue. Its success in treating fibrosis in adult heart patients has led to it being a sought for treatment in patients with DMD. Previous studies in mdx mice have shown that early treatment with this drug has the potential to reduce heart fibrosis and improve cardiac function. A phase 2/3 human clinical trial under the collaborative efforts of Cincinnati Children's Hospital Medical Center, Ohio State University and The Christ Hospital in Cincinnati is currently underway to assess if eplererone can delay cardiomyopathy and skeletal myopathy in DMD patients. For more information, please visit: www.clinicaltrials.gov and www.cincinnatichildrens.org.

SMART Linker Technology Platform

Safety Metabolized And Rationally Targeted (SMART) Linker platform is the proprietary of Catabasis Pharamceuticals, Inc. The drug development programs of this company are based on the principles of pathway pharmacology (treating diseases by simultaneously modulating more than one target in a disease pathway). Through SMART Linker technology, the drug developers can conjugate two drugs that act on

different components of a disease pathway. This helps to produce new chemical entities with significantly enhanced efficacy, along with an improved safety and tolerability profile. CAT-1004, a part of CAT-1000 chemical group, is a novel chemical entity developed by using the SMART Linker platform, combines salicylate and docosahexaenoic acid (DHA) to synergistically inhibit NFkB signaling. Animal model studies in mdx mice and GRMD dogs have demonstrated reduced NFkB signaling, increased muscle weight, and decreased inflammation. This drug is currently in the Phase 1 trial. For more information, please visit: http://www.catabasis.com

Spironolactone for DMD (still in preclinical stages)

Spironolactone, an FDA approved drug, is primarily used as an antihypertensive and diuretic (promotes the production of urine) or for reducing elevated levels of androgen activity. The use of this drug in MD is still in the preliminary stages of research. In DMD mice models, treatment with spironolactone along with lisinopril (also an antihypertensive) has shown profound improvements. Mice receiving this treatment showed improvements in respiratory, skeletal and cardiac muscles as compared to untreated mice. Ongoing muscle damage in skeletal muscles and the heart was almost completely prevented. Also, it was noted that early initiation greatly reduced myocardial disease and, for the first time with these drugs, improved skeletal myopathy. Thus, early initiation of such agents warrants further clinical evaluation to maintain ambulatory, respiratory, and cardiac function for patients with DMD and related myopathies. Furthermore, these findings offer clinically available medications with proven antifibrotic effect as a new therapeutic strategy in DMD. Pre-clinical studies are being carried out by Dr. Jill Rafael-Fortney. For more information, please visit www.duchenneconnect.org. Clinical trial information will be available on www.clinicaltrials.gov.

Tamoxifen for DMD and BMD (still in preclinical stages)

Tamoxifen is the generic name for Nolvadex which is an approved drug used in the treatment of breast cancer. This drug has the potential to trigger substantial improvements in muscle strength of dystrophin deficient mice (mdx mice). It can also reduce fibrosis and CPK (creatine phoshokinase) levels in these mice. Tamoxifen improved the structure of leg muscles and diminished cardiac fibrosis by about 50%. It also reduced fibrosis in the diaphragm (muscle involved in respiration). Preclinical research is currently being conducted at Dr. Urs Ruegg's laboratory at the University of Geneva. This drug may ultimately be a part of a "cocktail" along with other therapies that stop or slow the progression in DMD or BMD. For more information, please visit www.duchenneconnect.org. Clinical trial information will be available on www.clinicaltrials.gov.

VBP15: (still in preclinical stages)

Glucocorticoids (steroids) remain the only drug treatment clinically recognized to improve muscle function in DMD. Their use is, however, often limited by significant side effects such as weight gain, bone weakness, impaired growth, and unfavorable

changes in metabolism. VBP15 is a novel anti-inflammatory molecule which is similar to glucocorticoid/regular steroids. It may work better than regular steroids with fewer side effects. Its effects have been studied in mdx mice. This research is being conducted by ReveraGen Biopharma, Inc. Still in the preclinical stage, this drug will soon enter Phase 1 trial. More information can be obtained at www.reveragen.com. Clinical trial information will be available on www.clinicaltrials.gov.

Andrographolide for DMD (still in preclinical stages)

Andrographolide is the bioactive extract of the Andrographis paniculata plant, a medicinal plant well recognized in Asia. Andrographolide is known for its wide range of therapeutic actions which include anti-viral/bacterial, anti-diabetic, immunosuppressant, anti-inflammatory, etc. It has traditionally been used for treating colds, fever, laryngitis and other infections with minimal or no side effects. A recent study suggests that andrographolide has the potential to increase the efficiency of cell therapy in mdx mice. It was also found that this compound prevents muscle damage and progression of fibrosis by reducing the expression of TGF-? (transforming growth factor type beta, an important promoter of fibrosis). These findings were associated with enhanced muscle strength and improved exercise performance in the mdx mice. Hence, andrographolide could be useful to improve the quality of life in individuals with DMD.

Biglycan for DMD (still in preclinical stages)

Biglycan is a protein involved in organizing the system that protects muscle cells from damage and helps resist fatigue. This biglycan-based protection system is not affected by the genetic mutations that cause DMD. A study carried out by Dr Justin Fallon and his team at Tivorsan Pharmaceuticals, has showed that mdx mice injected with engineered biglycan show reduced muscle damage and improved function. This suggests that a biglycan treatment may slow down the muscle damage caused by DMD. The company has recently received a $1 million grant from the Muscular Dystrophy Association and $500,000 from Parent Project Muscular Dystrophy for developing a biglycan therapy. The research team is currently preparing bigylcan for entry into human clinical trials. For more information, please visit: www.tivorsan.com.

Eteplirsen and Drisapersen are experimental drugs which are described in Gene therapy chapter.

Myostatin inhibitors (Follistatin and MYO-29) MYO-029

It is a recombinant human antibody that binds to myostatin and inhibits its activity. The safety of MYO-29 was assessed in a double blind randomized clinical trial in Becker, limb-girdle, and facioscapulohumeral muscular dystrophies. Follistatin, a myostatin-binding protein inhibits myostatin activity and promotes muscle growth. A study in mice demonstrated greater potency of this agent than myostatin blockade. Preclinical studies show increase in muscle size and strength in follistatin gene delivered by AAV. For details please refer to Gene therapy chapter.

Recombinant IGF-1 for DMD:

A prospective, randomized, open labeled, controlled phase II clinical trial of recombinant IGF-1 has been initiated in glucocorticoid (GC)-treated DMD patients. The aim of the study is to test the ability of IGF-1 to help muscle function in DMD patients. The results of various preclinical studies show that Insulin Growth Factor-1 (IGF-1) increases muscle mass and strength. IGF-1 is a growth factor and key mediator of an anabolic muscle building pathway. Potential therapeutic benefits of IGF-1 have been seen in preclinical studies. Refer to www.clinicaltrials.gov

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22.

Stem Cell Therapy in Muscular Dystrophy

"An idea whose time has come"

Stem cell therapy is the new revolution in the field of science and medicine. It's a revolution that was awarded the Nobel prize in medicine for the year 2012. It's a revolution that will forever change the world of those having Muscular dystrophies. Its an idea whose time has come. This chapter endeavors to capture the essence of what stem cells are, how can they be of use in muscular dystrophy , what are the clinical results of this treatment and also tries to put into perspective the various arguments and counterarguments for and against this evolving science.

About stem cells

What follows is a brief description about what are stem cells and their role in Muscular dystrophy. For greater details on the methods and the results are available in our previous book "Stem Cell Therapy in incurable neurological disorders" and " Stem cell therapy and other recent advances in muscular dystrophy" which can be freely download from the website www.neurogen.in.

What are stem cells?

Stem cells are key elemental cells that are responsible for tissue formation in the body. Stem cells are naturally found specialized cells that have the ability to multiply and develop into different cell types in the body during early life and growth. They also help in the repair of the body by dividing and replenishing the damaged cells. When a stem cell divides, each new cell has the potential either to remain as a stem cell or to become another type of cell with a more specialized function.

What are the types of stem cells?

Stem cells are of different types, depending on the source from where they are obtained as well as their ability to form different types of cells. Broadly speaking they can be divided into two groups [1] Autologous (derived from the same patient) and [2] Allogenic (cells from an outside source). The accompanying table shows all the different types of stem cells.

Sr. No.	Types	Description	Description	Disadvantages
1	Embryonic stem cells	These are pluripotent cells obtained from the inner cell mass of blastocysts from the IVF clinics	These are pluripotent stem cells and have the ability to form any tissue of the body	Obtaining and processing these cells is tedious. There are various ethical, moral and religious issues involved in the use of these cells. They are also known to cause tumors.
2	Fetal Stem cells	The primitive stem cells located in the organs of the fetuses are referred to as fetal stem cells. They are pluripotent in nature.	These stem cells have a better homing and engraftment capacity as compared to adult cells	Obtaining and processing these cells is tedious. Not many studies have been carried out for the use of these cells
3	Bone marrow Stem cells	These are multipotent cells obtained from the bone marrow. They are a mixture of various hematopoietic and non hematopoietic cells.	Easily obtainable, high availability, high proliferative capacity, can have an autologous source, safe and no ethical issues involved	Incase of allogenic transplantation, there is a risk of immune rejection.
4	Umbilical cord blood cells	These cells are multipotent in nature obtained from the umbilical cord immediately after birth, which contains a rich source of hematopoietic stem and progenitor cells	Easy to obtain, high availability, do not produce strong graft-versus host disease, high proliferative capacity	Slow engraftment, storage issues, require quality control, after transplant, there remain no backup cells from same cord blood unit.
5	Mesenchymal Stem cells	They are 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	Safe, high proliferative capacity, No ethical concerns	Requires culturing of the cells before transplantation.

Sr. No.	Types	Description	Description	Disadvantages
6	Neural stem cells	These cells are isolated from various areas such as adult CNS including the spinal cord which have the potential to treat various incurable neurological disorders	No ethical concerns, specified to be neural lineage, cells from the affected individual can be obtained	Few cells available, difficult to expand, survive only for a few passages.
7	Adipose tissue stem cell	These stem cells are multipotent in nature and are obtained from the body fat.	Can be obtained in large numbers as they are available abundantly, easily obtainable	Their efficacy and feasibility in human use is yet to be proven
8	Muscle stem cells	Muscle stem cells are found in skeletal muscle tissue. They are activated in response to muscle injury.	Easy to obtain, Contributes to muscle regeneration, pure isolation, easily expands in vitro	May have a risk of immune rejection in case of allogenic transplantation, their efficacy in humans is yet to be proven
9	Induced Pluripotent Cells	These are adult cells, genetically reprogrammed to form embryonic stem cell-like cells.	Same potential as embryonic stem cells without the ethical controversy, Can form any tissue in the body	If not fully mature can cause cancer, tend to age prematurely and have a high rate of cell death

However for the sake of simplicity we would like to divide stem cells into 3 main types which are embryonic, umbilical cord and adult stem cells.

Embryonic stem cells:

Embryonic stem cells are derived from the embryo or an unborn foetus. These are obtained from spare embryos from IVF clinics. There are many controversies connected with the use of embryonic stem cells and there also the possibility of some serious adverse events like teratoma formation. Due to these ethical and medical issues these are not being used commonly at present.

Umbilical cord stem cells:

Umbilical cord stem cells are derived from the umbilical cord which connects the baby and mother at birth. Stem cells derived from the umbilical cord are stored by

various cord blood banking companies.. These stem cells do not have any major ethical issues surrounding their usage.

Adult stem cells:

Adult stem cells can be derived from the same patient, from either the hip bone or the fat/adipose tissue. These are the safest and most popularly used stem cells at present and availability is not a problem. There are no ethical issues with the use of these cells.

Some specific cell types that are of special relevance to Muscular dytophy are:-

Bone marrow Mononuclear Cells:

Bone marrow mononuclear cells are a heterogeneous mixture of cells which include hematopoietic (lymphocytes, monocytes, stem cells and progenitor cells) and non hematopoietic cells (mesenchymal stromal cells, endothelial progenitor cells (EPCs), very small embryonic like (VSELs) stem cells, etc) . Mononuclear cells can be obtained from human adult bone marrow, peripheral blood and umbilical cord. Studies have shown their therapeutic potential in various neurological conditions

Bone marrow stromal cells (BMSCs):

The bone marrow stroma consists of a variety of different cell types that provide structural and physiological support for hematopoietic cells. Additionally, it also contains cells with stem-cell-like character that allows them to differentiate into bone, cartilage, adipocytes, and hematopoietic supporting tissues.

Muscle derived stem cells:

These cells are also known as satellite cells. They are present beneath the basal lamina in the muscle. They are inactive and are activated only as a response to external stimuli. Hence, during the daily wear and tear of the muscles, these cells carry out the repair process naturally. They form a stable, self-renewing pool of stem cells in adult muscle where their function is tissue growth and repair.

What are the advantages of using adult stem cell therapy?

The advantages of adult stem cells are (1) There are no major side effects or complications associated with their use since, they are derived from the same patient. (2) There are also no ethical issues with regard to their usage. (3) Since, these are autologous cells there is no possibility of rejection and no need of immune suppressants. (4) They are easy to obtain through a simple needle aspiration from the bone marrow. (5) There are several published international as well as Indian papers in scientific journals that have clearly documented that safety and efficacy of adult stem cells in various neurological disorders.

How do stem cells work?

Stem cells in general work by following mechanisms:

1. They release growth factors which have a healing and regenerative effect on damaged tissue
2. They cause angiogenesis or increase in the blood supply of damaged tissue thereby helping in their repair process
3. They convert into the tissue type of cells into which they are implanted, thereby replacing non-functioning tissue.

What are the routes of administration of stem cells?

Stem cells can be administered through various routes such as intrathecal, intramuscular, intravenous and intraarterial.

1) Intrathecal route: Injection of stem cells into the spinal fluid through a lumbar puncture injection. This method is minimally invasive and is the safest targeted mode of transplantation. Studies using magnetic nanoparticles have shown that cells transplanted via this route reach the targeted damaged tissue and initiate the repair process.
2) Intramuscular route: Injections of stem cells directly into the affected muscles. This creates "local depots" of implanted cells with increased local paracrine activity. To inject the stem cells, the areas to be injected are stimulated via experts and identified as motor points.
3) Intravenous route: Is by a simple injection of stem cells into the veins like any other drug injection.It is one of the safest, minimally invasive and most widely used routes of administration. However, studies have shown that the cells administered via IV get trapped in organs (e.g. lungs) other than the target organ. They are also more susceptible to the host immune system.
4) Intraarterial This is an injection of stem cells through a catheter into the artery which is introduced through a artery in the thigh called the femoral artery. This is also called as interventional route.

Rationale for the use of stem cells in Muscular dystrophy?

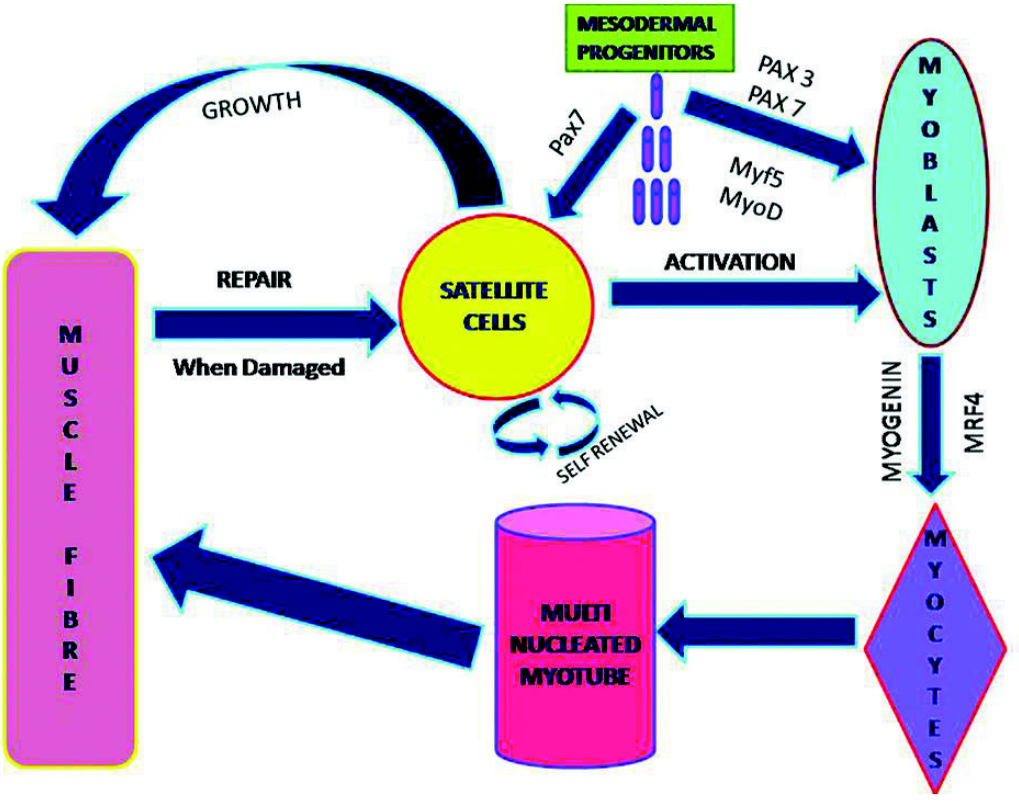
Relationship of Muscular dystrophy to stem cells

A scientific study from the Stanford institute of stem cell biology and regenerative medicine (Helen Blau, Donald E, Delia Baxter,etal) , published in the journal Cell, has stated that DMD is a disease or disorder of "stem cells". This means in DMD, the muscles start getting damaged when the existent muscle stem cells are not able to fix the damage anymore due to depleted stem cell pool.

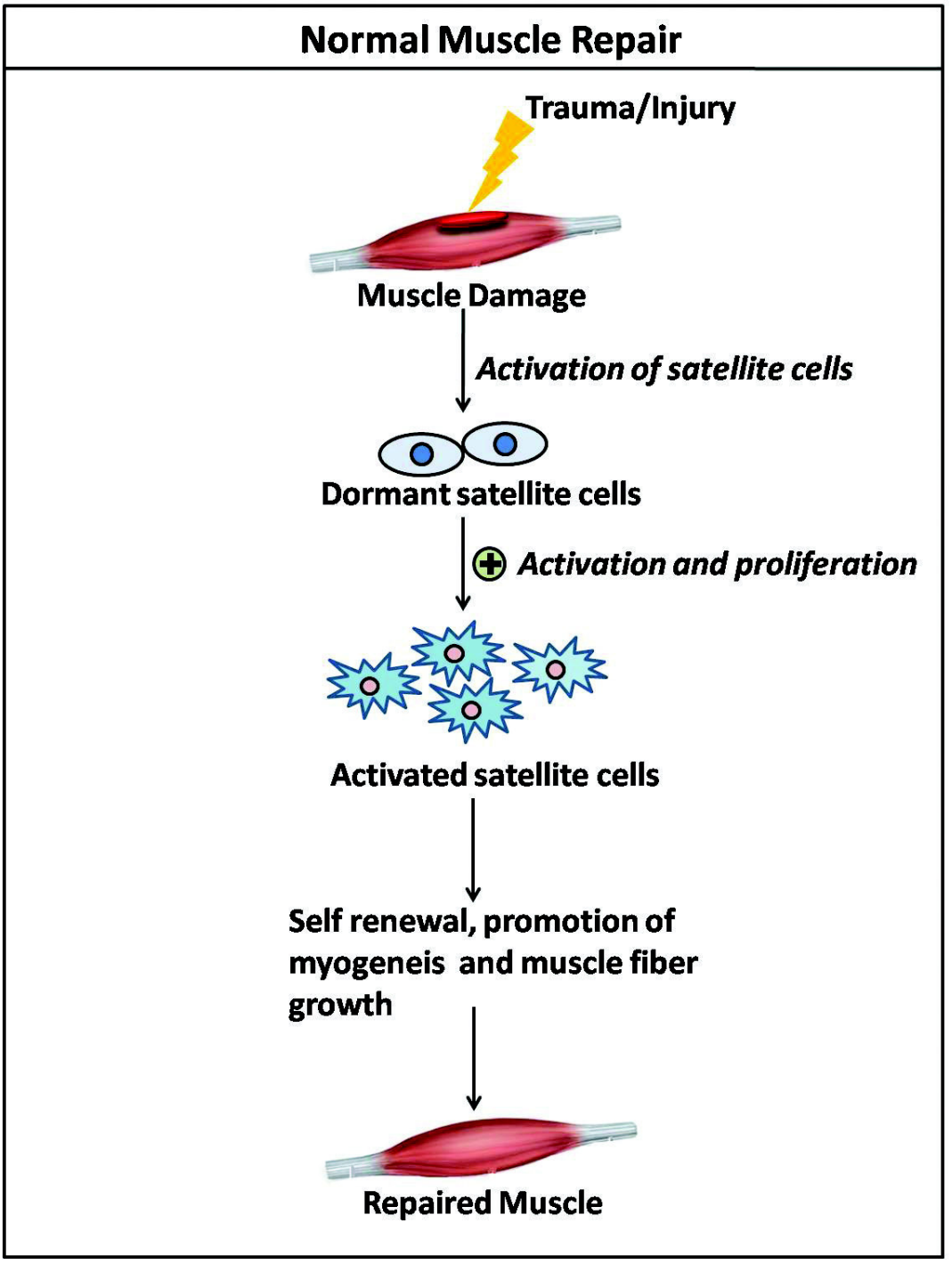
Hence, stem cell therapy may provide this deficit raw material for the muscles to use. In the words of the corresponding author of the paper Jason Pomerantz "If a treatment does not replenish the stem cell compartment, it will likely fail; it would be like pushing the gas pedal to the floor when there is no reserve."

The Biological basis to consider stem cell therapy as a treatment form for muscular dystrophy

When a stem cell divides, each new cell has the potential either to remain a stem cell or differentiate into a cell with a more specialized function, such as a muscle cells, a red blood cell, or a brain cells. Myogenic differentiation of these stem cells, especially the bone marrow derived stem cells has been proved in the literature. The stem cells exert reparative effects at the site of injury. They enhance angiogenesis and contribute to neovascularisation by the production of signaling molecules such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF2). Along with these effects, they also help in reducing inflammation, tissue remodeling, preventing apoptosis and activation of satellite cells, which are the adult skeletal muscle progenitor cells. Differentiation of stem cells in to muscle cells and fusion with the host fibers in conditions of myogenic deterioration, like muscular dystrophy is recorded in animal studies.

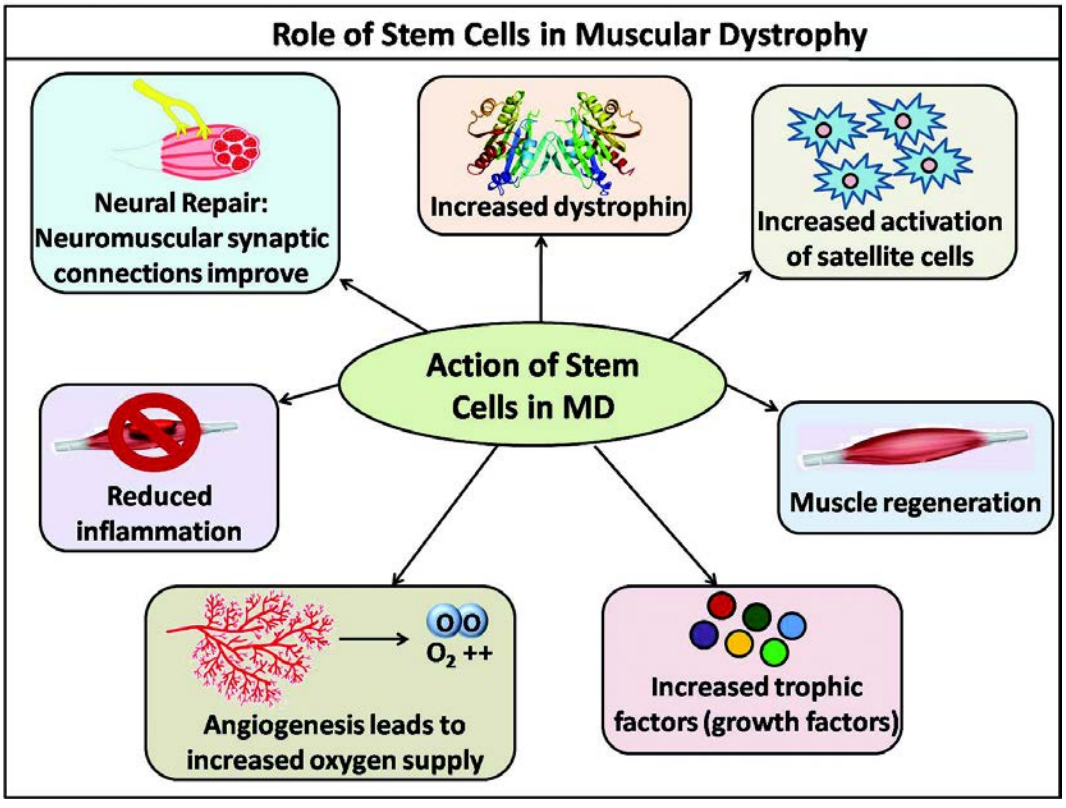


Summary of likely mechanisms of Action of stem cells that could have a beneficial effect in the management of Muscular dystrophy:


Normal Muscle Repair
Trauma/Injury
Muscle Damage
Activation of satellite cells
Dormant satellite cells
Activation and proliferation
Activated satellite cells
Self renewal, promotion of myogeneis and muscle fiber growth
Repaired Muscle

:

Below are few underlying mechanisms which explain the ability of stem cells to bring about repair of the damaged muscles in muscular dystrophy.



1. **Paracrine activity :** Stem cells release various cytokines, trophic factors, nerve growth factors, etc which are responsible for carrying out indirect repair.
2. **Stimulation of satellite cells :** The chemokines, cytokines, trophic factors when released stimulate the already existing "satellite cells" in the damaged muscles thereby initiating repair indirectly.
3. **Angiogenesis:** In muscular dystrophy, due to dystrophin deficiency there is impaired blood flow and consecutive decrease in oxygen supply to the muscles. Stem cells facilitate formation of new blood vessels known as angiogenesis thereby increasing the blood flow and oxygen supply.
4. **Neural repair:** Stem cells also help in neurogenesis which is formation of neural cells and/or muscle cells. They help in axonal growth, tightening of neuromuscular junctions, joining of the broken nerve endings of the muscle. Thereby, improving neuronal function in muscular dystrophy.
5. **Dystrophin production:** As discussed in the initial chapters, lack of dystrophin is one of the chief reasons responsible for muscle weakness in muscular dystrophy. However, along with muscle, dystrophin is also essential to maintain

the neuronal integrity. Studies have shown that stem cells increase the dystrophin production in the muscles of muscular dystrophy individual.

6. **Differentiation:** Depending on the type of cells transplanted, they can differentiate into various cell lines, in this case, myocytes (muscle cells).
7. **Homing :** On injection, stem cells have a unique ability to migrate to the damaged tissues from the site of injection and begin the repair process.

Along with these mechanisms stem cells also reduce inflammation, improve the immune function and prevent further damage to the muscle cells. All these mechanisms together, result in a positive outcome and improved functions.

In Muscular dystrophy, there often arises a question as to how autologous stem cells work when they are likely to have the same genetic defect in the muscles. The answer to this is that the stem cells don't cure the disease. The advantage is that by virtue of the fact that they are from the same patient they are likely to be accepted more easily at the recipient site without any rejection to the cells.

Stem Cell Therapy for Muscular Dystrophy as done at the NeuroGen Brain and Spine Institute(NGBSI)

How is the stem cell transplantation done?

Herein, we have describe our protocol in treating muscular dystrophy patients using autologous bone marrow mononuclear cells. We have treated over 700 Muscular dystrophy patients to date. The cells are injected both via intrathecal route into the CSF and directly into the affected Muscles. The procedure for stem cell transplantation at NGBSI is minimally invasive, with simple steps or processes. There is no major surgery or incisions required.

What is the procedure of Stem cell therapy at Neurogen BSI?

This is done in 3 simple steps.

Step1: Bone marrow aspiration: (done in the operation theatre)

This is done by putting a needle into the hip bone, after making the area numb with local anesthetic, so that the patient does not experience pain. 80-100 ml bone marrow is aspirated from the inside the bone. This takes about 20 minutes.

Step 2: Stem cell separation: (done in the stem cell laboratory)

The bone marrow removed from the patient is taken to the stem cell laboratory, where the stem cells are separated from the remaining cells of the bone marrow by the density gradient method. The number of cells, their viability and quality are all checked through specialized equipment. This entire process takes about 2-3 hours.

Step 3: Stem cell injection: (done in the operation theatre)

A lumbar puncture using a thin needle is done through the L4-5 space (needle is inserted in the lower back) after giving local anesthetic and some of the stem cells are injected into the CSF. The remaining cells are injected directly into the affected muscles.

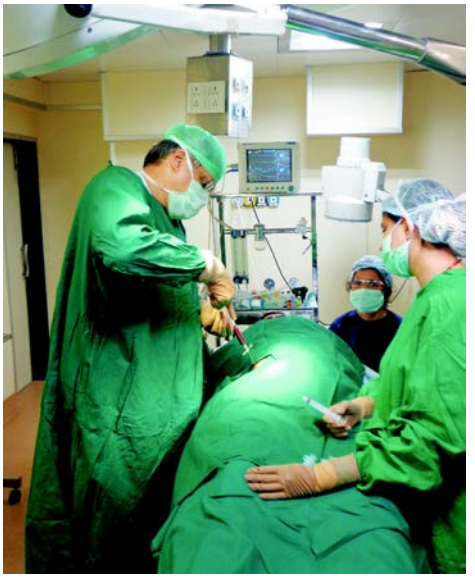


Fig. 22.4: Aspiration of cells from the bone marrow

Fig. 22.5 : Separation and purification of stem cells

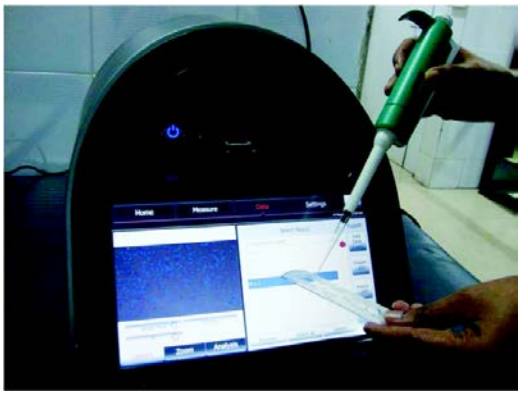


Fig. 22.6 : Checking cell viability using TALI machine

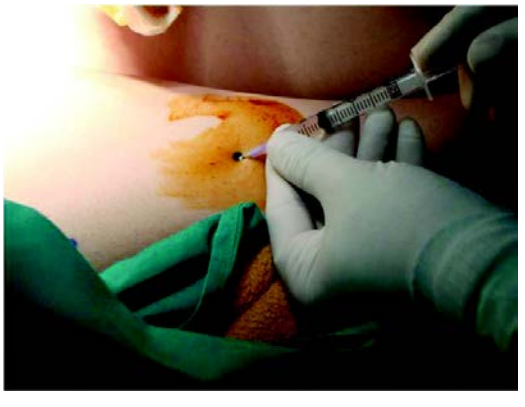


Fig. 22.7: Intramuscular administration of stem cells

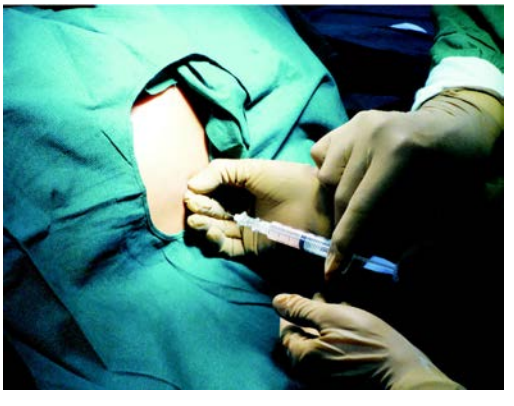


Fig. 22.8 : Intrathecal administration of stem cells

(the muscles into which the cells have to be injected are predecided and marked a day before the procedure. These are individualized for each patient depending on the state of their disease and their functional requirements. The muscle injection is done at a specific point in each muscle known as the motor point) A total of around 50 million cells are injected this way. This takes about 20 minutes.

All the above are completed on the same day.

What has to be done after the stem cell therapy and why rehabilitation plays a vital role after stem cell therapy?

Following the stem cell transplantation, from the very next day, patient undergoes an intensive rehabilitation process, consisting of physiotherapy, occupational therapy, psychological therapy, positive reinforcement processes, yoga therapy, etc. It is important that stem cell therapy be followed by a proper exercise regime to gain proper response. Stem cells are considered to be "blank slates", which means they are programmable.

At NeuroGen BSI, our experience has reaffirmed that the cells can be programmed and guided to help regenerate tissues by doing exercise. Rehabilitation augments the effects of stem cell therapy. Scientific evidence supporting this theory is available too. We believe that the stem cell therapy works along with an extended and aggressive Neurorehabilitation process. In fact we call our entire treatment of stem cell therapy and Neurorehabilitation as Neuro-Regenerative-Rehabilitation Therapy (NRRT). Our long term follow-up reveals that patients who participate in a regular rehabilitation program do overall better than those that don't. The availability of the transplanted stem cells makes the rehabilitation process more effective and efficient. Physiotherapists and occupational therapists report that the same therapy regimes that they were giving earlier start showing much better results after stem cell therapy. We can therefore state that stem cell therapy makes the results of rehabilitation more effective.

What are the results of stem cell therapy at NeuroGen BSI?

Our clinical results have been published as scientific papers in medical journals as follows.

1. Alok Sharma, Hemangi Sane, PrernaBadhe, Nandini Gokulchandran, Pooja Kulkarni, Mamta Lohiya, Hema Biju, V.C.Jacob. A Clinical Study Shows Safety and Efficacy of Autologous Bone Marrow Mononuclear Cell Therapy to Improve Quality of Life in Muscular Dystrophy Patients. Cell Transplantation. 2013; Vol. 22, Supplement 1, pp. S139-S146.
2. Alok Sharma, Hemangi Sane, Amruta Paranjape, Khushboo Bhagwanani, Nandini Gokulchandran, Prerna Badhe. Autologous bone marrow mononuclear cell transplantation in Duchenne muscular dystrophy - a case report. American journal of case reports. 2014; 15:128-34
3. Dr. A. Sharma, Ms. P. Kulkarni, Dr. G. Chopra, Dr. N. Gokulchandran, Dr. M. Lohia, Dr. P. Badhe. Autologous Bone Marrow Derived Mononuclear Cell

Transplantation In Duchenne Muscular Dystrophy-A Case Report. Indian journal of Clinical Practice 2012; 23 (3): 169-72

4. Alok Sharma, Amruta Paranjape, Hemangi Sane, Khushboo Bhagawanani, Nandini Gokulchandran, and Prerna Badhe. Cellular Transplantation Alters the Disease Progression in Becker's Muscular Dystrophy. Case Reports in Transplantation. Volume 2013, Article ID 909328, 7 pages

5. Sharma A., Sane, H., Paranjape, A., Badhe, P., Gokulchandran, N., & Jacob V. Effect of Cellular Therapy seen on Musculoskeletal Magnetic Resonance Imaging in a Case of Becker's Muscular Dystrophy.Journal of Case Reports, 2013 3(2), 440-447.

6. Alok Sharma, Nandini Gokulchandran, Guneet Chopra, Pooja Kulkarni, Mamta Lohia, Prerna Badhe, V .C. Jacob. Administration of autologous bone marrow derived mononuclear cells in children with incurable neurological disorders and injury is safe and improves their quality of life. Cell Transplantation, 2012; 21 Supp 1: S1-S12.

7. Dr. Suvarna Badhe, Ms. Pooja Kulkarni, Dr. Guneet Chopra, Dr. Nandini Gokulchandran, Dr. Alok Sharma Dystrophin Deletion mutation pattern and Cardiac involvement in 46 cases of Dystrophinopathies. Asian journal of clinical cardiology. Asian Journal of Clinical Cardiology, Vol. 15, No. 6, October 2012: 211-214

The original full text articles may be viewed at

www.stemcellspublications.com

Overall results of stem cell therapy carried out on patients with muscular dystrophy at NeuroGen Brain and Spine institute

At Neurogen BSI, we have treated over 700 patients with various types of muscular dystrophies. In an analysis of 332 patients with a minimum of one year followup improvements were graded as significant, moderate, mild and no change and the symptoms evaluated were ambulatory status, hand functions, balance, stamina/fatigue, trunk activation and standing. Out of 332 patients, 42.77% of patients showed significant improvements, 36.14% showed moderate improvements, 15.06% showed mild improvements while 6.02% showed no improvements in any of the symptoms

A further , indepth analysis of 139 boys detected with DMD who underwent autologous bone marrow mononuclear cell intrathecal and intramuscular transplantation was carried out. Their mean age was 11 years, ranging from 3 to 23 years. 39 boys were below the age of 10 years at at the time of treatment, 77 were between 10 to 15 years and 23 boys were over the age of 15 years. 57 of these boys were ambulatory at assessment and 81 were non-ambulatory. A thorough objective assessment was carried out using outcome measurements like Functional independence measurement, Brooke vignos scale, pre and post procedure musculoskeletal MRI and Electromyography.

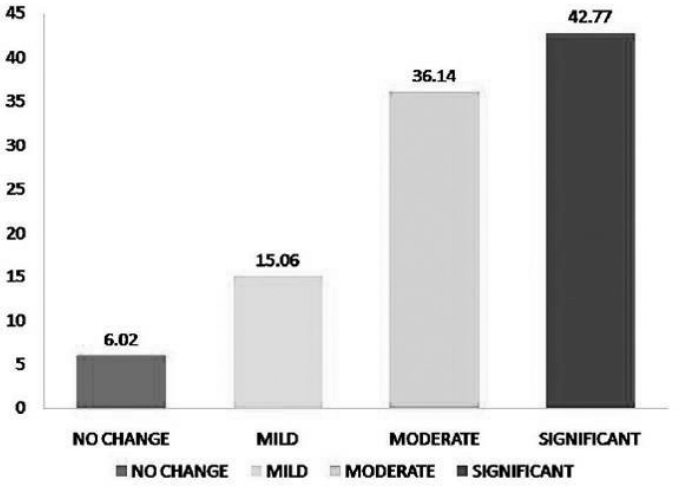


Fig. 22.9

Functional status and objective assessment scores;

At the median follow up there was statistically significant (p = 0.001) improvement on FIM score, which indicates improvement in function after the treatment.. The median score improved from 71 to 76.

In both Brooke and Vignos scales there was no statistically significant difference suggestive of arrested deterioration.

Muscle power testing:

There was statistically significant improvement in the strength of the major muscles of the body as noted on the manual muscle testing. This indicates significant improvement majorly in the upper abdominal muscles, muscles around the hip (flexors, abductors, adductors,),muscles around the knees(flexors and extensors).in upper limbs, internal rotators of the shoulders showed significant improvement, whilst adductors of the shoulders and the biceps, though should improvement, were not statistically significant. These changes are summarized in table below.

Table 2: Changes in muscle strength as measured on MMT 6 months post SCT

Muscle Group	Pre Therapy Mean Score	Post Therapy Mean Score	Statistical Significance
Hip flexors	6.00	6.69	0.001
Hip Abductors	5.42	6.08	0.001
Hip Adductors	4.21	5.00	0.001
Knee Flexors	9.1	9.48	0.004
Knee Extensors	5.26	5.69	0.003
Shoulder Adductors	5.26	6.02	0.04
Shoulder internal rotators	7.23	7.79	0.001
Biceps	7.96	8.32	0.01
Upper Abdominals	3.8	4.21	0.005

Improvement in clinical symptoms:

Children also showed improvement in the clinical symptoms as summarized in Figure below. The analysis of clinical improvement shows that a more than 50% of the children maintain their functional status, such as ability to stand ,walk, trunk control balance, upper limbs and lower limbs strength. Another 40% of the children show an improvement in all these functions, albiet to varying degrees.

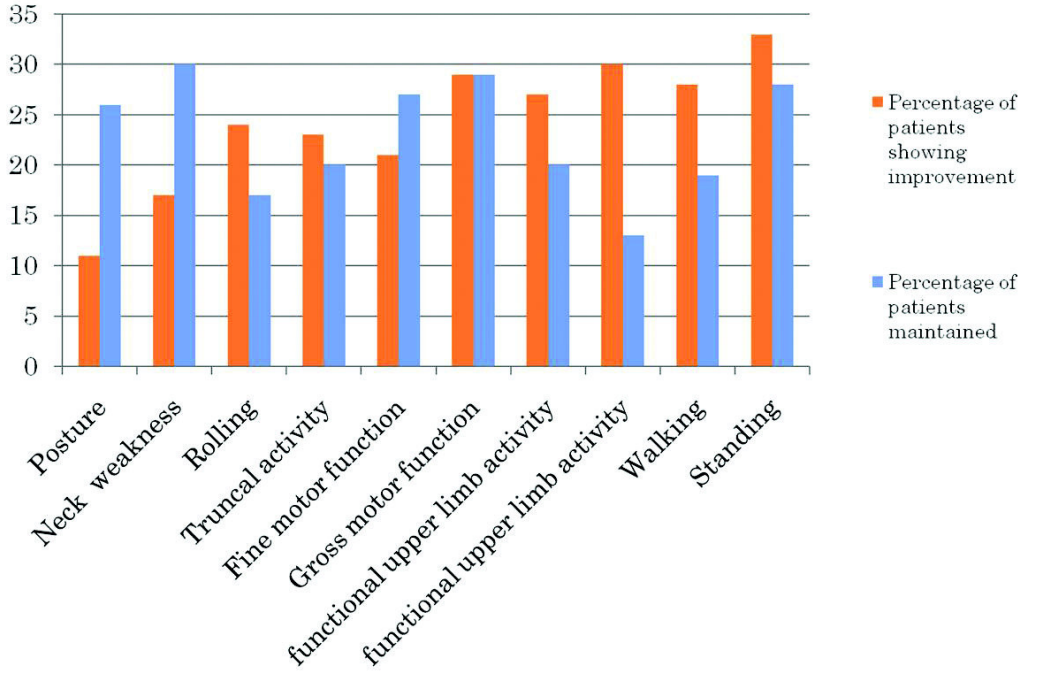


Fig. 22.10

Maintenance of Ambulatory status:

We further compared age at loss of ambulation for children who underwent autologous bone marrow mononuclear cell therapy and those who did not. Kaplan-Meier survival curve was used to predict the age at loss of ambulation. 42 children who were ambulatory and underwent stem cell therapy were compared to 35 children that did not receive stem cell therapy. This comparison showed a statistically significant ($p = 0.004$) difference between the age at loss of ambulation.

The children who underwent stem cell therapy were found to have maintained ambulation longer than those who did not.

Figure 22.11 shows the comparison of the graphs for both groups

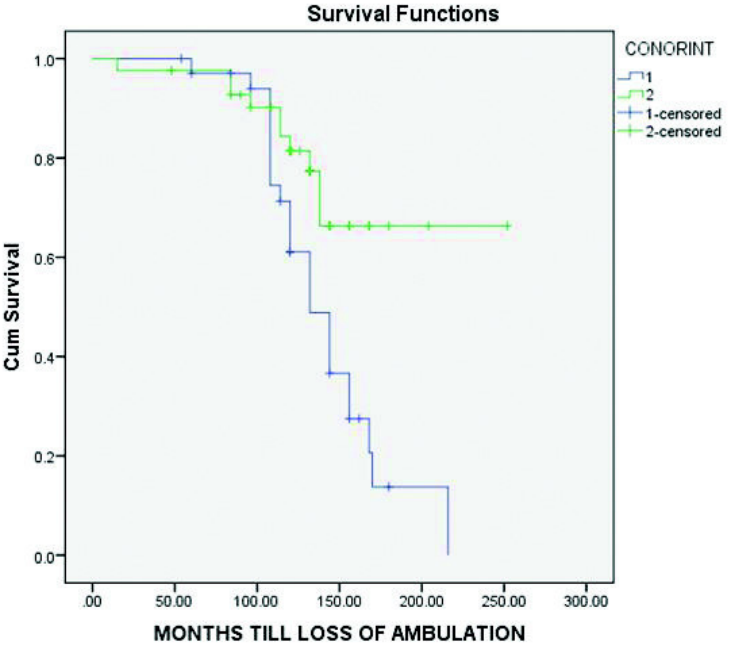


Figure 22.11:Comparison of the age at loss of ambulation for children with and without stem cell therapy

Objective improvements as shown on Musculoskeletal MRI (MRI-MSK) and Electromyography (EMG)

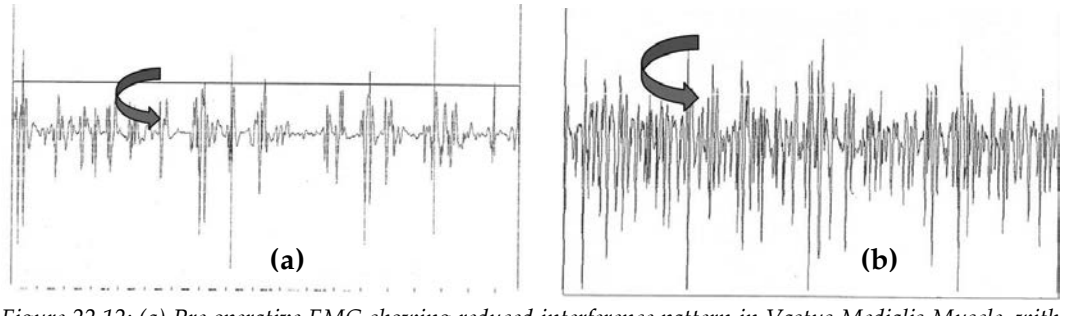


Figure 22.12: (a) Pre operative EMG showing reduced interference pattern in Vastus Medialis Muscle, with myopathic potentials.(b) Post operative EMG showed complete interference pattern in Vastus Medialis Muscle with normal motor unit potentials

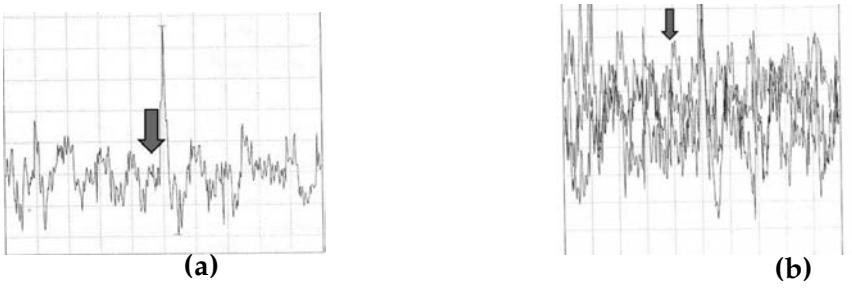
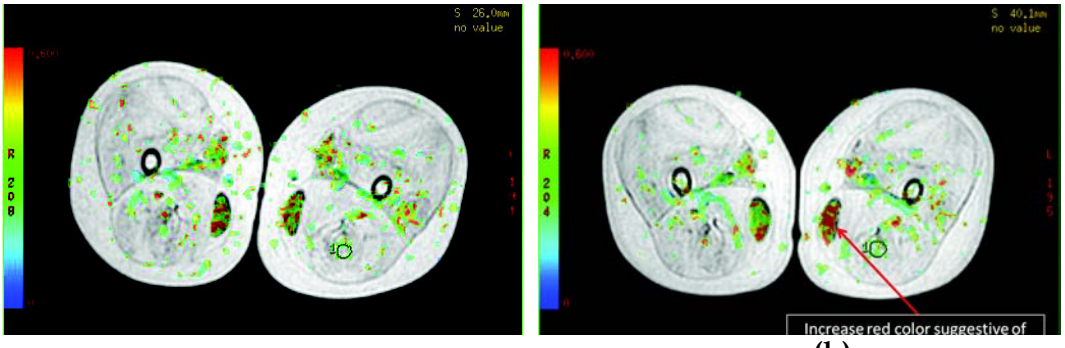


Figure 22.13 : a) Pre op EMG Showing reduced interference pattern in Left Deltoid Muscle, with myopathic potentials. b) Post op EMG showed complete interference pattern in Deltoid Muscle with normal motor unit potential amplitude duration and voluntary effort



(a) (b)

Fig. 22.14 : Increase in the red area (shown by arrow) suggestive of muscle repair

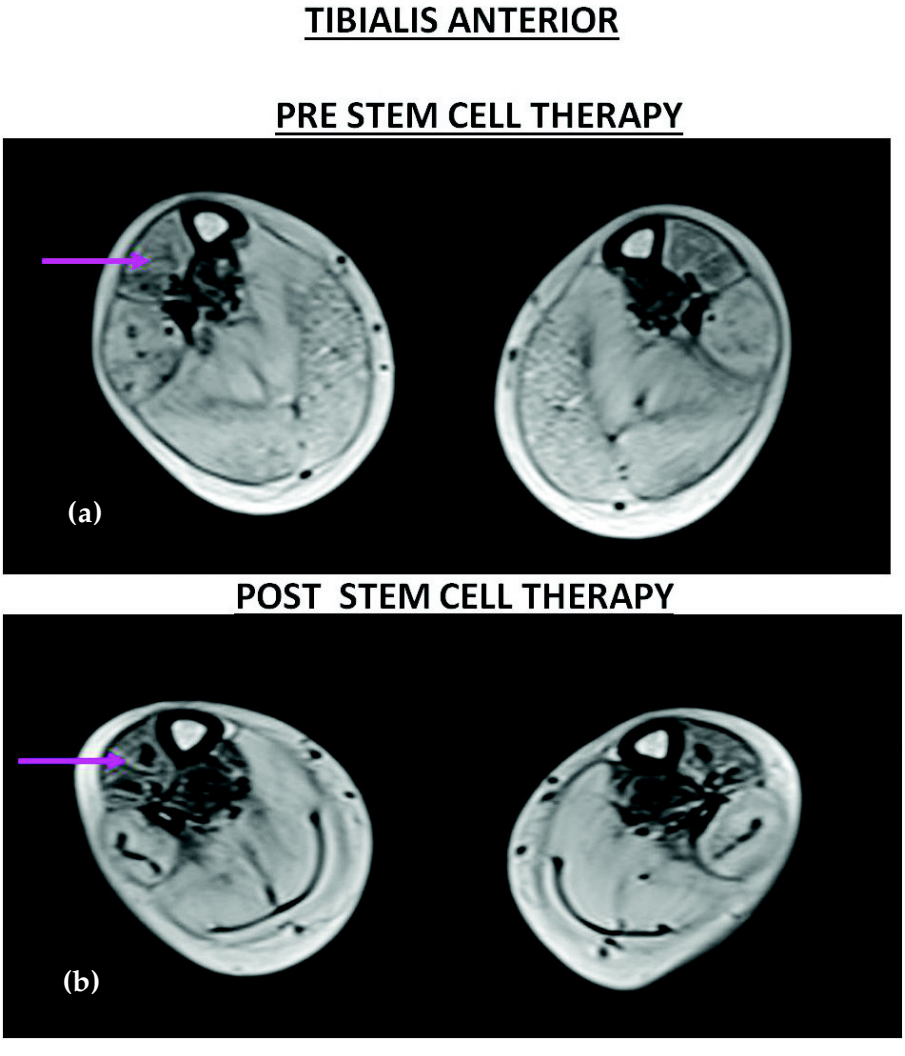


Fig. 22.15 : (A)Pre-stem cell therapy show marked fatty infiltration of the tibialis muscle (B) Post-stem cell therapy shows reduced high signal suggestive of less fatty infiltration and regeneration of muscle fibres

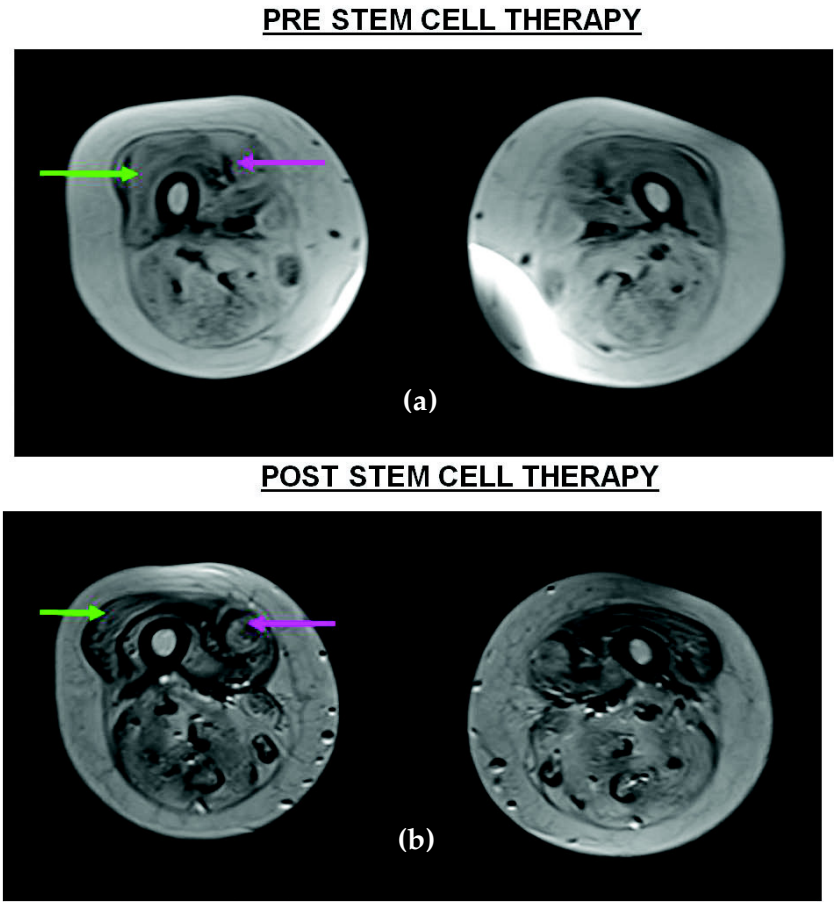


Fig. 22.16 : (A)Pre-stem cell therapy show marked fatty infiltration of the right vastus medials (thick arrow) and lateralis muscle (thin arrow), seen as high signal intensity. (B) Post-stem cell therapy shows reduced high signal in both the vastus medialis (thick arrow) and lateralis (thin arrow) suggestive of less fatty infiltration and regeneration of muscle fibres

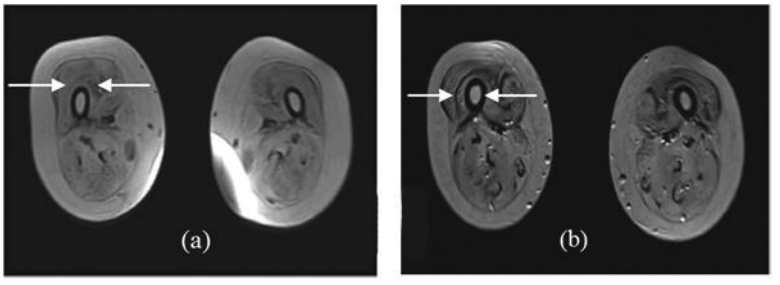
Published data from NeuroGen BSI:

Case reports of patients with DMD and BMD have been published. In an 18 year old boy with DMD, autologous bone marrow mononuclear cells (BMMNC) were transplanted intrathecally. Post transplantation he showed significant improvements in muscle strength and muscle fiber regeneration seen in MRI-MSK. In a patient with BMD, increase in muscle strength, ambulation with minial assistance, improved static and dynamic balance and improved score on Functional Independence Measure was noted post transplantation. Similarly, in another case with BMD, there were clinical, functional and radiological improvements seen after stem cell therapy (Fig. 22.17).

A clinical study was performed, where 150 patients with muscular dystrophy (DMD, LGMD, BMD) were administered autologous BMMNC intrathecally, followed by multidisciplinary rehabilitation. Evaluation after transplantation showed

improvements in the trunk muscle strength, limb strength on manual muscle testing, gait improvements, positive changes in the assessment scales such as the FIM and the Brooke and Vignos Scales.

Fig. 22.17



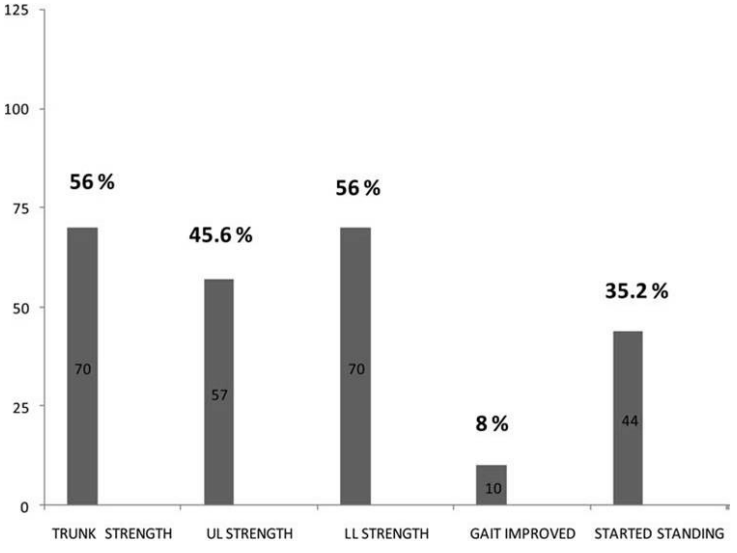
MRI of vastus medialis and vastus lateralis of a patient with MD. Fig (a) pre stem cell therapy. Fig (b) showing regeneration of muscle shown by white arrows

Further, Imaging and Electrophysiological studies also showed significant changes in selective cases. On a mean follow up of 12 months ± 1 month, overall 86.67% cases showed symptomatic and functional improvements, with 6 patients showing changes with respect to muscle regeneration and decrease in fatty infiltration on musculoskeletal Magnetic Resonance Imaging (MRI) and 9 showing improved muscle electrical activity on Electromyography (EMG). 53% cases showed increase in trunk muscle strength, 48% showed increase.

The graphical representation of improvements in each type of dystrophy is demonstrated.

Graph showing overall symptomwise improvement in patients with DMD after stem cell therapy.

Fig. 22.18



Graph showing overall symptomwise improvement in patients with LGMD after stem cell therapy.

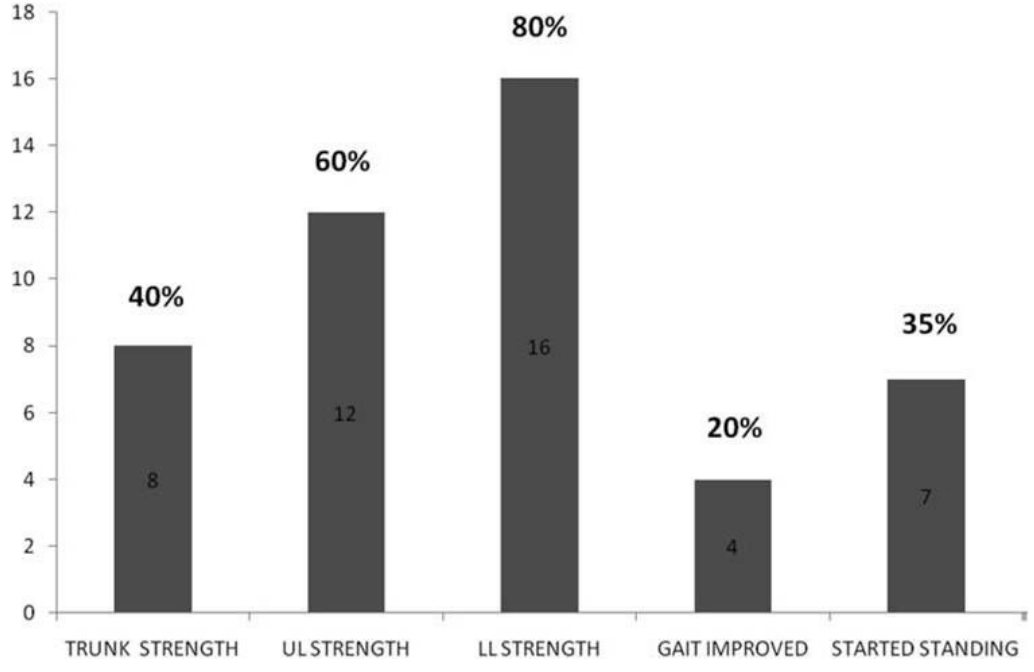


Fig. 22.19

Graph showing overall symptomwise improvement in patients with BMD after stem cell therapy.

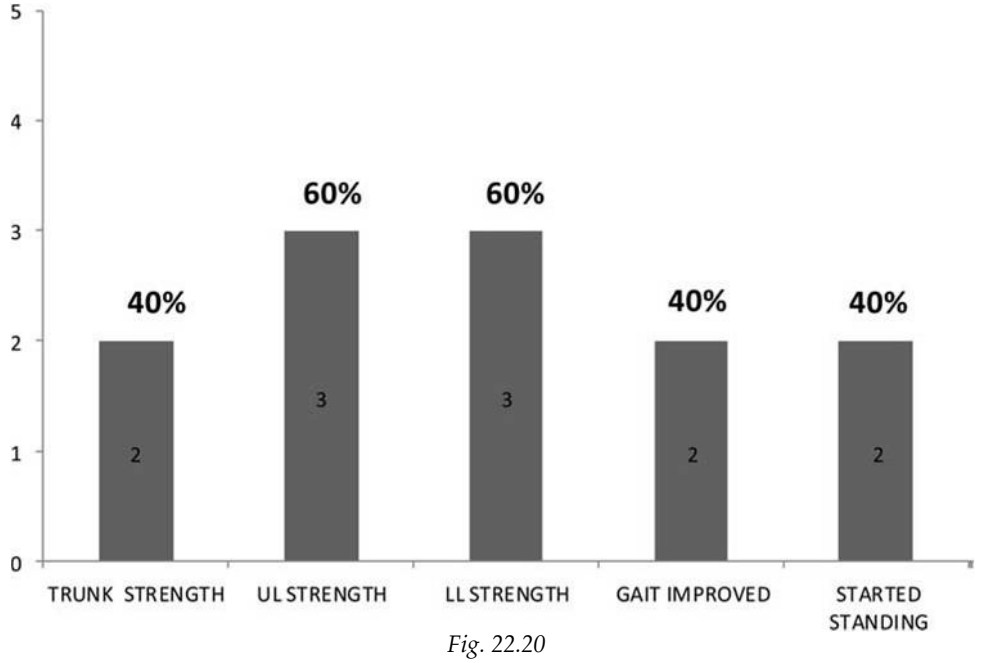


Fig. 22.20

Another study published from NeuroGen, analyzed 59 patients of LGMD who underwent cell therapy and rigorous rehabilitation. Detailed subjective and objective analysis was done using neurological assessment and outcome measures like Functional Independence Measure (FIM) and Manual Muscle Testing (MMT). The study was undertaken over the period of 5 years, with a follow up range from 9 months to 4.5 years. Mean age of the group was 32 with minimum of 16 and maximum of 57 years. Mean age of onset was 18 with minimum age of onset of 3, to maximum of 36 years. The comparison of FIM scores of the patients post procedure yielded no significant difference suggestive of maintained function over the time. There was a statistically significant improvement in the muscle strength of major body muscles like, hip and knee muscles, upper abdominals and shoulder muscles. The key finding of this study was the demonstration of a plateau phase in their progression. There were no significant adverse events noted. The results show that autologous BMMNCs may be a novel, safe and effective treatment approach to control the rate of progression of LGMD, thus improving the functional outcomes and enhancing their quality of life.

A brief review and summary of worldwide research for the role of Regenerative Medicine in Muscular dystrophy.

Stem cell therapy is one of the evolving treatments showing promising results for muscular dystrophy. Animal studies have suggested that myoblast transplanted in the damaged muscles give rise to dystrophin expressing myofibres.

Further research has also been carried out to isolate and study different types of cells which include mesangioblasts, muscle-derived stem cells (MDSC), blood- and muscle-derived CD133+ cells, bone marrow derived stem cells, side population cells, umbilical cord blood cells etc.

Results of few studies are mentioned below.

Huard et al in their study demonstrated that transplanted myoblasts from immunocompatible donors, with simultaneous immunosuppression, showed some improvement in muscle strength and muscle positivity for dystrophin. However, this was found to be decayed over time and antibodies against dystrophin gene were formed.

Gussoni et al showed that donor myoblasts persist after injection; however, their microenvironment influenced whether they fuse and express dystrophin. They also showed the presence of bone marrow-derived donor nuclei in the muscle of a patient documenting the ability of exogenous human bone marrow cells to fuse into skeletal muscle and persist up to 13 years after transplantation.

Similarly Skuk et al, through their trial on three Duchenne muscular dystrophy (DMD) patients concluded that significant dystrophin expression could be obtained in the skeletal muscles of following specific conditions of cell delivery and immunosuppression after myogenic cell injection.

However, Mendell et al reported that myoblasts transferred once a month for six months failed to improve strength in patients with Duchenne muscular dystrophy.

All the above studies were carried out with immunosuppression as Trembley et al in their study presented that myoblast transplantations without immunosuppression trigger a humoral immune response of the host. Antibodies fix the complement and lyse the newly formed myotubes suggesting that myoblast transplantations, as well as gene therapy for DMD, cannot be done without immunosuppression.

Though transplantation of myoblasts can enable transient delivery of dystrophin and improve the strength of injected dystrophic muscle, this approach was seen to have various limitations, including immune rejection, poor cellular survival rates, and the limited spread of the injected cells. It was thought that isolation of muscle cells that could overcome these limitations would enhance the success of myoblast transplantation significantly. The development of muscle stem cells for use in transplantation as treatment for patients with muscle disorders was thought to be an attractive proposition in the early 2000s.

However, all the publications reviewed here point towards some anatomic reconstitution of the dystrophin in the muscles, but fail to impress on the grounds of very mild functional improvement. Hence, other sources of adult stem cells have been explored, such as cord blood cells and bone marrow derived cells.

In the first case of prospective clinical transplantation reported by Zhang et al in 2005, it was demonstrated that allogenic cord blood stem cell transplantation reduces the serum creatine phosphokinase levels which slow down the necrosis of muscle cell. Hence, proving to be advantageous for the DMD patients.

Torrente et al (2007) tested the safety of autologous transplantation of muscle-derived CD133+ cells in eight boys with Duchenne muscular dystrophy. Stem cell safety was tested by measuring muscle strength and evaluating muscle structures with MRI and histological analysis. No local or systemic side effects were observed in all treated DMD patients. Treated patients had an increased ratio of capillary per muscle fibers with a switch from slow to fast myosin-positive myofibers.

Yang et al in 2009 investigated the feasibility of double transplantation of BMSC and CB-MSC in progressive muscular dystrophy (PMD). It was found to be a convenient, safe and effective treatment. 82.9% cases out of 82 cases showed a positive outcome in a follow up period of 3-12 months. Activity of daily living scale (ADL) in 72 patients (87.8%) increased as compared with pre-treatment ($P < 0.01$). Reduction in blood parameters such as LDH levels creatine kinase was also observed.

Autologous bone marrow derived cell transplantation, intrathecally and intramuscularly, is a safe and effective option for slowing down deterioration and degeneration in progressive muscular dystrophy.

Combinatorial action of different cellular components of bone marrow enhances satellite muscle cell stimulation, regeneration and helps reduce fibrosis in the muscle tissue. Sharma et al, demonstrated that the administration of autologous bone marrow-derived mononuclear cells in muscular dystrophy was safe and improves their quality of life. On a mean follow-up of 12 ± 1 months, overall 86.67% cases showed symptomatic and functional improvements, with six patients showing changes with respect to muscle

regeneration and a decrease in fatty infiltration on musculoskeletal magnetic resonance imaging and nine showing improved muscle electrical activity on electromyography. Fifty-three percent of the cases showed an increase in trunk muscle strength, 48% showed an increase in upper limb strength, 59% showed an increase in lower limb strength, and approximately 10% showed improved gait.

Summary

All the clinical work done at Neurogen and all the published literature worldwide suggest that cellular therapy helps in some way in the various muscular dystrophies. The types of cells may be different and the methods of transplanting them may be different but the overall results are promising. No other form of treatment has shown comparable results .

Worldwide Research Publications on stem cell therapy and muscular dystrophy

1. Dezawa M, Ishikawa H, Itokazu Y et al. Bone marrow stromal cells generate muscle cells and repair muscle degeneration. Science 2005; 309: 314-317
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Discussion ({A} The Dilemma, {B} The Debate, {C} Suggestions)

A) The Dilemma:

A major dilemma being faced nowadays by parents and patients of Muscular dystrophy is as to whether they should consider Stem Cell therapy as a treatment option. On one hand they are flooded with information on stem cells through the press, media, internet etc and on the other hand they are told by their primary doctors that this treatment is still unproven or that it does not work etc. These diametrically opposite views create a lot of confusion and conflict in the minds of the patients and their families. The information given earlier as well discussed in this section is meant to empower you to make informed choices. However we wish to state at the outset that since the authors of the book have treated over 500 cases of Muscular dystrophy with stem cell therapy and have observed and reported significant improvements with no major side effects or complications, there will be a bias in this chapter towards Stem cell therapy. Readers should however understand all aspects of this therapy and then make informed choices themselves.

The fundamental questions that arise in the minds of parents and patients are :-

1] Does Stem cell therapy work for Muscular dystrophy ?

2] Are there any dangers or risks of doing this therapy ?

3] What improvements are likely to be seen in the patients with this therapy ?

4] How do I choose a good center for stem cell therapy and how do I know for sure whether the center I have chosen for stem cell therapy is working to high professional, scientific and ethical standards ?

B) The Debate :

There are two sides to this debate and we shall address both. We believe that it is important to listen to, read about and discuss all the points of view before we finally subject our children or ourselves to any treatment that is new.

We shall debate this by dividing the views into two categories. Reasonable views and extreme views. Under each of these we shall look at the arguments for an against stem cell therapy.

Point of view - 1 (Supportive)

A) Reasonable view: That Stem cell therapy is safe and works in muscular dystrophy patients in terms of functional improvements and halting/ slowing down the disease progression

Is Stem Cell Therapy Safe ?

To understand this we must first realize that stem cells are not one single entity. There are broadly speaking three different types of stem cells. These are embryonic stem cells, umbilical cord derived stem cells and adult stem cells. Whereas it is true that embryonic stem cells are potentially dangerous (due to the possibility of their

forming tumors called teratomas) and have various ethical issues associated with them, umbilical cord and adult stem cells are not dangerous in any way (there is no risk of tumor formation with them) and are not associated with any major ethical issues. It is the lack of understanding the fact that there are different types of stem cells and that the risks associated with one are not applicable to the other is what creates a lot of confusion. There are several scientific publications to show that umbilical cord and adult stem cells are safe. In fact a review of all the publications based on these show that there are virtually no major adverse events reported that are connected to these types of stem cells. Based on all the scientific literature and our own clinical experience we can say with a reasonable surety that Adult Stem cell therapy is safe and without any major or significant risk factors.

Is Stem Cell Therapy Effective for Muscular dystrophy ?

Regarding the effectiveness of stem cell therapy in muscular dystrophy we would like to speak primarily of our own experience which is based on over 700 patients treated to date. We have used bone marrow derived autologous adult stem cells which were injected intrathecally and intramuscularly. Earlier in this chapter, we have shared our experience in treating 332 patients with muscular dystrophy. A part of our published work has also been summarized for your information. Some of this work has been published in scientific peer reviewed international and national journals as well as in a book. Based on this we can state with a reasonable and reliable confidence that Stem Cell therapy is effective in slowing down/halting the progression of muscular dystrophy and that it produces functional changes that improve the quality of life of our patients. Also from an Ethical point of view there is a basis for offering this form of therapy. As per the Helsinki declaration *"The ethical basis of offering stem cell therapy as a treatment option is based on the World Medical Association Declaration of Helsinki - Ethical"*

Principles for Medical Research Involving Human Subjects which states that : *"In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available."*

Muscular dystrophy definitely fits into this definition since "proven interventions" do not exist. Therefore from an ethical point of view, as per the Helsinki declaration, for muscular dystrophy patients it appropriate to use stem cell therapy as a treatment intervention. With our own clinical experience of over 500 patients of muscular dystrophy treated we can say that it definitely helps in "saving life, re-establishing health or alleviating suffering". So despite the fact that as per the principle of evidence based medicine, stem cell therapy is still an unproven treatment but on the basis of the Helsinki declaration it may be used since there are no other proven interventions. If instead of looking at this through the lens of evidence based medicine we look at it from the lens of practice based medicine then we cannot say that it is an unproven

therapy since there is enough clinical and published evidence to show that stem cell therapy definitely helps.

Counter argument: One swan does not make a summer. Just because at one or a few centers there are good results does not make it a standard of care. It will take many more centers to show the same results (preferably with a comparison with controls) before we can accept it as a standard of care.

Point of View 2 : (Uncertain)

A) Reasonable view:

That Stem cell therapy is not a proven treatment and we are not sure that it works.

There is substance to this point of view. Today the practice of Modern medicine is based on what is called "evidence based medicine". For a treatment to become a standard of care it should have been evaluated by multiple centers through what are called prospective, randomized, double blind, placebo controlled studies. This type of evidence is called class I evidence. At present we do not have class I evidence for the role of stem cell therapy in muscular dystrophy. So, when your doctor says that this is not yet a proven treatment then based on the principles of evidence based medicine that statement has a basis. By these standards it is also not incorrect for any doctor to say that "we are not sure that it works".

Counter argument: It will take several years (anywhere between 3-7 years) before class I evidence in the form as mentioned above is generated. But, till then patients are deteriorating and even dying. What about them? Will we let patients continue to suffer and deteriorate till enough evidence is generated to suit our thinking when a completely safe and reasonably effective treatment is available now that has in a large number of patients shown to halt/slowdown the progression of the disease and improve the quality of life of the patients. Why are we denying children with muscular dystrophy the opportunity to improve the quality of their lives and halt/slow down the progression of the disease? What is more important? Our principles and standards of evidence based medicine or the quality of lives and disease control of our patients?

Extreme view of points 1 and 2.

Point of View 1:

B) Extreme view:

Stem cell therapy is a definitive cure for muscular dystrophy

Point of View 2:

B) Extreme view:

Stem cell therapy is a dangerous, banned and unethical form of treatment.

Regarding the two extreme views we wish to state that neither is true. Stem cell

therapy does not cure muscular dystrophy. What it does is that it halts/slows down its progression and produces functional improvements in the patients and improves the quality of their lives. The other extreme view is also incorrect. Stem cell Therapy (specially with adult stem cells and umbilical cord stem cells) is not dangerous in any way whatsoever. It is also not a banned treatment. The confusion of it being banned comes from the fact that in the year 2001, President George Bush of America imposed a ban of the federal governmental funding of embryonic stem cell research. (This ban has since then subsequently been lifted by President Obama). It should be noted that [1] the ban was for embryonic stem cells and [2] That ban has subsequently been lifted. Different countries have different regulations and guidelines for use of stem cells. In the US the body to approve this is the US FDA. In India the regulatory body for Stem Cell research is the Indian Council of Medical Research and the Drug Controller General of India. It is also not unethical to treat Muscular dystrophy with adult stem cells since it falls under the category of diseases for which there is no proven intervention and so as per the Helsinki Declaration an unproven therapy can ethically be used. So in summary whilst Stem cell therapy is not a definitive cure for muscular dystrophy, it is neither a dangerous, banned or unethical form of treatment.

We would also like to highlight some statements made in the White paper published by the International Society for Cellular therapy (Gunter, K. C. et al , Cell therapy medical tourism: time for action. Cytotherapy, 12(8), 965-968.

A] It makes an important distinction between clinical trials and medical innovation

"Medical innovation in cellular therapy may be viewed as ethical and legitimate use of non-approved cell therapy by qualified healthcare professionals in their practice of medicine. Patients not eligible for controlled clinical trials should be able to choose unproven but scientifically validated cell therapy medical innovations, if the researchers are competent and those seeking treatment are truthfully and ethically informed. There is a place for both paradigms in the cell therapy global community"

B] It also highlights the patients' rights to seek treatments:

"Patients seeking medical treatment for cellular therapies have the following rights that must be respected by healthcare providers and all associated with their care.

1. *The right to seek treatment: patients and their families/partners have the right to seek treatments for their diseases. No entity should withhold this fundamental right unless there is a high probability of harm to the patients.*
2. *The right to information: patients have the right to an accurate representation regarding the safety and efficacy record of the cell treatment. This includes probable side-effects and a truthful record of efficacy.*
3. *The right to informed consent: patients have a right to a true informed consent process that includes all the elements described above."*

C] It recognizes the "valid compassionate use of unapproved therapies" by classifying centers offering cellular therapies into the following groups.

1. Approved/standard therapies (e.g. hematopoietic stem cell transplant and other cellular therapies approved for marketing)
2. Controlled clinical trials
3. Valid compassionate use of unapproved therapies
4. Treatments not subject to independent scientific and ethical review.

D] It identifies legitimate cell therapy centers on the following criteria:

"The following guidelines are useful in assessing scientific rigor and for differentiating between legitimate cell therapy medical services (including clinical trials and medical innovation) and fraudulent cell therapies.

1. *Peer review and transparency: consumers of cell therapy medical innovation should evaluate evidence from peer-reviewed publications, professional society presentations and scientific recognition. They should be encouraged to seek multiple professional opinions and have all questions answered to their satisfaction.*
2. *Safety and regulatory history: patients should consider the reputation of the investigator and clinic, as well as the record of disciplinary activities against these entities.*
3. *Informed consent: patients should expect to be informed fully and accurately of the risks, benefits, costs, safety, compensation for injury, investigator conflicts of interest and alternative therapies, as a minimum."*

For a more detailed reading on the two sides of this ethical debate and specifically our views on the subject we refer you to a paper published by Dr. Alok Sharma in the Journal of Neurorestoratology tilted " Rethinking on ethics and regulations in cell therapy as part of Neurorestoratology" . This can be downloaded from the website www.dovepress.com

Practical advice :

C) Suggestions to help you make decisions?

Now here are some suggestions on what you should do as parents :

There are two steps to this

Step one: *To decide whether to undergo stem cell therapy?*

This is a decision that has to be taken by you yourself after understanding all aspects (the pros and cons) of the treatment. We must realize that for every choice we make there are consequences of two types. Good outcomes and not good outcomes. This is true for whether we make a choice to do something and even when we make a choice to not do something. So if we do stem cell therapy there is the possibility of good and not good consequences. A not good consequence could be a lack of improvement or some adverse event. But, if we choose to not do the treatment then too, there are good and not so good consequences. For example, a not good consequence of not

undergoing the treatment is a progression and worsening of the disease. We hope that this book and this chapter in particle equips you with the knowledge to be able to make an informed choice. But the final call will still have to be taken by you.

Step two: *[a] If yes then where to undergo the Therapy [b] which type of stem cell therapy to undergo?*

Regarding which Stem cell center to take the treatment from our advice would be that you get answers to the following questions when visiting or consulting with a stem cell therapy :

Question 1: Has this center published their results in peer reviewed scientific journals??

This again differentiates genuine centers working with scientific and academic principles and values from those just set up for commercial purposes. The acceptance of papers for publication entails a process where other doctors and scientists review the data submitted and decide its merits and suitability for publication. This is called peer review and though not a guarantee, it does to some extent ensure that basic scientific and medical principles are being followed for the work that is being published.

Question 2: Does this center have an Institutional Ethics committee??

In India it is mandatory to have a separate stem cell ethics committee. This is important since an ethics committee evaluates and monitors the work being done at the center.

Question 3:- Is special informed consent being taken??

If yes you should ask for a copy of the consent and understand it before accepting to undergoing the treatment. As per the Supreme court of India ruling, an informed consent should have the following information [1] Diagnosis, [2] Nature of treatment , [3] Risks involved, [4] Prospects of success , [5] Prognosis if treatment not given, [6] Alternative treatments.

In any case these are questions you have the right to ask these from the treating doctors. If the doctors openly and authentically answer all these questions then it is worth considering this center. If the doctors do not give you this information or get upset and angry if you ask questions or are not open and honest about what they do then we recommend that you do not undergo therapy at this center. All this is information that you have a right to and no doctor is doing you a favour by giving it to you.

Question 4 : What are the past clinical results of this center with reference to safety and efficacy? What improvements have been noticed in the previous patients treated?

You should understand the improvements reported or published by the center and compare these to your own child and determine whether the symptoms that have been shown to improve are the ones in your own child that you want to see an improvement too. You should specifically enquire about any adverse events both minor and major as well as both short term and long term in the patients that have already been treated.

Question 5 : What type of stem cells are being used at the center?

Which type of stem cell therapy to undergo is a very major question.

a] With our present state of knowledge we would advice extreme caution in considering embryonic stem cell therapy due to the risk of teratoma formation. It will take a few more years before the safety of embryonic stem cells is completely established.

b] Umbilical cord derived cells are definitely safer than embryonic but one should know which company is manufacturing these cells and should obtain some more information on this company. Is it a reliable company and has good manufacturing facilities and practices then it may be alright to consider them.

c] However, Adult stem cell taken from the patient's body (autologous) and which have not been significantly manipulated outside the body are the safest of all types of stem cells. Unless there are other compelling reasons, these are the stem cells to be considered first.

So in summary our answers to the fundamental questions we started out with at the beginning of this chapter can be answered as follows:

1] Does stem cell therapy work for muscular dystrophy?

Answer: Yes, it does to halt/slowdown the progression of the disease and to cause functional improvements.

2] Are there any dangers or risks of doing this therapy?

Answer: Almost none with the use of adult stem cell therapy.

3] What improvements are likely to be seen in the patients with this therapy?

Answer: Improvements in strength in the trunk, upper and lower limbs as well as in standing and gait.

4] How do I chose a good center for stem cell therapy and how do I know for sure whether the center I have chosen for stem cell therapy is working to high professional, scientific and ethical standards?

Answer: Select a center that has that has published its results in scientific journals, has an institutional ethics committee, where special informed consent is taken and all your queries are satisfactorily answered, that can show you documented improvements in its earlier treated patients as well as safety data and that is preferably working either with adult stem cells derived from the patient or umbilical cord stem cells obtained from a reliable company.

Conclusion:

1] There is a definitive scientific and medical basis to consider stem cell therapy as a form of treatment for muscular dystrophy.

2] The published results specially with adult stem cells show excellent safety and good clinical outcomes. The results shown are better than any other form of

treatment currently available.

3] It may not be a standard of care at present, but for that to happen will take several years and many of our Duchenne boys do not that time.

4] It is important that parents / patients understand all aspects of the treatment before deciding to have their children / themselves undergo this treatment.

Researchers fromStanford state that Duchenne Muscular Dystrophy Is Ultimately a Stem Cell Disease.

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 firstever 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.

23.

Gene Therapy : Revolutionizing the World of Medicine

"We used to think that our fate was in our stars, but now we know that, in large measure, our fate is in our genes"- James Watson.

Genes and Gene Expression: The Blueprint of Life

DNA (deoxyribonucleic acid) is the molecular building block of life. It is the storage repository for the information required by a cell to synthesize proteins and replicate itself. DNA molecules are tightly packed in the nucleus of our cells in the form of chromosomes. Fragments of DNA form genes which are the basic and functional units of heredity. Passed from parents to offspring, genes contain the vital genetic code for producing proteins through gene expression. The process of gene expression (see Figure 1) is orchestrated by a plethora of specialized molecules and pathways. The DNA within genes is first transcribed into RNA (transcription). This RNA (ribonucleic acid) is then processed and translated into proteins (translation). These proteins play a vital role in all the body functions at the cellular level. A multitude of regulatory pathways or check points control gene expression at every stage. Thus, gene expression coupled with effective regulatory mechanisms give rise to the "blueprint of life", which is crucial for the survival of all living organisms. Disruptions in the fine tuning of gene expression or the mechanisms that regulate it can lead to faulty production of proteins, which in turn leads to a genetic disorder. These disruptions, usually in the form of mutations (alterations), deletions, duplications; can either be inherited from parents or can be acquired spontaneously (environmental, lifestyle factors).

Gene Therapy: From the bench to the bed side

Gene therapy is the introduction of genes into existing cells to prevent or treat a wide range of diseases. This therapy has been proposed as a treatment for a variety of disorders including Parkinson's, Alzheimer's, cancers and AIDS. The first gene therapy in humans was carried out by Dr French Anderson (often called "the father

of gene therapy") in 1990. He treated a 4 year old girl who was suffering from a severe immune-deficiency disease called adenosine deaminase deficiency (ADA). It is caused by a faulty ADA gene and Dr Anderson was able to successfully introduce functioning copies of the gene. A notable gene therapy success story includes gene therapy trials in the United Kingdom and the United States to treat an inherited degeneration of the retina called Leber's congenital amaurosis (LCA). Functioning copies of the faulty RPE65 gene which is involved in LCA were injected into several patients who had some of their sight restored. Glybera (uniQure Biopharma, Amsterdam) is the first and currently the only gene therapy product to have received regulatory approval for clinical use in either the European Union or the United States.

Principles of Gene Therapy

The principles of gene therapy are simple in concept but harder in practice. The challenge is to introduce a functioning gene into a cell's nucleus, and to target it to the desired location in a way that it will be replicated normally during cell division and will also have a lasting effect. In the early stages of human gene therapy, complications due to problematic gene delivery vehicles plagued the beneficial therapeutic outcomes. However, with the advancement of technology, gene delivery techniques are constantly evolving and gene therapy clinical trials have surged in the past decade. Diverse gene delivery techniques have been developed over the years and are laying the foundation for gene therapy applications for the treatment of various human diseases.

Gene Delivery Techniques

The emergence of recombinant DNA technology has enabled the use of vectors as effective gene delivery vehicles. These techniques are used to deliver a therapeutic gene expression cassette (see Figure 2) to the patient. A therapeutic gene expression cassette typically consists of a promoter region that drives gene transcription, the transgene of interest and a termination region to stop gene transcription. Alternatively, cell-based gene transfer can also be used. The use of vectors and cell-based gene transfer in gene therapy are outlined below.

What are vectors?

A vector is a fragment of DNA which is used as a carrier or vehicle to artificially deliver foreign genetic material into a cell for gene expression. Vectors can be broadly classified into two categories: Viral vectors and Non-viral (DNA) vectors.

Viral Vectors

All viruses infiltrate their hosts and introduce their genetic material into the host's cells. They hijack the host's normal production machinery in order to serve the needs of the virus. The host cell will then produce additional copies of the virus, causing more and more cells to become infected. Certain viruses can actually physically incorporate their genes into the host's genome. Thus, viral genes are introduced among the genes of the host cell for the life span of that cell. This innate ability of

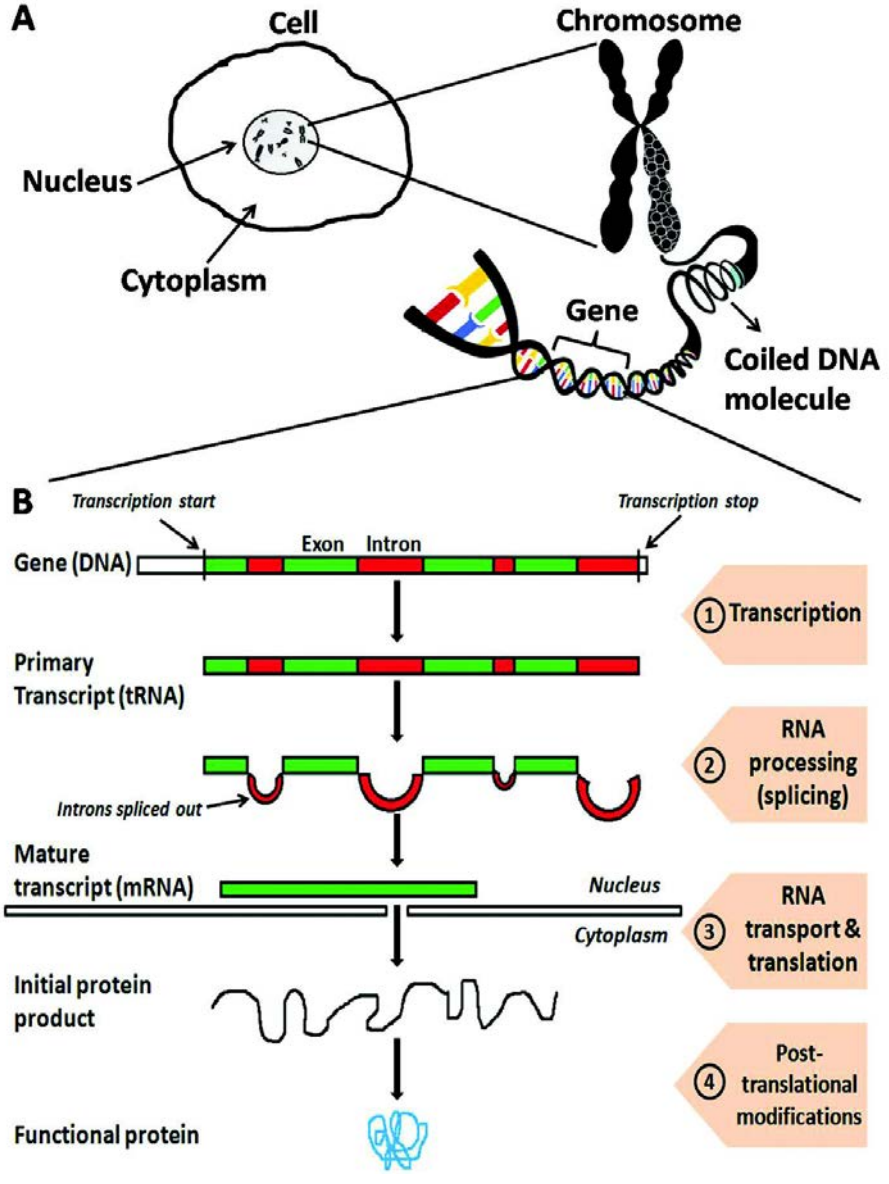

Figure 1: Depiction of gene expression in humans.(A) Chromosomes are contained in the cell's nucleus. Humans have 46 chromosomes (23 pairs). DNA is tightly coiled and packaged within these chromosomes. (B) Genes are subunits of DNA. They contain different regulatory regions like a transcription start and end site, exons (areas coding for proteins) and introns (areas that do not code for proteins). (1) Transcription - Genes are first converted within the nucleus into a primary RNA transcript (tRNA - transfer RNA). (2) RNA processing (splicing) - Introns are spliced out to form mature mRNA (messenger RNA). (3) RNA transport & translation - mRNA is transported to the cytoplasm where the initial protein product is formed. (4) Post-translational modifications - Active and functional proteins are formed by further modifications.

viruses makes them naturally evolved gene delivery vehicles. With DNA recombinant technology, scientists can engineer viruses in vitro (in a laboratory) and replace most of the viral genes with a therapeutic gene cassette. The vectors are tailored in a way that the virus retains its ability to incorporate the therapeutic gene into its host without causing an infection. The most commonly used viral vectors in current gene therapy research are based on: lentivirus, adenovirus (AdV), adeno-associated virus (AAV), gammaretrovirus and herpes simplex virus (HSV).

Non-viral (DNA) vector

Non-viral vectors called plasmids are effective tools for gene delivery. A plasmid is a small circular double-stranded DNA molecule which is distinct from a cell's chromosomal DNA. The genes in this molecule are usually responsible for providing bacteria with genetic advantages like antibiotic resistance. The desired therapeutic

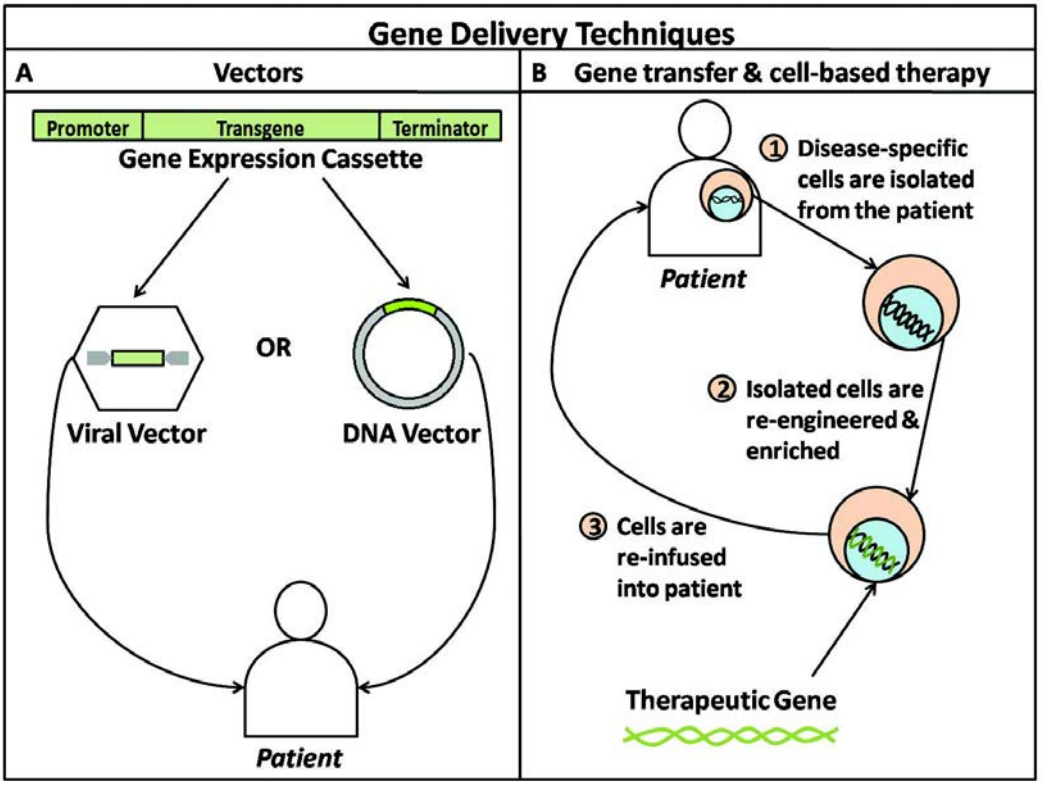

Figure 2: Schematic representation of gene delivery techniques utilized in gene therapy. (A) A therapeutic gene expression cassette containing a promoter (region involved in regulating transcription), the desired transgene (therapeutic gene of interest) and a terminator (region involved in halting transcription) can be delivered to the patient by embedding it into a viral vector or a DNA (non-viral) vector. (B) In diseases affecting specific cells, the affected cells can be (1) isolated from the patient, (2) reprogrammed or re-engineered to express the desired therapeutic gene followed by their enrichment with factors promoting their growth and (3) re-infused or injected back to the patient.

gene expression cassette can be embedded into a plasmid. This engineered plasmid can then either be injected in vivo (in the body) directly in its naked form or by coating it with chemicals to enhance its stability.

Gene transfer and cell based gene therapy:

Some disorders primarily affect specific types of cells like red blood cells in sickle cell anemia. In cell based gene therapy, these affected cells are isolated, cultured and genetically engineered ex vivo through either viral or non-viral mediated gene transfer. These cells are enriched and then re-infused into the patients. This method may improve safety along with specificity as the human body is not directly exposed to gene delivery vectors. Importantly, this involves the modification of cells isolated from the patient's own body (autologous), which prevents the risk of graft versus host rejection. Furthermore, the cells for modification can be selected and expanded to enhance efficacy, before or after reinfusion.

Gene Therapy Strategies

Gene therapy strategies can be broadly categorized as: gene replacement, gene addition, strategies targeting gene expression and gene editing (see Figure 3). The gene replacement technique represents the prototype of gene therapy. However, other gene manipulation strategies have also been developed for treating disorders that are mechanistically different.

Gene replacement

Gene replacement is a straightforward approach for treating diseases that are clearly defined by a single gene defect e.g. muscular dystrophies. A mutation in the gene disrupts protein production and leads to manifestation of the disease. In gene replacement, an engineered functional therapeutic copy of the gene is inserted, which corrects the disease by providing normal proteins. It can be carried out either directly in vivo (into the body) or through cell-based gene transfer.

Gene Addition

Unlike single gene defects that cause monogenic disorders, the combinatory effects of multiple genes and environmental factors lead to complex disorders like diabetes, cancer and heart disease. In such disorders, gene replacement is not feasible as a multitude of mechanisms are at work. In gene addition, a therapeutic gene that targets a specific aspect of the disease mechanism can be administered to the patient in order to alleviate the condition.

Targeting Gene Expression

Various techniques are being developed to target the different stages of gene expression. RNA has diverse functions in biological pathways and disease. It can be an intermediate (e.g. mRNA or messenger RNA) or a final gene product (miRNA or microRNA). Due to its versatility in controlling gene expression, gene therapy strategies specifically targeted at RNA are being developed. One approach employs the principles

of gene knockdown (complete silencing of the target gene) through RNA interference (RNAi). RNAi is a gene silencing process in which certain specialized RNA molecules inhibit gene expression by causing mRNA degradation. Hence, a target disease gene that produces toxic proteins can be silenced by utilizing this method. Another approach involves the reprogramming of mRNA splicing by using antisense oligonucleotides (AONs). These AONs are short strands of DNA that specifically bind to mRNA and cause its degradation. By using AONs, mRNA splicing and ultimately gene expression can be controlled by skipping exons (exon skipping) or by including exons (exon inclusion).

Gene Editing

This approach involves the use of designer or tailor made nucleases. Nucleases are like "molecular scissors" within the body responsible for regulation of gene expression by cutting or cleaving the bonds that hold nucleic acid molecules together, thus leading to their degradation. These nucleases can be engineered and used to produce a targeted change from a disease-promoting gene to disease-preventing gene by inserting, replacing or removing DNA from the genomes (The simplest analogy: Gene editing is much like editing a statement on a word processor where the nucleases play the role of the functions cut, copy and paste).

Muscular Dystrophy and Dystrophin: Good Gene Gone Bad

Muscular dystrophy (MD) is caused by alterations in the dystrophin gene which is responsible for the expression of the dystrophin protein. Located on the X chromosome, it is one of the largest known human genes, measuring 2.6 million base pairs. It contains 79 exons (areas of the gene that code for protein) and takes about 16 hours to be transcribed. Its mammoth size makes dystrophin more susceptible to recombination events and rearrangements that cause mutations. Several different types of mutations can affect this gene, which include:

(1) Deletions (large missing areas of the gene)
(2) Duplications (large doubled areas of the gene)
(3) Small missing or extra bits (insertions) of the genetic code
(4) Base substitutions (tiny substitutions in the genetic code)

Mutations in specific areas of the dystrophin gene lead to the different types of muscular dystrophy.

Gene Therapy in Muscular Dystrophy

Since the initial characterization of the genetic defects involved in muscular dystrophy, much effort has been expended in developing therapies for this debilitating disorder. Initially, the dystrophin gene and its protein product seemed too large and complex for gene therapy. However, our increasing knowledge of the gene and the role of dystrophin in muscle function has identified ways to manipulate them both. Gene therapy for MD now seems to be within our reach. Various gene therapy methods are undergoing clinical trials and are now in the therapeutic pipeline. Some of these with significant outcomes so far are detailed below.

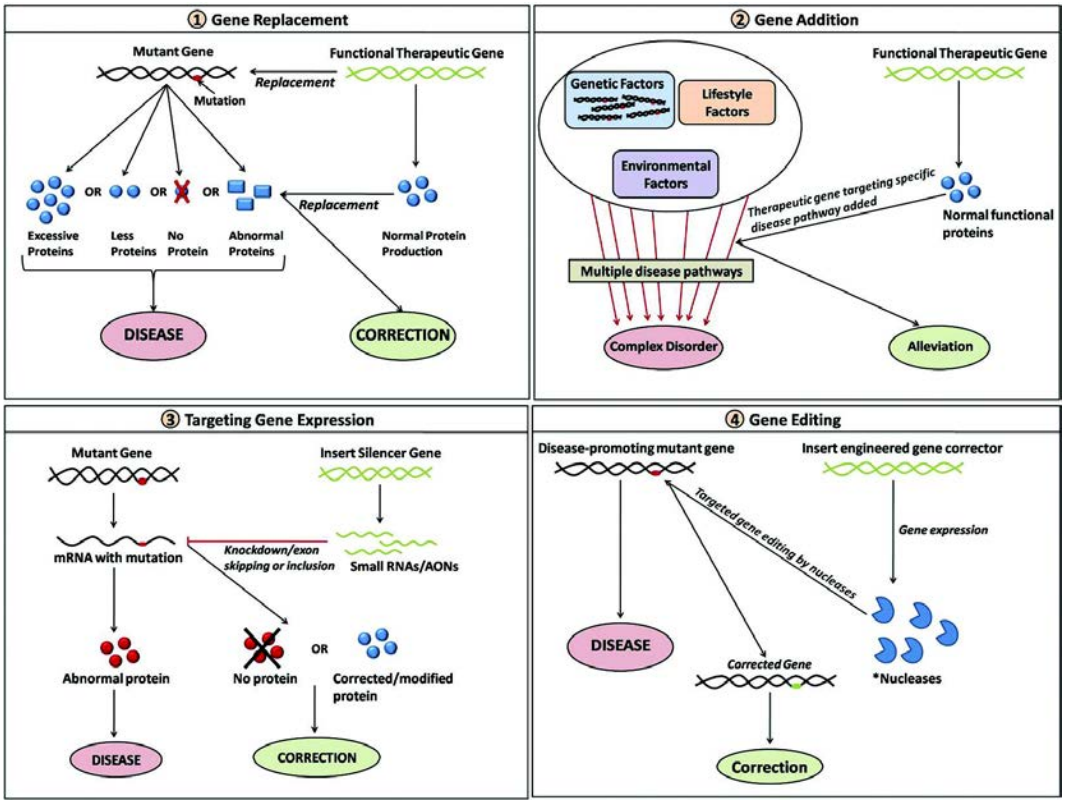

Figure 3: Schematic representation of various gene therapy strategies. (1) Gene mutation produces abnormal proteins causing a disease. Gene replacement provides an artificially engineered functional copy of that gene which produces normal proteins and aids in correction of the disease. (2) Multiple factors (genetic, environmental and lifestyle) result in a complex disorder through various disease pathways. Addition of a therapeutic gene targeted at a particular pathway can alleviate the underlying complex disorder. (3) A mutant gene produces abnormal or toxic proteins which result in a disease condition. Small RNA molecules are utilized to knockdown (completely silence) the gene OR AONs (antisense oligonucleotides) are used to induce disease-specific exon skipping or inclusion. Thus, the synthesis of the abnormal proteins is prevented or modified resulting in correction of the disease. (4) A disease-promoting gene is edited and corrected by engineered nucleases. (*Nucleases are enzymes. Enzymes are essential proteins involved in all body functions)

Ataluren for DMD (Trial study number: NCT01826487)

a) Phase 3 Study of Ataluren in Patients with Nonsense Mutation Duchenne Muscular Dystrophy (ACT DMD)

This is a phase 3 trial of a potential drug called ataluren (PTC124) in boys with DMD which is caused by a nonsense mutation. A nonsense mutation creates a premature

"stop signal" within a gene and therefore interrupts the expression of a complete functional protein. About 10 to 15% of boys with DMD have a nonsense mutation in the dystrophin gene. This may result in either reduced or no production of the dystrophin protein. Ataluren is an oral drug by PTC Therapeutics, which was developed to aid our cells to "read through" a nonsense mutation by making the ribosomes (structures within cells involved in protein production) less sensitive to the "stop signal". The trial is taking place in over 50 locations across the world including USA, UK, Israel, Australia and Korea. The researchers of the study aim to recruit 220 boys with DMD caused by a nonsense mutation, aged between 7 and 16 to receive either ataluren or a placebo for 48 weeks. Ataluren is administered in the form of a powder which can be mixed with water or milk. The expected completion date of this trail is June 2015 and will provide more information about the effectiveness of ataluren to confirm previous trial results. For further information, please visit: www.clinicaltrials.gov.

Ataluren under the trade name Translarna is permitted for conditional marketing authorization in the European Union for the treatment of nonsense mutation DMD in ambulatory patients above age five years. The European Medicines Agency has designated ataluren as an orphan medicinal product. The U.S. Food and Drug Administration (US FDA) has granted orphan drug designation to ataluren for the treatment of nonsense mutation DMD.

Eteplirsen for DMD (Trial study number: NCT02286947, NCT01540409 and NCT02255552)

Research suggests that at least 13% of DMD patients may be treated with an exon 51 skipping therapy. Eteplirsen (AVI-4568), an exon skipping product candidate, is designed to skip exon 51 in the dystrophin gene. It is an AON which triggers the selective excision of exon 51 during splicing of the dystrophin mRNA, resulting in a shorter but functional form of the dystrophin protein. It is currently being analyzed in three ongoing studies being conducted in the United States by Sarepta Therapeutics. These studies are:

a) Safety Study of Eteplirsen to Treat Advanced Stage Duchenne Muscular Dystrophy (Phase 2 - not recruiting)

b) "Efficacy, Safety and Tolerability Rollover Study of Eteplirsen in Subjects with Duchenne Muscular Dystrophy" (Phase 2 - not recruiting)

c) "Confirmatory Study if Eteplirsen in DMD Patients (PROMOVI)" (Phase 3 - recruiting participants).

These studies are focused on assessing the efficacy, safety and tolerability of eteplirsen. Available data suggests that up to 80% of patients with DMD have gene defects that can be amended by exon skipping. Sarepta Therapeutics is also developing other drug candidates that are designed to skip exons 45, 53, 44, 52, 50, 55 and 8. These drugs are currently in the preclinical stages. For more information, please visit: www.sarepta.com and www.clinicaltrials.gov.

Drisapersen for DMD (Trial study number: NCT01803412)

a) A Study of the Safety, Tolerability & Efficacy of Long-term Administration of Drisapersen in US & Canadian Subjects.

Drisapersen (previously PRO051) a candidate drug developed by Prosensa is an exon 51 skipping agent like eteplirsen. This drug is currently in an ongoing phase 3 extension study open to eligible US and Canadian subjects who participated in previous drisapersen studies. This study is aimed at assessing the safety and tolerability of the drug. It will also evaluate an alternative intermittent dosing regimen for patients who have previously experienced significant safety or tolerability issues. For more information, please visit: www.prosensa.eu and www.clinicaltrials.gov.

PRO044 for DMD(Trial study number: NCT01037309)

a) Phase I/II Study of PRO044 in Duchenne Muscular Dystrophy (DMD)

PRO044 is another candidate drug being developed by Prosensa. It induces exon 44 skipping in the dystrophin gene and is intended for approximately 6% of all DMD patients. The underlying mechanism of this drug is similar to drisapersen but it exhibits higher skipping efficiency at lower concentrations. It has recently completed phase 1/2 trails in Europe. The results of this study showed that the drug is generally well tolerated and no adverse events were reported. The extension study for participants of this study and a pivotal study are now being planned. PRO044 has been granted orphan drug (a pharmaceutical agent developed specifically to treat a rare disease, the disease itself being referred to as orphan) status in the European Union and Unites States. For more information, please visit: www.prosensa.eu and www.clinicaltrials.gov.

SMT C1100 for DMD (Trial study number: NCT02056808)

a) A Phase 1b Study of SMT C1100 in Subjects With Duchenne Muscular Dystrophy (DMD)

Utrophin is a protein produced during fetal and regenerating muscle development but is then switched off in mature muscle fibers. If production could be maintained, utrophin has the potential to substitute for the missing dystrophin to restore and maintain the healthy function of muscles. A significant advantage of increasing or upregulating utrophin is that it will benefit all DMD patients, regardless of the specific genetic mutation that is causing the underlying disease. Summit PLC, a UK based drug discovery company has developed a utrophin modulation programme which uses oral small molecules to increase utrophin production. The company's molecule SMT C1100 has recently completed phase 1 trial and is expected to start its next patient study by the end of 2014. The completed study gave encouraging results suggesting that SMT C1100 is safe, well-tolerated and achieved plasma levels shown to increase utrophin in DMD boys. For more information, please visit: www.summitplc.com and www.clinicaltrials.gov.

Mini-dystrophin Gene to Treat DMD (ClinicalTrials.gov Identifier: NCT00428935)

a) Phase 1 randomized double blind clinical trial of rAAV2.5-CMV-mini-Dystrophin

Gene Vector in DMD is completed. The aim of the study was to assess the safety of a miniature dystrophin gene in DMD. A recombinant adeno-associated virus was used as a vector to transfer the gene. The gene was injected directly into both biceps muscles. Muscle biopsy was performed at the follow up. The trial did not demonstrate long-term dystrophin expression. For more details please visit: www.clinicaltrials.gov.

Gene Transfer of rAAV1.CMV.huFollistatin344 for DMD (ClinicalTrials.gov identifier: NCT02354781)

a) A phase I/II Clinical Intramuscular Gene Transfer of rAAV1.CMV.huFollistatin344 Trial to Patients With Duchenne Muscular Dystrophy. The aim of the study is to assess the safety and efficacy of rAAV1 and follistatin in DMD patients. The viral vector will be injected intramuscularly in both the lower limbs' muscles. The efficacy will be measured by the distance walked on the 6MWT, functional tests by PT, life quality questionnaire, MRI, EIM, and muscle biopsy. This study is undertaken following functional improvements seen in the BMD follistatin gene therapy trial. For more information please visit: www.clinicaltrials.gov.

Follistatin gene therapy trial for BMD.

a) A phase I/II a trial of follistatin gene therapy for BMD.

A potent myostatin antagonist, follistatin (FS), was used to inhibit the myostatin pathway in this study. Adeno-associated virus (AAV) was used to deliver follistatin in previous studies which had shown an increase in strength. In this study, AAV1.CMV.FS344 was delivered to six BMD patients by direct bilateral intramuscular quadriceps injections. No adverse effects were observed. The distance walked on the Six minute walk test (6MWT) was the primary outcome measure. Four out of six patients showed improvement in 6MWT. The results also showed reduced endomysial fibrosis, reduced central nucleation, increased normal fiber size distribution with muscle hypertrophy. The findings of this study were encouraging.

Adeno-associate virus (AAV) gene therapy for LGMD2C

a) A phase I trial of adeno-associated virus serotype 1-?-sarcoglycan gene therapy for limb girdle muscular dystrophy type 2C

LGMD2C also called gamma-sarcoglycanopathy, a rare form of LGMD is caused by mutations in the gamma-sarcoglycan gene. A group of researchers in collaboration with a French company called Genethon have released results of their phase 1 clinical trial of a gene therapy for LGMD2C. The aim of this trial was to determine if it is safe to use an adeno-associated viral (AAV) vector to deliver a functional copy of the gamma-sarcoglycan gene to LGMD2C patients. Nine participants were recruited and divided into three groups, in which each group was given a different dose of the functional gene through AAV vectors. Each participant received the therapy through an injection in one wrist and was monitored for up to six months. None of the participants suffered from any serious side effects. Results showed that the participants

receiving a higher dose of the gene showed the presence of the gamma-sarcoglycan protein in the injected muscle. Hence, this study has provided proof of principle that a viral vector could be used to deliver a healthy and functioning copy of the gamma-sarcoglycan gene to treat LGMD2C. The associated researchers are now carrying out more pre-clinical work which will them formulate a second clinical trial to deliver the viral therapy to an entire limb. For more information, please visit: www.genethon.fr.

AAV gene therapy for LGMD2D (Trial study number: NCT00494195)

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

In LGMD2D, a defect in the alpha-sarcogylcan gene leads to insufficient levels of the alpha-sarcoglycan protein. This causes muscle weakness that worsens over time. A recently completed phase 1 clinical trial evaluated the safety and effectiveness of gene therapy in treating children and adults with LGMD2D. This study was carried out in the USA through the collaborative efforts of the Muscular Dystrophy Association and National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). In the study, six participants received AAV vectors carrying a functional copy of the alpha-sarcogylcan gene by intramuscular administration in foot muscles. The results suggest that five out of the six participants produced the alpha-sarcoglycan protein in the injected muscle. The therapy was generally well tolerated (with the exception of one participant who showed a significant immune response to the therapy). The researchers are currently planning on taking the study further with a trial of whole-limb delivery of the alpha-sarcogylcan gene. Based on the success of this therapy, scientists are also carrying out the preliminary research to develop a similar therapy for patients of LGMD2B. For more information, please visit: www.mda.org and www.niams.nih.org.

Conclusion

We cannot change our stars but we can now change our genes. Gene therapy is a fascinating technique that will revolutionize the world of health care and medicine. Although it is still in its preliminary stages, with the rapidly evolving world of genetics, gene therapy will soon find its place among routine therapeutic regimens. Muscular dystrophy researchers around the world are now focusing on gene therapy techniques. A recent breakthrough in MD research by the Nobel Prize winning Dr. Shinya Yamanaka and his team has successfully converted patients' cells into healthy muscle cells using gene editing techniques. In the future, it is likely that gene therapy in combination with other treatment modalities like stem cell therapy, rehabilitation therapy and medications will provide a definitive treatment and possibly a cure for MD.

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24.

Recent Clinical Trials

Sr. No.	Title of the Research	Status of the trial	Organization conducting the research
1	Double Push Acoustic Radiation Force (DP ARF) Ultrasound for Monitoring Muscle Degeneration in Duchenne Muscular Dystrophy	recruiting	University of North Carolina, Chapel Hill
2	Stem Cell Therapy in Duchenne Muscular Dystrophy	recruiting	Neurogen Brain and Spine Institute
3	Test-Retest Reliability of Pulmonary Function Tests in Patients With Duchenne's Muscular Dystrophy	withdrawn prior to enrollment	Children's Healthcare of Atlanta
4	Safety and Efficacy Study of IGF-1 in Duchenne Muscular Dystrophy	status unknown	Children's Hospital Medical Center, Cincinnati.
5	Efficacy of Umbilical Cord Mesenchymal Stem Cells in Duchenne Muscular Dystrophy	recruiting	Acibadem University
6	Research of Biomarkers in Duchenne Muscular Dystrophy Patients	recruiting	institute of myology, france
7	Study Safety and Efficacy of BMMNC for the Patient With Duchenne Muscular Dystrophy	recruiting	Chaitanya Hospital, Pune
8	Safety and Efficacy Study of PTC124 in Duchenne Muscular Dystrophy	completed	PTC Therapeutics
9	Open Label, Extension Study of PRO044 in Duchenne Muscular Dystrophy	enrolling by invitation	Prosensa Therapeutics
10	Eplerenone for Subclinical Cardiomyopathy in Duchenne Muscular Dystrophy	Active, not recruiting	Subha Raman, The Ohio State University
11	Safety and Efficacy Study of Antisense Oligonucleotides in Duchenne Muscular Dystrophy	completed	Imperial College London
12	Phase 2a Extension Study of Ataluren (PTC124) in Duchenne Muscular Dystrophy	terminated	PTC Therapeutics
13	Safety and Efficacy of Umbilical Cord Mesenchymal Stem Cell Therapy for Patients With Duchenne Muscular Dystrophy	unknown	Shenzhen Beike Bio-Technology Co., Ltd.

Sr. No.	Title of the Research	Status of the trial	Organization conducting the research
14	Phase IIb Study of PRO045 in Subjects With Duchenne Muscular Dystrophy	recruiting	Prosensa Therapeutics
15	L-citrulline and Metformin in Duchenne's Muscular Dystrophy	Recruiting	University Hospital, Basel, Switzerland
16	The Preventive Efficacy of Carvedilol on Cardiac Dysfunction in Duchenne Muscular Dystrophy	unknown	Suzuka Hospital
17	Whole Body Vibration Therapy in Boys With Duchenne Muscular Dystrophy	recruiting	Hugh McMillan, Children's Hospital of Eastern Ontario
18	A Phase I/II Study of PRO053 in Subjects With Duchenne Muscular Dystrophy	recruiting	Prosensa Therapeutics
19	High-dose Prednisone in Duchenne Muscular Dystrophy Neuromuscular Research Group	recruiting	Cooperative International
20	Observational Study of Patients With Duchenne Muscular Dystrophy Theoretically Treatable With Exon 53 Skipping (pre U7-53)	recruiting	Genethon
21	Historically Controlled Trial of Corticosteroids in Young Boys With Duchenne Muscular Dystrophy	recruiting	Washington University School of Medicine
22	A Trial of Chronotherapy of Corticosteroids in Duchenne Muscular Dystrophy	withdrawn prior to enrollment	Ann & Robert H Lurie Children's Hospital of Chicago
23	Electrical Impedance Myography and Ultrasound as Biomarkers of Duchenne Muscular Dystrophy	recruiting	Children's Hospital Boston
24	The PTC124 (Ataluren) Clinical Trial for Duchenne Muscular Dystrophy: Exploration of the Experiences of Parents, Clinician Researchers, and the Industry Sponsor	completed	National Human Genome Research Institute (NHGRI)
25	A Phase 2 Study to Evaluate the Safety, Efficacy, Pharmacokinetics and Pharmacodynamics of PF-06252616 in Duchenne Muscular Dystrophy	recruiting	Pfizer
26	Efficacy and Tolerability of Idebenone in Boys With Cardiac Dysfunction Associated With Duchenne Muscular Dystrophy	completed	Santhera Pharmaceuticals
27	Phase 2b Study of PTC124 in Duchenne/Becker Muscular Dystrophy	completed	PTC Therapeutics
28	Longitudinal Study of the Natural History of Duchenne Muscular Dystrophy	recruiting	Cooperative International Neuromuscular Research Group
29	Magnetic Resonance and Optical Imaging of Dystrophic and Damaged Muscle	recruiting	University of Florida
30	Phase II Study of NPC-14 (Arbekacin Sulfate) to Explore Safety, Tolerability, and Efficacy in Duchenne Muscular Dystrophy (NORTH POLE DMD)	recruiting	Kobe University

Sr. No.	Title of the Research	Status of the trial	Organization conducting the research
31	Phase 2b Extension Study of Ataluren (PTC124) in Duchenne/ Becker Muscular Dystrophy (DMD/BMD)	terminated	PTC Therapeutics
32	Study of Ataluren (PTC124®) in Nonambulatory Patients With Nonsense-Mutation-Mediated Duchenne/Becker Muscular Dystrophy	terminated	PTC Therapeutics
33	Revatio for Heart Disease in Duchenne Muscular Dystrophy and Becker Muscular Dystrophy	terminated	Hugo W. Moser Research Institute at Kennedy Krieger, Inc
34	CRD007 for the Treatment of Duchenne Muscular Dystrophy, Becker Muscular Dystrophy and Symptomatic Carriers	completed	Cardoz AB
35	Sunphenon Epigallocatechin-Gallate (EGCg) in Duchenne Muscular Dystrophy	recruiting	Charite University, Berlin, Germany
36	Safety Study of Flavocoxid in Duchenne Muscular Dystrophy	completed	University of Messina
3	Tadalafil and Sildenafil for Duchenne Muscular Dystrophy	completed	Cedars-Sinai Medical Center
38	Duchenne Muscular Dystrophy Clinical Trial	completed	Alan Neuromedical Technologies, LLC
39	Finding the Optimum Regimen for Duchenne Muscular Dystrophy	recruiting	University of Rochester
40	DART Electrical Impedance Myography (EIM) Trial in Duchenne Muscular Dystrophy (DMD) and Healthy Controls	completed	Dart Therapeutics. LLC
41	Long-term Safety, Tolerrecruiting Kobe Universityability and Efficacy of Idebenone in Duchenne Muscular Dystrophy	completed	Santhera Pharmaceuticals
42	Duchenne Muscular Dystrophy < 18y in Norway: Genotype/ Phenotype, Growth, Puberty, Bone Health and Quality of Life	recruiting	Oslo University Hospital, norway
43	"An Open-Label, Multi-Center Study to Evaluate the Safety and Tolerability of Eteplirsen in Patients With Advanced Stage Duchenne Muscular Dystrophy“"	recruiting	Sarepta Therapeutics
44	Phase 1 Clinical Trial of rAAV2.5-CMV-mini-Dystrophin Gene Vector in Duchenne Muscular Dystrophy	completed	Nationwide Children's Hospital
45	The purpose of this study is to determine the safety of a miniature dystrophin gene in the treatment of progressive muscle weakness due to Duchenne Muscular Dystrophy (DMD).	Not available	Not available
46	A Phase I Study of Single and Multiple Doses of TAS-205 in Patients With Duchenne Muscular Dystrophy	recruiting	Taiho Pharmaceutical Co., Ltd.
47	The objective of this study is to evaluate the safety and pharmacokinetic of TAS-205 in patients with Duchenne Muscular Dystrophy.	Not available	Not available
48	Biomechanical Analysis of Gait in Individuals With Duchenne Muscular Dystrophy	ongoing but not recruiting	Shriners Hospitals for Children

Sr. No.	Title of the Research	Status of the trial	Organization conducting the research
49	A Six Month Randomized, Clinical Trial of Gentamicin in Duchenne Muscular Dystrophy Subjects With Stop Codon Mutations	completed	Nationwide Children's Hospital
50	A Prospective Natural History Study of Progression of Physical Impairment, Activity Limitation and Quality of Life in Duchenne Muscular Dystrophy	ongoing but not recruiting	Prosensa Therapeutics
51	Allogeneic Transplantation of Human Umbilical Cord Mesenchymal Stem Cells (UC-MSC) for a Single Male Patient With Duchenne Muscular Dystrophy (DMD)	enrolling by invitation	Allergy and Asthma Consultants, Wichita, Kansas
52	SMT C1100 - A Phase 1b, Open-label, Single and Multiple Oral Dose, Safety, Tolerability and Pharmacokinetic Study in Paediatric Patients With Duchenne Muscular Dystrophy	completed	Summit Corporation Plc.
53	An Open-Label Extension Study to Evaluate the Safety, Tolerability, and Pharmacodynamics of ACE-031 (ActRIIB-IgG1) in Subjects With Duchenne Muscular Dystrophy	terminated	Acceleron Pharma, Inc.
54	Therapeutic Potential for Aldosterone Inhibition in Duchenne Muscular Dystrophy	recruiting	Ohio State University
55	Nebivolol for the Prevention of Left Ventricular Systolic Dysfunction in Patients With Duchenne Muscular Dystrophy	recruiting	Assistance Publique - Hôpitaux de Paris
56	Phase III Randomized, Double-Blind Study of Prednisone for Duchenne Muscular Dystrophy	completed	National Center for Research Resources (NCRR)
57	A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Efficacy, Safety, Tolerability and Pharmacokinetics Study of AVI-4658 (Eteplirsen), a Phosphorodiamidate Morpholino Oligomer, Administered Over 28 Weeks in the Treatment of Ambulant Subjects With Duchenne Muscular Dystrophy		Sarepta Therapeutics
58	A Phase 1b Open Label, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of HT-100 in Patients With Duchenne Muscular Dystrophy	recruiting	Halo Therapeutics, LLC
59	The Role of Family Functioning in Promoting Adaptation in Siblings of Individuals With Duchenne Muscular Dystrophy	completed	National Human Genome Research Institute (NHGRI)
60	Exploratory Study of NS-065/NCNP-01 in Duchenne Muscular Dystrophy	ongoing but not recruiting	National Center of Neurology and Psychiatry, Japan
61	A Phase III Double-Blind, Randomised, Placebo-Controlled Study of the Efficacy, Safety and Tolerability of Idebenone in 10-18 Year Old Patients With Duchenne Muscular Dystrophy	completed	Santhera Pharmaceuticals
62	A Device for Rapid, Painless, Bedside Muscle Evaluation of Children	recruiting	Skulpt, Inc.

Sr. No.	Title of the Research	Status of the trial	Organization conducting the research
63	Myocardial Involvement in Carriers of Duchenne Muscular Dystrophy: An MRI-study	unknown	Hospital Rudolfstiftung
64	Duchenne Muscular Dystrophy Tissue Bank for Exon Skipping	recruiting	Cooperative International Neuromuscular Research Group
65	An Exploratory Study to Assess Two Doses of GSK2402968 in the Treatment of Ambulant Boys With Duchenne Muscular Dystrophy (DMD)	completed	GlaxoSmithKline
66	An Open Label Extension Study of HT-100 in Patients With Duchenne Muscular Dystrophy Who Have Completed Protocol HALO-DMD-01	ongoing but not recruiting	Halo Therapeutics, LLC
67	A 2-Part, Randomized, Double-Blind, Placebo-Controlled, Dose-Titration, Safety, Tolerability, and Pharmacokinetics Study (Part 1) Followed by an Open-Label Efficacy and Safety Evaluation (Part 2) of SRP-4053 in Patients With Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping	recruiting	Sarepta Therapeutics
68	Efficacy Study of Oral Glutamine Supplementation in Duchenne Muscular Dystrophy	completed	Assistance Publique - Hôpitaux de Paris
69	Assessment of Cardiopulmonary Function in Duchenne Muscular Dystrophy	recruiting	University of Florida
70	A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Tadalafil for Duchenne Muscular Dystrophy	ongoing but not recruiting	Eli Lilly and Company
71	Evaluation of Skeletal Muscle, Cardiac, and Diaphragm Imaging Biomarkers for GSK2402968 Effects in Ambulatory Boys With Duchenne Muscular Dystrophy	completed	National Institute of Neurological Disorders and Stroke (NINDS)
72	Compare Efficacy of the Angiotensin Converting Enzyme Inhibitor (ACEi) Lisinopril With Angiotensin II Receptor Antagonist Losartan (ARB) for the Cardiomyopathy of Duchenne Muscular Dystrophy	completed	Nationwide Children's Hospital
73	A Phase 3 Efficacy and Safety Study of Ataluren (PTC124) in Patients With Nonsense Mutation Dystrophinopathy	ongoing but not recruiting	PTC Therapeutics
74	Effect of Eicosapentaenoic Fatty Acid(EPA)and Docosahexaenoic Fatty Acids(DHA) Supplementation in the Inflammation State and Metabolic Disorders in Patients WithDuchenne Muscular Dystrophy or Becker Muscular Dystrophy	enrolling by invitation	Coordinación de Investigación en Salud, Mexico
75	Transplantation of Myoblasts to Duchenne Muscular Dystrophy (DMD) Patients	recruiting	Centre Hospitalier Universitaire de Québec, CHU de Québec
76	DuchenneConnect: An International, Patient-Report Registry for Individuals With Duchenne/Becker Muscular Dystrophy (Member of TREAT-NMD Neuromuscular Alliance)	recruiting	Duchenne Connect

Sr. No.	Title of the Research	Status of the trial	Organization conducting the research
77	Phase I/II Clinical Intramuscular Gene Transfer of rAAV1. CMV.huFollistatin344 Trial to Patients With Duchenne Muscular Dystrophy	enrolling by invitation	Jerry R. Mendell, Nationwide Children's Hospital
78	An Open-Label, Multi-Center, 48-Week Study With a Concurrent Untreated Control Arm to Evaluate the Efficacy and Safety of Eteplirsen in Duchenne Muscular Dystrophy	recruiting	Sarepta Therapeutics
79	A Phase I/IIa, Open Label, Escalating Dose, Pilot Study to Assess the Effect, Safety, Tolerability and Pharmacokinetics of Multiple Subcutaneous and Intravenous Doses of PRO044 in Patients With Duchenne Muscular Dystrophy	completed	Prosensa Therapeutics
80	A Multi-center Study to Evaluate the Pharmacokinetics of 21-Desacetyldeflazacort and the Safety of Deflazacort After Oral Administration of Deflazacort Tablets to Children and Adolescent Subjects With Duchenne Muscular Dystrophy	recruiting	Marathon Pharmaceuticals, LLC
81	Magnetic Resonance Imaging and Biomarkers for Muscular Dystrophy	ongoing but not recruiting	University of Florida
82	An Open-Label Pilot Study of Pentoxifylline in Steroid-naive Duchenne Muscular Dystrophy	completed	Cooperative International Neuromuscular Research Group
83	A Multicenter Randomized Placebo-controlled Double-blind Study to Assess Efficacy and Safety of Glutamine and Creatine Monohydrate in Duchenne Muscular Dystrophy	completed	Cooperative International Neuromuscular Research Group
84	Profile of Mother-caregivers of Children With Duchenne Muscular Dystrophy	recruiting	Monica Levy Andersen, Federal University of São Paulo
85	An Open-label, Safety Study for Previously Treated Ataluren (PTC124) Patients With Nonsense Mutation Dystrophinopathy	enrolling by invitation	PTC Therapeutics
86	An Open-Label Study for Previously Treated Ataluren (PTC124) Patients With Nonsense Mutation Dystrophinopathy	enrolling by invitation	PTC Therapeutics
87	A Phase II, Double Blind, Exploratory, Parallel-group, Placebocontrolled Clinical Study to Assess Two Dosing Regimens of GSK2402968 for Efficacy, Safety, Tolerability and Pharmacokinetics in Ambulant Subjects With Duchenne Muscular Dystrophy	completed	GlaxoSmithKline
88	A Multicenter Randomized Placebo-Controlled Double-Blind Study to Assess Efficacy and Safety of Glutamine and Creatine Monohydrate in Duchenne Muscular Dystrophy(DMD)	completed	National Center for Research Resources (NCRR)
89	Endomysial Fibrosis, Muscular Inflammatory Response and Calcium Homeostasis Dysfunction : Potential Links and Targeted Pharmacotherapy in Duchenne Muscular Dystrophy (DMD)	recruiting	University Hospital, Montpellier

Sr. No.	Title of the Research	Status of the trial	Organization conducting the research
90	A Phase I/II, Open Label, Escalating Dose, Pilot Study to Assess the Effect, Safety, Tolerability and Pharmacokinetics of Multiple Subcutaneous Doses of Drisapersen in Patients With Duchenne Muscular Dystrophy and to Assess the Potential for Intravenous Dosing as an Alternative Route of Administration	ongoing but not recruiting	Prosensa Therapeutics
91	Stacking Exercises Attenuate the Decline in Forced Vital Capacity and Sick Time	recruiting	Children's Hospital of Eastern Ontario
92	A Double-Blinded Randomized Placebo Controlled Study of Daily Pentoxifylline as a Rescue Treatment in DMD	completed	Cooperative International Neuromuscular Research Group
93	A Double-blind, Escalating Dose, Randomized, Placebo-controlled Study to Assess the Pharmacokinetics, Safety and Tolerability of Single Subcutaneous Injections of GSK2402968 in Non-ambulant Subjects With Duchenne Muscular Dystrophy	completed	GlaxoSmithKline
94	An Open-label Pilot Study of Coenzyme Q10 in Steroid-Treated Duchenne Muscular Dystrophy	completed	Cooperative International Neuromuscular Research Group
95	An Open-label Extension Study of the Long-term Safety, Tolerability and Efficacy of GSK2402968 in Subjects With Duchenne Muscular Dystrophy	terminated	GlaxoSmithKline
96	An Open-Label, Multi-Center, Long-Term Extension Study to Evaluate the Safety and Tolerability of Orally Administrated Deflazacort in Children and Adolescent Subjects With Duchenne Muscular Dystrophy	recruiting	Marathon Pharmaceuticals, LLC
97	A Two-Part Study to Assess the Safety and Tolerability, Pharmacokinetics, and Effects on Histology and Different Clinical Parameters of Givinostat in Ambulant Children WithDuchenne Muscular Dystrophy	ongoing but not recruiting	Italfarmaco
98	Pilot Study of Cough Peak Flow And Airway Clearance in Pediatric Patients With Neuromuscular Disease	recruiting	University of Pittsburgh
99	"An Open-label Extension Study of the Long-term Safety, Tolerability and Efficacy of Drisapersen in US and Canadian Subjects With Duchenne Muscular Dystrophy.“"	recruiting	Prosensa Therapeutics
100	Constipation and Gut Transit in Duchenne Muscular Dystrophy Patients	recruiting	Children's Hospital Medical Center, Cincinnati
101	Comparative Study of Clinical Endpoint in DMD: HHM vs. CQMS	completed	Cooperative International Neuromuscular Research Group

Appropriateness

To be appropriate, to act appropriately. This is to follow the Tao.

Appropriateness is a readiness for the situation as it really is, and not as one might wish it to be. Appropriateness thus has to do with creation and is indeed always creative. It is creative even when it creates nothing-for it is sometimes appropriate to create nothing. And to refrain from creating precisely when one is in a position to create itself is creative. This is true control.

Appropriateness cannot be gauged or measured in terms of necessary and sufficient conditions, for the later only exist in the physical universe- in the realm of doing and having- while the former exists in the realm of being.

To do what is appropriate is to do what is fitting or suitable to a situation. The situation is, however, in flux or change from moment to moment. To carry over "standards of appropriateness" from one moment to another is to fail to complete one moment and to set up a barrier to experiencing the next moment. This is to become stuck. What is appropriate is to have completed and always to be beginning anew-from and as cure. Any "standard of appropriateness" is thus a recipe for a lie.

Appropriateness, the Tao, the way, is revealed as unconsciousness is removed. As one begins to experience life, one's behavior effortlessly becomes more and more appropriate just in the process of life itself.

Appropriateness in a situation and control of a situation without force are thus identical. For appropriate action is not doing anything: it is neither submitting nor resisting; it is just being there.

The definition of the verb form, to appropriate, can now be understood. To appropriate is to take over something as one's own, is to be at cause.

-Werner Erhad

SECTION - V

Living with Muscular Dystrophy

25.

Frequently Asked Questions

Patient, parents and caregivers have lots of questions in their mind, about the disorder, the progress,the treatment options, transmission, how it will affect the other members of the family,etc.The questions are endless,but in the previous sections, we have tried to answer most of them.

Still, for ease of understanding(even if repetitive) some of the most common and frequently asked questions have been addressed here.This list is not exhaustive by any means.Any questions not included here, would be addressed in specific chapters, as far as possible.

Q1 Is muscular dystrophy a contagious or an infectious disease?

A: No, it is not a contagious or an infectious disease.It is a genetic disorder and can be hereditary.

Q2 Is muscular dystrophy always hereditary?

A: Not always. Many investigations state that about 1/3 of all boys suffering from Duchenne or Beckers muscular dystrophy have no family history.

Q3 Which are the most common muscular dystrophies?

A: The most common is Duchenne and second most common is Beckers, followed by Limb Girdle muscular dystrophy which is the third most common form.

Q4: What is the first sign I will notice if my child has Duchene muscular dystrophy?

A: He may start talking and walking late. But these features occur in many other different conditions. Overall, movements are slower, the child may not be able to run like other kids, could have difficulty in getting up from the floor.The best option is to do a serum creatinine phosphokinase level (blood test), which would give a raised result(almost to the degree of thousands, eg.20,000 IU/ML, etc.).

Q5: Is muscular dystrophy a disease of the childhood only?

A: Not necessary.Some types, such as facioscapulohumeral, myotonic and limb girdle muscular dystrophy,manifest or appear or begin late, either in teenage or early youth .They are slow in progression and less severe than the childhood forms.

Q6: What are the few early signs of adult muscular dystrophy?

A: Facioscapulohumeral muscular dystrophy: weak smile or inability to whistle. Limb girdle muscular dystrophy: weakness of shoulders and hip muscles, leading to difficulty in getting up from lower surfaces and raising hands above head.

In adult or teenage onset muscular dystrophy, symptoms or difficulties atrt a bit later in life, as opposed to DMD or congenital muscular dystrophy where problems a re noticed, many a times, in infancy itself.

Q7: How is muscular dystrophy transmitted?

A: It is a genetic disorder. It could be passed on from either of the parent via an affected gene.It could also be inherited, partly from mother and partly from father.

- In Duchene muscular dystrophy, the mother is a carrier of affected gene and the disease is transmitted to the male child. Each male born to a carrier mother has a 50% risk/chance of being affected and each female child born is at 50% risk of being a carrier.
- In myotonic dystrophy and facioscapulohumeral dystrophy, one parent could be the carrier (autosomal dominant).
- In limb girdle muscular dystrophy, either both the parents could be a carrier, which means that a combination of defect carried by both parents causes the disease in the child. Both male child and female child can be affected with the disease.

Q8: My son had/has Duchenne muscular dystrophy, can my daughter or me be a carrier?

A: If the genetic defect has been inherited from the mother, there are 50% chances of the daughter being a carrier too. Blood tests, such as genetic testing for carrier can be done to identify it.

Q9: Can this disease be detected during pregnancy?

A: Yes, if a mother is a known carrier, then amniocentesis or chorionic villi sampling (amniotic fluid from the womb) can be subjected to genetic testing for Duchenne or Becker's muscular dystrophy.If positive, it indicates the child is a sufferer. However,if the test is negative, it does not completely rule out the disease.

Q10: Why are muscles enlarged in muscular dystrophy children/patients?

A: The muscles, especially in the calf, are slowly replaced by fat which is known as pseudohypertrophy,i.e. muscles look large, but are falsely big.

Q11: What are the treatment options to help a child with muscular dystrophy to prolong his walking?

A: Surgical release of tight or contracted muscle can lead to immediately standing next day. Second option would be serial casting. These options can help children of muscular dystrophy to prolong independent walking. Regular rehabilitation and stretching also help in improving quality of life. Some people are of the opinion that steroids may help keep the child walking for longer periods.These are conventional methods.

New treatment option, such as stem cell therapy has also been found help improve muscle strength and prolong ambulation in a child.

Q12: In a child confined to the wheelchair,can surgery help him to regain his walking?

A: Surgery may help, but it depends on the status of the child's muscle power. Surgery becomes the best option when the muscles become very tight and are not stretchable at all.

Q13: How does physiotherapy and occupational therapy help muscular dystrophy patients?

A: It helps prevent contractures, keep muscles strong, improve efficiency of functional activities like standing, walking , learning proper methods for transfers (chair to bed, etc,)

Q14: Why should muscular dystrophy patient's exercise? Can exercises be harmful?

A: It is important to exercise, as it enhances physical, social and emotional development.Also, as mentioned earlier, it helps to maintain the child's condition, prevent contractures and deformities.However, if done beyond the capacity or in excess and not under proper supervision, it may lead to deterioration or worsening of condition.

Q15: Can swimming be beneficial?

A: Swimming could be beneficial for the patient.It is advised to start this activity from a very early age as it helps to increase endurance, increase muscle strength and is a good work up for the respiratory and cardiac muscles.

Q16: How do stretches help? : Can stretching be harmful?

A: Stretches prevent development of contractures. A regular stretching program, under proper supervision of a therapist,is a must as it keeps muscles and tendons supple. Yes, it can be harmful, if not done properly.Hence,it should preferably be done by the therapist. Alternatively, parents should learn the correct method under the supervision of a therapist.

Q17: Can weights be used to strengthen muscles in patients with muscular dystrophy?

A: No, using weights won't make the muscles strong because these muscles are different from other people.Lifting heavy weights can ,infact,damage the muscles. There are other exercises which help to strengthen the muscles. Please talk to your therapist about them.

Q18: What are contractures?

A: Contractures are the tightening of the muscles which occurs because not all muscles loose strength at the same time and patients develop irregular postures to compensate for the weak muscles. These irregular postures lead to more tightness in some muscles leading into development of contractures.

Q19: Is wearing night splints compulsory?

A: Wearing of night splints is often recommended as soon as the diagnosis is made.

It should be well tolerated and should be accepted by the patient. Ankle foot orthosis holds up the feet ,which is the most comfortable and desired position for the foot.

Q20: Is massage recommended in patients with muscular dystrophy?

A: We generally do not recommend massage for muscular dystrophy patients due to the following reasons:

a) It can fasten muscle damage or degeneration

b) Pressure during massage can inadvertently cause fracture of already brittle or fragile bones of the patients.

Q21: Are alternative therapies like Acupuncture, Acupressure or Ayurvedic recommended?

A: Since, we are not experts in this field, we would not be able to comment on its utility or otherwise for muscular dystrophy. We would recommend you to consult your physician regarding the same.

Q22: Are there any medicines to treat muscular dystrophy?

A: Corticosteroids are used to control the disease progression. But, due to side effects their use is limited. Recently, Ataluren is approved by US FDA as an orphan drug for DMD. There are more experimental drugs in the pipeline.

Q23: Do stem cells work in muscular dystrophy?

A: Different types of stem cell have shown a potential benefit in muscular dystrophy. Adult stem cells are being extensively studied. Autologous bone marrow cells are known to be safe and devoid of any ethical issues. At NeuroGen, we have shown efficacy of autologous bone marrow cells in muscular dystrophy.

Q24: Where are we with gene therapy for muscular dystrophy?

A: Gene therapy is rapidly expanding, and Ataluren (Translarna) is the first gene therapy drug being used in the treatment of specific subtypes of DMD. There are more gene therapy products under experimentation.

Q25: What kind of diet is recommended in muscular dystrophy?

A: A balanced high protein diet is recommended for muscular dystrophy patients. Supplements which include Vitamin C, D and E, Calcium and CoQ10 are also recommended.

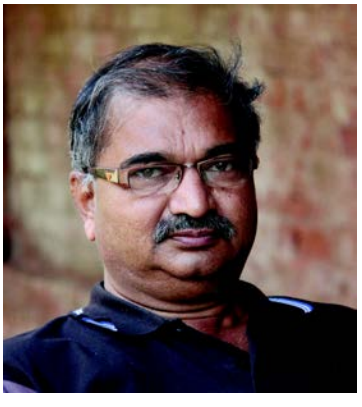
Q26: Can adults with muscular dystrophy get married and have children?

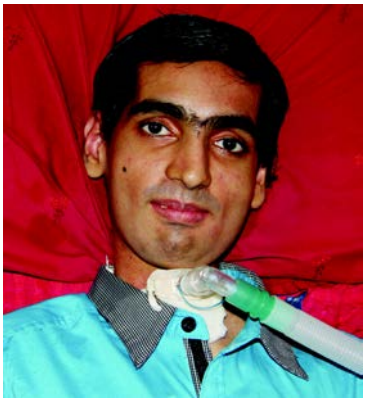
A: Yes. Adults with muscular dystrophy can lead a healthy sexual life. It is recommended to undergo premarital counseling with the potential partner at a specialized counseling center. Adults with muscular dystrophy can also have children and make a family. It is recommended that genetic counseling advice be taken before conception. Adults with muscular dystrophy can lead a complete happy life.

26.

A Word from Parents / Patients

Mr. Chandrashekhar Kant- father of Ankur Kant 26 years old Duchenne Muscular Dystrophy





"We have learned to live powerfully and enjoy it fully in every moment of life, but it was not so 22 years back. What happened was I took my son Ankur for a normal checkup to a child specialist Dr. Athavle. In his routine checkup everything was normal.

As we were about to get out of his cabin I shared my normal observation about my son's activity. I told him my son is like all other kids, the only difference is that when he gets up from floor he takes the support from floor and then of his knees by his palms and stands up straight. He also can run but stops abruptly and falls down.

After I told this to doctor, he examined him by rubber hammer and by making him sit down and get up again and again. I was observing doctor and he looked confused and stressed. He referred us to another doctor at Hinduja Hospital.

Dr. Bernard D'Soza examined him and said your son is a patient of Duchenne muscular dystrophy but let us do the muscle biopsy to confirm it. After the reports, it was confirmed and we had meeting with doctor. They told the same story which parents

of every Duchenne muscular dystrophy patient has to listen, like no cure, no possibility, you have to live with it and the ultimate eventuality that you have max 18 to 20 years.

I was absolutely blank, did not know how to react or respond and what to think and the most important was how to accept what is so. When our relatives and friends came to know about it, they came to visit us to express how bad they feel because we were the most unlucky father and mother.

My life was on hold, I did not know what to do, how to do, how to proceed in life and most important was why of all the people it is me. There were only questions without any answer. This life was fired at me from point blank range and there was no way it could miss.

I was left with no choice than to accept what is unacceptable, undesirable and absolute unjust to me. I was not a bad person so that God will enforce such a punishment for me. When I have not hurt anybody emotionally or grabbed somebody's happiness then why it is me. All the time I was occupied by these thoughts. This made me more upset, helpless and totally isolated.

As I had no answer to any of the questions even I was scared to look at my son. My wife was crying all the time, she kept herself away from son. I did not know how to support both of them. I thought best is to go away from this situation and I did it. I went to Goa. Even in the company of beer the thought about my son never vanished, on the contrary it became more torturous.

That is where the first insight came that I cannot run away from what is happening to my family. I had no guts to face the situation and standing in this uncertain position in life made me go crazy.

Even when I was sitting alone my mind did not allow me to get out of this vicious circle. Suddenly I remembered one of the things which doctor said, that the possibility of having such a son is one in 3500. One such boy is sacrificed by the GOD to complete the cycle of mutation and to ensure that other 3499 kids live normal healthy life. So my son happened to be the unique outstanding sole and because of him I have become a special father of a special son. This has happened only to me among 3500 families because God has full faith in me that I can take care of him and support him completely, what he is supposed to complete in his life time. He is a special gift from God to us. Out of this awareness, my being upset completely disappeared.

My thoughts became clear and now I could think about what is workable in alignment with how life works. Every creation of God has definite intentions for things to be the way they are. My son is born with some intentionality and the intention of me being born as his father is to support him, to complete his intentions he is born for. It is important to fulfill the intentions of the creator otherwise we will be discarded as complete human being.

The bottom line of my interpretation was that he is my son because God has faith in me to take care of him and support him completely, what he is supposed to complete in his available life span. This shift in my paradigm has transformed my approach to

living life powerfully.

My son was still the same, his sickness was the same but it stopped diffusing me and making me upset. On the contrary it gave me additional strength to live life powerfully. I HAD THE DEFINITE INTENTION TO LIVE MY LIFE.

This person who was coming back from Goa was a totally different person willing to live for the purpose intentionally. I entered my home with full of vitality and bulldozed everyone. All the complains from everyone's thoughts had disappeared. This is how we have learned to distinguish distinction in life.

We gave up all the conversation which the doctor had given to us about my son's disorder and learned to live up every moment made available to us to generate joy and happiness. In response to attitude towards life, my son has never complained till date that why it is me. He answered this question by saying that it is me because I am capable enough to handle it and I will make a difference in the attitude of other kids so that they could create a new dimension of living a powerful life.

He is my Guru, I have learned all the values of life, I am the way I am because Ankur was gifted to me by God. In support of calling him my Guru, I will share the most important insight he gave to me.

From my young age I had one question "what is the difference between life of a human being and life of animal, say life of a man and life of a dog?. That man is born from mother and even the dog. Man's first feed is mother's milk, same for a dog. Man gets educated in how to earn food and comfort &even dog gets his education. Man finds a match and produces kids, even it is true for dog. Man becomes old and dies, even this happens with dog. Then what is the difference between life of a man and dog?" I have asked this question to some transformed people. Either they have dodged my question or they have given me some irrelevant answer.

I asked the same question to Ankur and he said he knows the difference between life of a man and life of a dog. The difference is that there is no difference in the life. There is a difference in the way they die. I said I did not understand, so he said dog is born as dog and he dies a death of a dog, but the man is born as a man and he dies a death sometimes worst than a dog, like a dog, like a bad man, good man, like a saint or even like a god. All these possibilities exist for a man and not for a dog. The man who chooses today how he is going to die and lives in accordance with it, that man is born like a man lives like a man and dies according to what he chooses to accomplish in life.

So many changes kept on happening in Ankur's life. He stopped walking then he was unable to stand. We used to lift him and take him to school. Then CO2 retention, hospitalization occurred again and again. Ankur came from hospital with tracheotomy and ventilator which has not left him till today. He has taken 4 stem cell treatments and has shown definite improvement at the age of 26 years. This has made a difference in his life and promises to do so in the lives of many young kids. In spite of all these happenings, he is still cool, calm, charming, and joyful and lives a fulfilled life every moment."

Kadambari Karalkar -Shreyas's mother

My son Shreyas,12 years old, is known case of DMD since the age of 6 yrs. I could not believe that I had given birth to a very healthy child whose weight was nine and half a pounds. It was only later that we found out that he is suffering from an incurable disease called Duchenne muscular dystrophy.

At the age of 6 yrs, Shreyas was attending Christ Church School, Byculla and was traveling by school bus every day. One day, his teacher called me and said that whenever he has computer period which was on first floor, "he always comes last so please check if there is any problem and we will help you". I was surprised to hear that. I remember it was in August 2006. I took Shreyas to his regular doctor-Child specialist Dr. Satoskar on Aug 12 2006.I told him about Shreyas .Dr. have asked me check up for CPK. I went for it on next day morning. I went to pathologist Dr. Beke for blood test. Next morning he called me again for blood test when we went there. I had no doubt that Shreyas was healthy. However, CPK level was too high 18,000.

Next morning I went to Dr. Satoskar and showed him the reports. He was very calm and cool because he had prepared himself to talk to both the parents. He told us about DMD. Until that day we were not aware of this DMD. Muscular Dystrophy is an inherited disease.

Muscular Dystrophy Society was founded in 1973 to give cheer to the afflicted, as there was no treatment available for this disease. The society has concentrated on

improving their life style, increasing their ability to stand and walk for more number of years. It is characterized by progressive weakness of the muscle which control movement.

That day it was very difficult for me and Shreyas' father to accept this TRUTH. We cried a lot. We didn't know what to do. On Sept 04, 2006 DMD reports confirmed that Shreyas was DMD positive. I cried for half an hour in the Bombay Hospital, telling nothing to anyone about this. We kept asking a question to GOD-why this to my child? We kept asking help from God. It was HEART breaking news for us, as his mother and father.

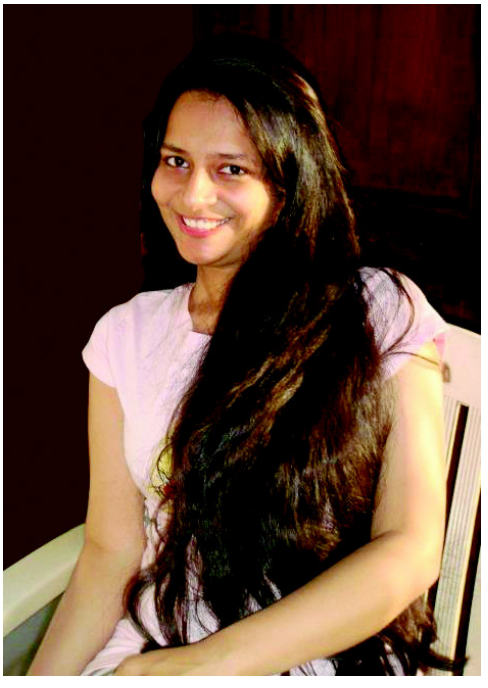
Hence, Shreyas new life journey started with Wadia Hospital for physiotherapy. We had to meet neurologist and physiotherapists as well. It was very hard time for me to accept the fact because there is no hope for a life for DMD patient. Doctor suggested steroids. But we decided not to give him any steroid. There was a big question mark about what to do?

Until age of 8 years he was riding the cycle. In between age 6 to 8 years, DMD started showing symptoms. His school was changed when he was in 2nd standard. We shifted him to nearby school. Going on scooter sitting in front of me. He used to climb up and down the first floor with me. For two years, he used to walk himself to school. When he went to 4th std, he stopped climbing up. Then I used to carry him on the first floor. 5th and 6th std was on ground floor so it was easy to take him to the school. Slowly slowly, he stopped climbing down and then walking. We could see Shreyas walking on toes and finding it very difficult to get up from floor, taking support of wall & then knee and then straight up. As his mother, it was very hard for me to see his condition day by day, becoming dependent on me. It felt like someone was hammering on my heart.

At last God listened to my prayers. As per the news in Times of India, dated 2nd January 2010 about Ankur Kant, a miracle of STEM CELL inspired me a lot. We ran to meet Dr.Alok Sharmaji. Finally we met and Shreyas new journey started towards LIFE. We could see a RAY OF HOPE. First Stem Cell shot was taken on 10th may 2010. In the follow up visit, after 3 months, Shreyas reported feeling of well-being and improved stamina. His upper limb and grip strength had increased with independence in activities of daily living like eating, bathing, dressing, washing up after toilet activities. He could sustain standing for 30 mins initially but gradually progressed to 50 mins. At the end of 8 months post therapy, he was able to stand independently with a walker.

One thing about Shreyas was that he NEVER EVER complained about PAIN. He is a very co-operative and obedient child. I am very proud of my son Shreyas that he wants to WALK and he will. During these years he has worked hard to achieve his GOAL.

Payal Jain, 25 years old Duchenne Muscular Dystrophy



The birth of every child marks the beginning of a new life and makes us marvel at the wonders of the creations of the Almighty. I am sure, when my parents held me for the first time; they must have gone through these wonderful emotions. Being born in a joint family, my happiest memories are those of my childhood when I, like every normal child, was an active, healthy & enthusiastic child and I enjoyed a lot with my same-aged siblings & cousins.

But when I turned seven, things began to change. My calves had become quite bulky & as hard as a stone, wherein I started having difficulty walking. I felt uncomfortable standing even on my heels & I began walking on my forefeet. There came a point where everyone started scolding me which now I can understand as the insecurities & fears of my elders and also because I WAS A GIRL.

Now began the battle against those unknown fears. At the age of 9, I under-went muscular biopsy from which it was diagnosed that I have D.M.D. (Duchenne Muscular Dystrophy), which was not only shocking for my parents but also for the doctor because in his 25 years of experience, it was his first case.

Unable to apprehend the severity of the situation, I felt scared, lost & totally confused as frequent falls during walking, difficulty with jumping and other motor skills became prominent. Each night, I would weep in my mother's lap and she would console me saying that everything would be alright soon.

Every morning became a torture because going to school became an uphill task. My classroom being on the first floor, I could only go there with the help of others. My

sports activities were brought to an abrupt halt. It was as if everything had come to a standstill. I stopped going to school regularly and only attempted exams.

Not only were my legs affected, but my overall physical well-being was hampered to the extent that since 2005, I became totally dependent on others. From dressing to combing my hair, from having a bath & even going to the loo, I NEEDED HELP. And that's where the word 'BURDEN' engulfed me into a more lonely despair.

I started losing contact with my friends may be because I discontinued my studies. I was feeling alone, tormented & would keep asking myself why was I not like others and the only thought that kept creeping forth & back was 'WHY ME?'

Staying in a small town, many people would keep coming home and stare at me, making me feel like a butt of ridicule & advised my parents in different ways. On their advice, my parents even took me to tantrics, but deep down, we all knew, it was to no avail.

By this time, I had actually come to terms with the fact that this is what DESTINY had in store for me. I had to accept myself as I was but there was this constant gnawing lingering within me which kept asking, "IS THIS IT?" "HAS EVERYTHING ENDED FOR ME?"

The head would tell me, "accept yourself & try to think positive," but the heart would say, "THERE HAS TO BE A WAY." The heart prevailed & began yet another battle, this time it was FOR ME, WITHIN ME & against my OWN DOUBTS.

I started making myself more aware of the disease under the able guidance of Dr. Bharucha. He made things more clear for me and assured me things were much better for me than others who suffered the same fate.

The first thing I did was I accepted myself as I was. Then came the formidable task of doing what I believed in. I started to concentrate on what I had rather than what I didn't have.

With the permission and support of my family, I decided to share the talents I had. I was always good at painting, drawing, sketching, handwriting & mehendi. My arms were weak but I continued my interest. I started taking classes at home itself and I got a beautiful response. I had small children keeping me occupied & busy the entire mornings & evenings. The best thing I felt, I could relive my childhood memories because they would share all their secrets and happenings at school with me & last but not the least, I felt WANTED.

They say that one step leads to another. My classes gave me such a huge popularity and entirely different outlook. My first solo painting exhibition was held at Jodhpur and this was yet another beginning. Today, when I look back, I hold no grudges and my zeal to try to do something new & creative keeps me in that positive frame of mind.

A special thanks to the Almighty because he gave me the strength to cope with this where many would have given up without a fight and to my entire family which never made me feel less fortunate.

If given a chance, I would love to do something for the children with special needs & one message to all - We don't need your PITY but your ACCEPTANCE and SUPPORT.

Rahul Deshpande, 29 year old male with Limb Girdle Muscular Dystrophy

My name is Rahul Deshpande. I am 29 years old. I was diagnosed with muscular dystrophy at the age of 17. No one in our family had ever heard of it. We had no history of it in our family. The doctor explained to us the progressive nature of the disease. We were shocked and a bit scared by the diagnosis. Because, living with any kind of disability, no matter how severe it is, has many challenges. You have to make so many adjustments, both physical as well as psychological.

Though the doctor had told us that this condition was incurable, we tried different types of treatments. But, none of them made much difference. Some of them were really weird having no scientific base. But, when you are in such a situation, you just don't think about it and ignore the truth. You only want results. But, it is just a matter of time. Soon you start realizing it and you have to accept the reality. I was not an exception to that. I did not try these methods for a long time as there was always a risk of getting into a worse condition.

Doctor had advised me to exercise daily but it was not easy, especially after a long day at college. My college was not too far from my place. So, walking was the best option. That involved some risk, but walking was the easiest and less time consuming exercise. I used to fall many times, had many injuries, but fortunately, I never had any fracture. I had to climb more than 100 stairs to reach my classroom. I was able to climb stairs with the support of railing and a quadruped stick but it was painful and risky. The descending part was riskier than climbing. A little loss of balance and the consequences could have been severe. But, I didn't have any other option because I wanted to do a full time course. With lots of struggle, I managed to complete my graduation. After that, I did my MBA and then started looking after my family business.

During this period, the weakness continued to progress, though at a slower rate. So, there was always an uncertainty about future. Then I came to know about stem cell therapy. So, again there was a ray of hope. As I had tried so many things earlier, I decided to try this too. I underwent stem cell therapy in March 2013 for the first time and had the second shot in September 2013. After undergoing stem cell therapy, I experienced many positive changes. My standing balance improved and walking over rough surface became easier. Getting in and out of car/rickshaw also became easier. There was significant improvement in my stamina and I could perform all my daily activities with ease. In the last twenty two months I have not noticed any deterioration. I feel, looking at the nature of the disease, this is the biggest improvement. Now I am just trying to remain as active as possible.

Because of my disability, I may have slowed down a bit, missed out on some opportunities in my life, but I have never stopped. It has been a journey full of difficult and painful situations. But, my family and my friends have always been there to support me. I always keep telling myself that there are other people in this world

who have been through a lot tougher situation than I did or I will ever have to deal with. This helps me to bear the pain and deal with the situation.

Life is never easy. It never goes the way you expect it to go. It keeps on changing and you have to learn to adapt to these changes. You may face many obstacles and challenges in your life. Sometimes you try really hard to overcome them but still fail. Whenever you come across such a situation, you should keep in mind that failure is sometimes better than trying nothing. You learn a lot from it. You should never surrender without putting up any resistance. All you need is a little amount of courage, determination, hard work, perseverance and love and support from your family. If you add all these ingredients to your life, I can assure you that life will definitely taste better. Just be OPTIMISTIC but REALISTIC.

Poonam Vishwakarma, Mother of 2 children with Duchenne Muscular Dystrophy, Rupesh (17) and Om (7)

I am Poonam Vishawakarama, My elder son Rupesh was diagnosed with muscular dystrophy early in his childhood. He had no apparent symptoms before that. He was like any other child. As the time passed first symptoms shown in him was difficulty in getting up from floor, he was unable to get up without help or support of his hand. After that slowly he started with sudden falls which became more and more frequent. We were told by the doctors that there is no treatment for this disease and the only thing to do will be to continue regular physiotherapy to prevent speeding up of the muscle weakness and prevent deformities. One day my father's family doctor in Mumbai suggested about stem cell therapy. He said that the therapy is new and is not a cure for the disease but it will help to stop the progression and maintain the child the way he is. Looking at Rupesh's condition at that age we were afraid about

when he enters the teenages and grows older. We waited for a year, but then he almost lost his ability to walk. He started falling after every 2 steps and we decided that he had to undergo stem cell therapy. When we came to NeuroGen Brain and Spine Institute, Dr. Alok Sharma suggested that along with stem cell therapy Rupesh will need to take regular rehabilitation also. We continued rigours exercises for 8 -9 months after stem cell therapy. He regained his blance while walking after that. Number of falls reduced significantly. He started walking with walker with minimal support. As per the doctors suggestions we continued with the therapy twice more. After the second stem cell therapy he could walk properly without any support. He also climbs stair with support from his physiotherapist. We are still observing changes in him. We could not have thought of leving him alone even for a minute before stem cell therapy but after all of his improvements we were confident that he can manage on his own with other family members. He has now successfully completed his 10th standard education and will be studying further.

Om, my second son, was also diagnosed with DMD when he was just 2 years old. He was diagnosed because of the genetic testing we done after we found out about Rupesh's illness and that it can affect my other son's as well. We decided to undergo stem cell therapy even before any symptoms were evident in Om. But the genetic test had confirmed his diagnosis. He is 7 years old now and has no symptoms still. He is just like a normal child. He can perform all his activities. He plays football, dances, and goes swimming regularly in the summers.

So If you think that giving stem cell therapy is enough then you are wrong, I will like to emphasize on how important rehabilitation therapy is after stem cell therapy. We have to be consistent with exercises and activities and be patient as the changes may be seen as late as 8 to 9 months. But you will see the changes. I am very happy with the progress of my son and I am confident he will get better and better. We are thankfull to Dr. Alok Sharma that when there was no treatment of muscular destrophy in whole world, he gave us a hope of life. We are also very much and equally thankful to our senior physiotherapist Dr.chintan shah(MPT -Neurology) for his timely treatment and care for OM and RUPESH...

27.

Association and Support Groups of Muscular Dystrophy

Associations, societies and groups supporting Muscular Dystrophy

The world over, parents, patients, care-givers and other professionals have come together to form unions dedicated to muscular dystrophy. From funding research to providing education & advice to sharing emotional support, the objectives of these organizations span across all aspects related to the disorder. Millions have benefited from their activities.

This section details some of the bigger associations and lists down other popular associations across different parts of the world.

India:

1. The Association for Muscular Dystrophy:

Plot No.5, Rockland, IC colony,
Borivali (West), Mumbai 400103.

www.musculardystrophyindia.com
help.amd@gmail.com
Tel: Mr Jeegar Mota - 9821151851
Tel: Mr. Chandrashekhar Kant - 9870105515

2. Indian Muscular Dystrophy Society
16, Tolaknagar, Paldi, Ahmedabad 380 007, Gujarat.

Website : imdsindia.org

3. Indian Association of Muscular Dystrophy:

Indian Association Of Muscular Dystrophy (IAMD)
C/o. M/s Stich-n-Style, Hospital Road, Solan,

Distt. Solan, Himachal Pradesh, India
Pin-173212

www.iamd.in / info@iamd.org
Tel: (+91)1792-223183/1792-220212

4. **Muscular Dystrophy Society,**
   4th Floor, J.J. Hospital, Byculla,
   Mumbai 400 027, Maharashtra.

   Tel.: 022 - 2375 3875

5. **Muscular Dystrophy Association India**
   C/o. V.J.Clinic, New no: 6, (Old 21),
   Fourth Cross Street, Sastri Nagar, Adyar, Chennai 600 020, Tamilnadu.
   Website : www.mdaindia.org E-mail : mdaindia.org@gmail.com
   Tel.: 91-90032 95482

6. **Sundaram Medical Foundation**
   A Network Center of the Co-operative
   International Neuromuscular Research Group
   Shanthi Colony, 4th Avenue, Anna Nagar, Chennai 600 040, Tamilnadu.

   Website : www.smfhospital.org
   Tel.: 91-44-26268844

7. **Muscular Dystrophy Foundation India**
   C/o. People's Watch, No.6, Vallabhai Road,
   Chokkikulam, Madurai-625 002, Tamilnadu

   Website : www.mdfindia.org E-mail : louis@mdfindia.org
   Tel.: 91-9994368550

8. **Jeevan Foundation**
   Head Office : 12/5, Sandilya Apartments,
   Jagadambal colony, 2nd Street, Royapettah,
   Chennai 600 014, Tamil Nadu.

   Website : www.jeevanfoundation.com
   E-mail: help@jeevanfoundation.com
   Tel.: +91 44 28474400 Fax: +91 44 43526647

9. **All India Muscular Dystrophy Association**
   Anaj Mandi, Nabha Gate, Patiala 147 001, Punjab

   Website : www.mdaindia.com E-mail: contact@mdaindia.com
   Tel: 91-175-2215786

10. **Indian Muscular Dystrophy Association**
    M.I.G.72, APHB Colony, Machilipatnam 521 001, Andhra Pradesh

    Tel.: 91-086-722817

11. **All India Muscular Dystrophy Association**

Anaj Mandi, Nabha Gate, PATIALA 147 001

aditi98172@yahoo.com Tel.: 91-175 215 786 • Fax: 91-175 200 786

12. **Muscular Dystrophy India**

    Website : www.mdaindia.com
    Tel. : +91-0715-2215786
    E-mail : contact@mdaindia.com / amardeephira@yahoo.com

13. **Muscular Dystrophy Support Group, South India**
    Muscular Dystrophy Society 'Ratnakar' 2nd Floor, Block 5,
    Narayan Dabholkar Road, Malabar Hill, Walkeshwar, Mumbai 400 006.
    E-mail : ranil@vsnl.com

United States of America:

1. Duchenne Alliance

About :

Duchenne Alliance, is an alliance of alliance of independent non-profit organizations dedicated to defeating Duchenne muscular dystrophy.

Aim :

The aim of Duchenne Alliance is to provide support to the families of children with DMD, support research in the field of DMD, find cure for DMD and find different treatments for DMD.

Objectives:

The Duchenne Alliance member foundations collaborate to co-identify, co-review, and co-fund the most promising biomedical research. We have established the Duchenne Alliance Research Fund to receive monetary donations and direct these resources to advancing the top biomedical research and clinical trials.

The alliance team members are -

1. Action Duchenne

- The founders are Dr Janet Hoskin and Nic Catlin who desire that the Charity is to be led by parents and young people affected by Duchenne and Becker Muscular Dystrophy.
- It works across the UK, the EU, the US and the southern hemisphere by gathering support and information from all parts of the duchenne community: researchers, clinicians, physicians, pharmacological companies and other duchenne charities.

  Registered Charity Number 1101971 Scottish Charity No: SC043853
  The Epicentre, 41 West Street, London
  E11 4LJ
  http://www.actionduchenne.org E-mail: info@actionduchenne.org.

2. Alex's Wish

- The charity was set-up in late 2012 by Emma and Andy Hallam to eradicate Duchenne Muscular Dystrophy, after their son Alex was diagnosed with Duchenne.
- It is a non-profit making charity registered with the Charity Commission with the sole aim to fund world-class science and clinical trials to bring about a cure or new treatments to help delay symptom.
- The focus to help children and young adults by investing money into clinical trials that have the best shot of delivering viable treatments in their lifetime along with other world-wide charities.

Alex's Wish, 5 Oldfield Lane, Rothle
http://alexswish.co.uk
emma@alexswish.co.uk
Emma Hallam on 07903 349475

3. Charley's Fund

- The sole mission of the foundation is to fund a cure or treatment for Duchenne.
- They invest their money into translational research - research that focuses on moving science from the lab into human clinical trials.

36 Mian Street, PO Box 83 Stockbridge, MA
Tracy & Benjamin Seckler

Tel: 413- 289-4300

4. Coalition Duchenne:

- Coalition Duchenne brings together organizations from around the world, in a quest to raise global awareness and to find a cure for Duchenne muscular dystrophy.
- Their mission is to raise global awareness for Duchenne muscular dystrophy in order to fund research and to find a cure for Duchenne.

Newport Beach, CA, Cath Jayasuriya,

www.coalitionduchenne.org
catherine@coalitionduchenne.org

5. Duchenne Foundation:

- The main aim of this foundation is to work together to improve the lives of Australian persons and families affected by Duchenne and Becker muscular dystrophy by applying for funding from government, semi-government and private organizations for the purpose of pursuing the Company's objects.
- It also promotes public awareness of Duchenne & Becker muscular dystrophy through media, educational and fund raising campaigns.
- They also network globally to identify viable research, treatments and quality care standards which will enhance the lives of persons everywhere affected by Duchenne and Becker muscular dystrophy.

6. Duchenne Ireland:

- Duchenne Ireland is a patient organization established to faciliate funding translational research into Duchenne Muscular Dystrophy. it is affiliated with numerous patient groups and clinical, research and support networks for Duchenne Muscular Dystrophy.
- The aims of the organization is to raise awareness of Duchenne Muscular Dystrophy at local, national and government level and raise funds which

go directly to the researchers and clinicians whom they believe have the best chance of developing improved therapies which will benefit this generation.

- The organization is also working towards achieving an infrastructure which is on a par with best international practice.

7. Duchenne Now:

- The Charity was formed by parents of children LIVING WITH DUCHENNE of varying ages from 7 to 19.
- They are dedicated to treating everyone with Duchenne.
- They believe in funding projects with a clear road map to market within a reasonable time frame to quickly find, test and make available Intermediate treatments for all people living with Duchenne,

Parklands, Block P1 Unit 9, Heywood Distr. Park
Pilsworth Road, Heywood, Lancashire, OL10 2TT
www.duchennenow.org E-mail - contact@duchennenow.org
Office number - 01706 693 399 Mobile - 07969035595

8. Foundation to Eradicate Duchenne:

- The Foundation to Eradicate Duchenne was established by Dana and Joel Wood of Alexandria, when their son James Wood was diagnosed with Duchenne Muscular Dystrophy. They have devoted much of their time and energies to this cause, working with others to achieve millions of dollars in federal earmarks for Duchenne Muscular Dystrophy research and a significant increase in the attention devoted to DMD at the National Institutes of Health.
- Also, through the FED and other fundraising efforts, they have raised nearly $10 million in private donations and worked with Congress to secure nearly $40 million in federal appropriations.
- The overwhelming majority of the funds spent by the Foundation to Eradicate Duchenne have gone to the muscular dystrophy lab at Children's National Medical Center (CNMC) in Washington, and to the Cooperative International Neuromuscular Research Group (CINRG), which is the only human clinical trials network for Duchenne Muscular Dystrophy in the world, and was established by the scientists at CNMC.

P.O.Box 2371, Alexandria, VA 22301

www.duchennemd.org
jwood@duchennemd.org
Tel: 703-683-7500

9. Foundation for a Future

PO Box 270036, Louisville , CO 80027

www.foundationforacure.org
pamela@foundationforacure.org
Tel:303-257-7287

10 Foundation for their SAKE

5 Cherry Hills Farm Ct,Englewood, CO 80113

www.perkyjerky.com

11. Harrison's Fund :

- It was formed by Harrison's parents.
- The foundation has one single and important goal to get as much money as possible into the hands of the world's best researchers, who are working to find a cure for Duchenne.
- They are focusing on treatment rather than palliative care.
- They work internationally and invest in research that takes the science out from the lab, and into human clinical trials.

  PO 377, Cobham, Surrey, KT11 9EA, United Kingdom

  E-mail : alex@harrisonsfund.com / info@harrisonsfund.com

  Tel.: +44 (0)7887 571 654 Web.: http://harrisonsfund.com/contact.php

12. Hope for Gabe:

- Scott and Traci Griffin parents of Gabe are the founders of the foundation Hope for Gabe, after he was diagnosed with duchenne.
- Its mission is to to ensure a cure for Duchenne is found in time for this and all future generations of boys inflicted with this disease, including Gabe.
- The organization is doing so by directing all fundraising dollars into the hands of lab researchers or other organizations that are determined to find a cure.
- Hope for Gabe is doing so by organizing and developing creative fundraising efforts among friends, family, and concerned volunteers, while at the same time, serving as an information database for the most current clinical trials and research programs taking place.

  Birmingham, AL

  www.hopeforgabe.org

13. Hope For Gus:

- Hope for Gus requires that 100% of its grants support our mission to find effective near term treatments.
- Their mission is to raise research dollars and awareness of Duchenne Muscular Dystrophy.

- They are committed to funding research that will result in effective treatments in the near-term and their specific focus is on treatments that will preserve muscles in DMD boys while researchers continue to search for the cure to DMD.
- Additionally, they are also involved in raising public awareness through fund-raisers, family events and corporate sponsorship.

  Francestown, NH

  www.hopeforgus.com
  hopeforgus@yahoo.com

14. Hope for Javier:

- The KEY ACCOMPLISHMENTS of Hope for Javier has been successful in getting two promising treatments into human clinical trials, HT-100 and Sildenafil (repurposed).
- They raise money to help fund cutting-edge translational research - research that focuses on moving science from the laboratory into human clinical trials - to accelerate the development of life-saving treatments.
- They also support the best clinics, to educate medical professionals and caregivers on the latest treatment protocols.
- They are dedicated to transforming care and improving the healthcare quality of life for all boys with DMD.

  P.O.Box251, East Setauket, NY

  www.hopeforjavier.org
  infor@hopeforjavier.org

15. JB's keys:

- The organization was formed by JB's parents Jeff and Beth Harvey
- The organization is Educating others about DMD through gatherings, traditional media, and social media
- They Support The Pediatric Neuromuscular Clinic at Massachusetts General Hospital for Children by Providing quality medical treatment while practicing bench to bedside research
- Donate items to entertain patients during long appointments including ipads, toys and books
- Fund research to improve physical complications of DMD such as Lung Function Study, Sleep Study, Stander Wheelchair Study and Fund Bone Density Study.
  67 Forrest Ave, Norwood, MA 02062
  Jbskeys.org
  Tel: 781-269-1175

16. Jett Foundation:

- Jett Foundation was formed by Christine and Stephen McSherry, Jett's parents.
- They were determined to save Jett and the thousands of boys like him by establishing a foundation dedicated to searching for and funding DMD research that will ultimately cure this deadly disease.
- The Foundation offers outreach and support to families with Duchenne diagnoses
- the Foundation seeks out and supports cutting edge research, promising clinical studies and scientists whose work endeavors to stop the progression of Duchenne and provide immediate therapy for muscle health
- The foundation is an educational resource for administrators, teachers, nurses about the special daily needs of a child with Duchenne
- They are also raising awareness of Duchenne to the general public in hopes of encouraging moral and financial support.

  42 Elm Street, Kingston, MA

  www.jettfoundation.org Tel:781-585-5566

17. John Owen's Adventure

- (JOA) is dedicated to discovering a treatment, improving research and establishing education and awareness programs about DMD for all individuals who are affected by this disease.
- JOA is committed to raise awareness and research dollars to treat juvenile diabetes, a chronic disease affecting nearly 26 million Americans.
- JOA is a proud member of the Duchenne Alliance, which is a group "of independent Duchenne organizations dedicated to advancing our missions to improve quality of life, care, and treatment of those affected by Duchenne. Their goal is achieved by building trust, sharing knowledge, leveraging resources, and streamlining business practices. Each organization will be held to achieve their own mission as we collectively serve the entire Duchenne community."

  5715 Bunker Road, North Royalton, OH 44133

  www.Joainc.org
  Tel: 440-230-1555

18. Joining Jack

- Joining Jack is committed to ensure that as much as possible funds goes to developing research into a treatment or a cure for Duchenne Muscular Dystrophy.
- They are particularly focused on transitional research, research that takes potential therapeutics out of laboratories and into clinical trials.

Joinging Jack c/o ADM, Unit 1 appleton street, Wigan, WN# 4BZ
info@joiningjack.org
http://joiningjack.org

19. Liam's Leep:

To support families, further research and increase awarness about DMD

Norwood, MA

www.Wix.com/kdm114/liams-leep

20. Little Hercules Foundation:

- The Little Hercules Foundation was created by three moms, two of which have 3 sons-Jake, Noah and Jackson DIAGNOSED living with Duchenne MD.
- They are working hard to raise money to fund groundbreaking research that will save this current generation of boys.
- They raise funds primarily through fun, event-based fundraising.

  http://littleherculesfoundation.org

21. Misko Foundation:

- The foundation aims to provide a networking platform for the DMD community and increase the chance of eventually finding a cure for the children affected by the disease.
- They keep track of research conducted in Hungary and abroad and publish summaries of these efforts.
- The foundation also plans to finance DMD research and provide researchers and doctors with grants to finance their studies and professional training.
  http://www.treat-nmd.eu/organisations/misko.foundation/
  info@treat-nmd.eu
  Institute of Genetic Medicine
  University of Newcastle upon Tyne
  International Centre for Life
  Newcastle upon Tyne
  NE1 3BZ
  United Kingdom
  T: +44 (0)191 241 8617
  F: +44 (0)191 241 8770

22. Muscular Dystrophy Australia:

- Muscular Dystrophy Associations have been serving people with neuromuscular disorders in Australia for over 50 years.
- The associations have been established in many other states, including: New South Wale, Queensland South Australia, Tasmania, Victoria and Western

Australia.

- The state and territory-based Muscular Dystrophy Associations throughout Australia have a long history of serving people with neuromuscular disorders, contributing significantly to the well-being of their clients and their families.
  http://www.mda.org.au/
  l36-38 Henley Beach Road
  Mile End SA 5031PO Box R1920
  Royal Exchange NSW 1225
  info@mdaustralia.org.au
  Phone: 02 9247 0055
  Fax: 02 9247 0066

23. Muscular Dystrophy Foundation India:

- Psychological support to Patients and Parents
- Dissemination of information on the disease
- Promote interaction and communication amongst Doctors, Patients, Parents and Scientists
- Promote Research and Development for this disease.
- Create a National task Force for Public awareness.
- Interaction with Government bodies and recommendations for important healthcare reforms
- Rehabilitation measures

24. RaceMD:

- RaceMD is a nonprofit organization which was formed in 2008 to accelerate the search for intermediate therapies to prolong the lives and health of children with DMD.
- Possible therapies have been identified by them and have been tested positively in over 200 DMD boys.
- They have a collaboration formed to bring it to the US and Europe with partners for study and implementation.

  1501 SW Taylor St. Suite 200 Portland, OR 97205,

  www.Racemd.org
  infor@racemd.com
  Tel: 503-278-3273

25. Rally for Ryan

- Rally for ryan is dedicated to finding a cure for this disease.
- 100% of all money raised goes to researcher's that is diligently trying to find treatments and ultimately a cure for Duchenne Muscular Dystrophy.

- They are committed to making sure this disease does not get passed down to another generation.

  2623 Evercrest Ct., Naperville, IL 60564

  www.rallyforryan.org
  contact@rallyforryan.org
  Tel: 630-922-6049

26. Romito Foundation

The mission of this foundation is to improve the treatment and quality of life for all persons living with Duchenne's muscular dystrophy.

They are aiding current and future medical research and support established non-profit organizations with like interests.

Firestone, CO,

Romitofoundation.org
Tel: 303-718-2538

27. Ryan's Quest:

- The mission of Ryan's Quest is to increase awareness of Duchenne muscular dystrophy with the purpose of allocating funds for research that has the greatest potential of finding a cure or treatment for this disease.
- It is primarily focused on supporting research for near-term, potential therapeutics and better testing platforms (tools) for development of DMD compounds.
- They are also interested in helping support families that are enrolled in clinical trials.

  P.O. Box 2544, Hamilton, NJ 08690

  www.Ryansquest.org
  infor@ryansquest.org
  Tel: 609-947-3611

28. Save our Sons:

- Save Our Sons is a charity organisation raising funds and awareness to help find a cure for DMD.
- It was Founded by Elie Eid and shortly followed by Vice President Bass Abboud.
- The Save Our Sons team has grown to include one full-time staff member and strategic volunteer members specialising in support areas of Accounting, Media & Marketing, Website Development, Events Management and day to day operations.
- Their goal today is to raise $3.5 million to fund two human clinical trials, which have been recognized by the world's leading medical researchers in

the field of DMD that has the real potential to effect the lives of boys with DMD.

- Save Our Sons hold a series of spectacular events each year, which are our main fundraising drivers. Attended by the community and a large number of celebrity supporters these events have continued to grow year on year.

http://www.saveoursons.org.au/
PD BOX 350, Marrickville
NSW 2204, Australia
info@saveoursons.org.au
0295546111

29. Team Joseph

- Team Joseph is a non-profit organization whose mission is to aggressively fund cutting edge research to find a treatment or cure for Duchenne muscular dystrophy.
- Their focus is on rapidly moving basic research into applications that can make a difference for the current generation of boys afflicted with this devastating disease as well as for generations that aren't even born yet.
- They are a caring community of motivated people joined together in efforts to give young boys affected by Duchenne muscular dystrophy, not only a chance at a better life, but simply a chance at a life.

Detroit , MI

www.Wix.com/danted/josephpenrod-com2

30. The Duchenne Children's Trust:

- The Duchenne Children's Trust was set up by Emily and Nick Crossley, after their son, Eli was diagnosed with Duchenne Muscular Dystrophy.
- Their mission is quite simpe is to raise money to give to the best global research effort to fund a treatment or cure in time to save Eli's life and the hundreds of thousands of other boys like him.

31. The Duchenne Research Fund:

- The Duchenne Research Fund has the simple vision that, through our work, a cure will be found for Duchenne Muscular Dystrophy (DMD).
- It exists to find and fund research that will bring a cure for DMD closer, improving the conditions of those living with DMD along the way.
- They are committed to looking at any possible route for such a cure and will not stop until a cure is found.
- They will facilitate and fund new research into minority strains of DMD and focus on the exceptions of the condition with the belief that this will hold the key to a cure.

- The Duchene Research Fund will continue to raise the funds needed to facilitate this process.

  www.Duchenne.org.uk

32. Two Smiles One Hope

- It is a Syracuse-based Foundation created by the Willis Family soon after their sons, Nolan and Jack, were diagnosed with DMD.
- The goal of the Foundation is to end Duchenne Muscular Dystrophy through either treatment of the disease, which would permit an acceptably sustainable way of life; alteration of the disease to a less aggressive disorder; or by curing the disease all together.

33. Zack Heger Foundation:

- Their mission is to fund important research to find a cure or treatment for Duchenne, as well as to fund programs that extend, and improve, the quality of life of children afflicted with this disease.
- It was established to support efforts to discover cures for neuromuscular disorders in children and to devise therapies and provide other forms of support for those already suffering from such disorders.

  285 Prospect St.,Norwell, MA 02061

  www.Zackhegerfoundation.org
  Tel: 617-529 - 9612

34. Zubin's Wish:

- Their goal is to direct money into the hands of researchers who are working on a cure for Duchenne Muscular Dystrophy.
- They want to find a cure or treatment for Zubin and the thousands of boys worldwide afflicted with this disease.

  http://zubinswish.org

35. Michaels's Cause

www.michaelscause.org
michaelscause@gmail.com
6462586152/9174435384

36. Pietro'sfight

http://www.pietrosfight.org/
Pietro'sfight.org
301 88th Street
Brooklyn, NY 11209
Call: 917-363-5820
Fax: 212-954-5087
Email: info@pietrosfight.org

Other organizations in USA:

1. Parent Project Muscular Dystrophy (PPMD) :

About :

Parent Project Muscular Dystrophy is a non-profit organization, based in USA. It was founded in 1994 by Pat Furlong, a mother of 2 DMD boys. As the name suggests, it comprises of parents, grandparents & other care-givers of young men suffering from this debilitating disorder. Over the years, PPMD has grown from a small group of people to the largest American organization dedicated to the cause of Duchenne muscular dystrophy, with one aim in mind-to end Duchenne. It focuses strongly on research, to determine the causes, treatment & cure for DMD. Many families have received support in all forms through this organization.

The strength of this organization lies in the unwavering care & concern of parents & grandparents of such individuals and their constant efforts towards improving the lives of their loved ones who have been afflicted with DMD.

Objectives:

- To fund, promote & encourage research & development.
- To create awareness and extend care & support.
- To work with government bodies to ensure that concern for DMD is accounted for during decision-making.
- To integrate the efforts of all medical & paramedical professionals across the globe for the betterment of DMD individuals.
- To build a DMD friendly environment by providing information, care, community support, legislative support, medical help, financial aid & in all other ways possible.
- To connect such similar communities the world over, facilitate an exchange of ideas and extend care & support.

Contact:

401 Hackensack Avenue, 9th Floor,
Hackensack, NJ 07601

info@parentprojectmd.org
http://www.parentprojectmd.org
Tel: 800-714-KIDS (5437)
Fax: 201-944-9987

2. Muscular Dystrophy Association

About:

For more than 60 years, MDA has provided help and hope for families living with neuromuscular diseases. MDA today is one of the world's leading voluntary health agencies, fostering research and medical care. It is a nonprofit health agency in the United States of America dedicated to curing muscular dystrophy, ALS and related diseases by funding worldwide research. It helps assist with the cost of repairs and help locate durable medical equipment for those it serves. It provides thousands of free flu vaccines. It funds around 200 neuromuscular specialty clinics across the United States of America. It is dedicated to finding treatments and cures for more than 40 neuromuscular diseases which cause progressive muscular weakness. It funds around 300 research projects, spearheaded by scientists worldwide.

Objectives:

- To conduct ongoing public health education programs through webinars, educational speakers, seminars, videos and newsletters.
- To provide comprehensive health care and support services, advocacy and education
- To accelerate therapy development by sponsoring national and international scientific meetings about disease research (such as 2012 MDA Clinical Conference), and through collaborative efforts with federal agencies and other organizations in the U.S. and around the world.
- To both accelerate therapy development and expand resources for families affected by muscle disease.

Contact :

3300 East Sunrise Drive
Tucson, AZ 85718-3208

Website: http://www.mda.org
Email: mda@mdausa.org
Tel: 520-529-2000 800-572-1717
Fax: 520-529-5300

3. Jain Foundation

About :

The Jain Foundation is a non-profit foundation whose mission is to cure muscular dystrophies caused by dysferlin protein deficiency, which includes the clinical presentations Limb-girdle muscular dystrophy type 2B (LGMD2B) and Miyoshi muscular dystrophy 1 (MMD1).

Objectives :

- To fund and actively monitor the progress of scientific research projects in key pathways towards a cure.
- To provide financial and logistical support to promising drug candidates to accelerate them to clinical trials.
- To fund clinical trials and studies.
- To encourage collaboration among scientists.
- To educate LGMD2B/Miyoshi patients about their disease and help them with their diagnosis (e.g., funding dysferlin protein and gene mutational analysis).

Contact:

2310 130th Ave NE, Suite B101, Bellevue, WA 98005

Website: https://www.jain-foundation.org/
Email: ehwang@jain-foundation.org
Tel: 425-882-1440
Fax: 425-658-1703

4. Coalition to Cure Calpain 3 (C3)

15 Compo Parkway, Westport, CT 06880

http://www.curecalpain3.org/
info@curecalpain3.org
Tel: 203-221-1611
Fax: 734-668-4755

5. Facioscapulohumeral Muscular Dystrophy (FSH) Society

64 Grove Street, Watertown, MA 02472

http://www.fshsociety.org
info@fshsociety.org
Tel: 617-658-7877
Fax: 617-658-7879

6. International Myotonic Dystrophy Organization

P.O. Box 1121, Sunland, CA 91041-1121

http://www.myotonicdystrophy.org
info@myotonicdystrophy.org
Tel: 818-951-2311/866-679-7954

7. National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

National Institutes of Health, DHHS
31 Center Dr., Rm. 4C02 MSC 2350, Bethesda, MD 20892-2350

http://www.niams.nih.gov
NIAMSinfo@mail.nih.gov
Tel: 301-496-8190 877-22-NIAMS (226-4267)

8. Centers for Disease Control and Prevention (CDC)

U.S. Department of Health and Human Services
1600 Clifton Road, N.E., Atlanta, GA 30333

http://www.cdc.gov
inquiry@cdc.gov
Tel: 800-311-3435/404-639-3311/404-639-3543

9. National Institute of Child Health and Human Development (NICHD)

National Institutes of Health, DHHS,
31 Center Drive, Rm. 2A32 MSC 2425, Bethesda, MD 20892-2425

http://www.nichd.nih.gov
Tel: 301-496-5133
Fax: 301-496-7101

10. Cure CMD

P.O. Box 701, Olathe, KS 66051

http://www.curecmd.org
info@curecmd.com
Tel: 1-866-400-3626

11. Muscular Dystrophy Family Fund

1033 Third Avenue SW, Suite 108, Carmel, IN 46032

http://www.mdff.org
info@mdff.org
Tel: 317-249-8488
Fax: 317-615-9140

12. Angel's Muscles

Avalon, NJ, Melissa Barone

www.angelsmuscles.org E-mail: chrbaro@aol.com

13. CIMRG, Centre for Genetic Medicine

Research Centre 3, Children's Research Institute,
111 Michigan Avenue, NW, Washington, DC 20010

www.cinrgresearch.org
info@cinrgresearch.org
Tel: 202-476-5241

14. Cooper's Cure

P.O.Box # 604, Hermosa Beach, CA 90254,
Cathy and Scott Jones.

www.cooperscure.org

15. Cure Dale's Duchenne

The Gainesville Community Foundation
5214 SW 91 Drive, Suite A Gainesville Fl 32608

www.curedalesduchenne.com
ginders@curedalesduchenne.com
Tel: 352- 367-0060

16. Cure Duchenne

3334 East Coast Highway # 157,
Corona Del Mar, CA 92625

www.cureduchenne.org
debra@cureduchenne.org
Tel: 949 - 872-2568

17. Darius Goes West

135 Pine Tops Court, Athens, GA 30606

dariusgoesweat@gmail.com
Tel: 706-613-7337

18. Disabled Children's Relief Fund

PO Box 89, Freeport, NY 11520

Tel: 516-377-1605

19. DMD Fund

PO Box 17371, Encino, CA 91416

www.dmdfund.org
kyle@dmdfund.org
Tel:818-692-5500

20. Duchenne San Diego

12630 MonteVista Road,
Suite 202, Poway, CA 92064,

www.duchennesandiego.org
info@duchennesandiego.org
Tel:858-775-7057

21. Dylan's Footprint

98 Taylor Avenue,Greenlawn, NY 11740-1497

www. dylanfootprint.org
info@dylanfootprint.org
Tel: 631-754-5360

22. Gals for Cal

Boston, MA,

www.galsforcal.com

23. Liam Hiatt Foundation

P.O.Box 832, Downers Grove, IL 60515

www.liamhiattfoundation.org

24. MDA

National Headquarters :
3300 E. Sunrise Dr, Tucson, AZ 85718

www.mdausa.org
Tel:800-572-1717

25. MDFF

7220 US 31 South, Indianapolis, IN 46227

www.Mdff.org
Tel: 800-544-1213

26. National Center on Birth Defects & Developmental Disabilities

1600 Clifton Road, MS E - 87, Atlanta, GA 30333

cdcinfo@cdc.gov
Tel: 800-232-4636

27. Nash Avery Foundation

2427 East Lakes of the Isles Parkway Minneapolis, MN 55405

www.nashaveryfoundation.org

28. **NJCatastrophic Illness in Children Relief Fund Comission**
    P.O.Box 728, Trenton, NJ 08625 - 0728
    Tel: 609-292-0600

30. **Noah's Feat**
    www.noahsfeat.org

31. **Ryan's Hope for a Cure Charitable Foundation, Inc.**
    6 Maple Terrace, Plaineville, MA 02762
    www.hopeforryan.com
    info@hoperforryan.com
    Tel: 508-699-3888

32. **Save Our Boy Foundation**
    26 Mariscal Place, The Woodlands, TX 77389
    www.saveourboy.org
    Tel: 713-392-6001

33. **Suneel's Light**
    5140 Main St, Unit 303- 152 Williamsville, NY 14221
    www.suneelslight.org
    suneelslight@gmail.com

34. **Teens for Duchenne**
    Newport Beach, CA
    www.teensforduchenne.com

35. **Two Smiles one HOPE**
    P.O.Box 435, Fayetteville, NY 13066
    www.twosmilesonehope.com
    Tel: 315-415-4414

United Kingdom:

1. Muscular Dystrophy Campaign

About :

The Muscular Dystrophy Campaign is among the oldest and most established non profitable organizations in the UK dedicated to muscular dystrophy. It was founded in 1959 with the primary aim to help the affected children & their families.

Its main focus is on research towards finding a cure and treatment for MD.

Over the years, the campaign has enlisted the support of many distinguished personalities. Lord Richard Attenborough, an acclaimed actor, director and producer served as President for over 30 years & is now an Honorary Lifetime President. His-Highness, Prince Philip- Duke of Edinburgh, has been a patron for over 40 years, since 1966, providing funds and help-in-kind to the campaign for its activities.

Objectives:

- To fund research for developing the cure or treatment for muscular dystrophy.
- To spread awareness about MD and educate families on how to cope with it.
- To provide help to families by way of education, assistive devices, finance, etc.
- To lobby for the cause of MD in the British government.
- To provide information & advice to families.
- To create a community for mutual support of MD.

Contact:

Muscular Dystrophy Campaign
61 Southwark Street, London SE1 0HL

www.muscular-dystrophy.org
info@muscular-dystrophy.org
Tel: 020 7803 4800

2. Duchenne Family Support Group (DFSG)

About :

The DFSG was started in 1987 by a small group of parents who had children diagnosed with Duchenne Muscular Dystrophy (DMD). Since then, the number of families has increased dramatically and contacts have been established all over the country, as well as abroad, creating a wealth of information.

Objectives:

- To provide a positive national support network of parents, their families and professionals.
- To bring families together for mutual support, sharing of information and experience, and social activities.
- To provide workshops in such areas as adaptations, physiotherapy, complementary medicine, equipment, lifting and education with the help of relevant professionals.
- To conduct workshops with guest speakers and the opportunity to socialize at our annual conference.

Contact:

78 York Street, London W1H 1DP

http://www.dfsg.org.uk
Tel: 0870 241 1857
Helpline number - 0800 121 4518

Other organizations in United Kingdom:

3. **Action Duchenne**

   Headquarters: Epicenter, 41 West Street
   London, UK E114lj

   www.actionduchenne.org
   nick@actionduchenne.org
   Tel: 020 8556 9955

4. **Treat-NMD**

   United Kingdom

   www.treat-nmd.eu
   info@treat-nmd.eu
   Tel: +44(0)191 241 8605

Australia:

1. Save Our Sons: Australia

About :

Save Our Sons was incorporated in February 2008 by the Eid family as a charity, seeking to raise public awareness and much needed funding for research on Duchenne Muscular Dystrophy (DMD). Save Our Sons was founded with one goal in mind, to find a cure for Duchenne Muscular Dystrophy.

Objectives:

- To find a cure for Duchenne Muscular Dystrophy
- To support clinical trials for potential cures and treatment.

Contact:

PO box 3 Roseland NSW 2196, Australia
info@saveoursons.org.au
Tel: 0424 669 340

Other organization in Australia:

2. **Duchenne Foundation :Australia**

   www.Duchennefoundation.org.au

Few in the other parts of the world:

1. **United Parent Project Muscular Dystrophy**

   Postbus 821, 3900AV Veenendaal, The Netherlands

   www.uppmd.org
   Tel: +31 164 230270

2. **Cura UPA! Duchenne**
   Mexico
   www.Curaupaduchenne.org

3. **Misko Foundation**

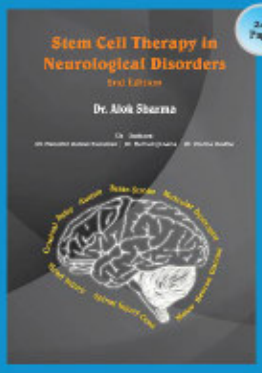
   1092 Budapest, Raday u. 8. 1/5, Hungary
   www.misko.hu
   info@misko.hu

4. **Duchenne Heroes**

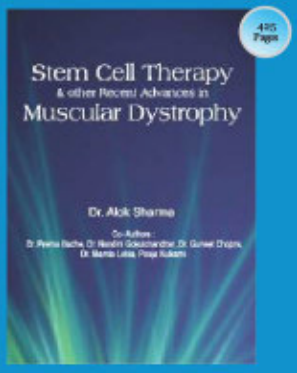
   Post box 11220, 1001 GE Amsterdam
   www.duchenneheroes.nl
   info@duchenneheroes.nl
   Tel: 088 366 54 60

Other *NeuroGen* Publications

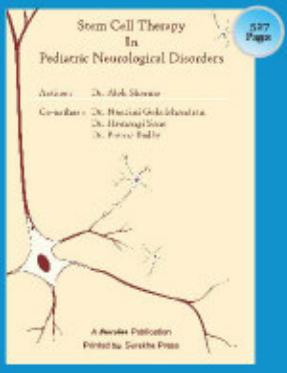
Stem Cell Therapy in Neurological Disorders 2nd Edition



Stem Cell Therapy & Other Recent Advances in Muscular Dystrophy

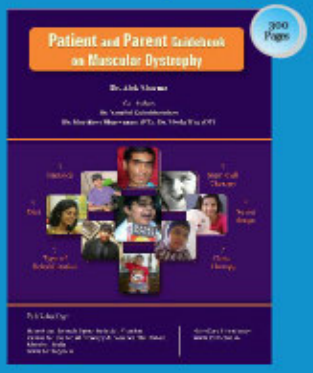


Stem Cell Therapy In Pediatric Neurological Disorders

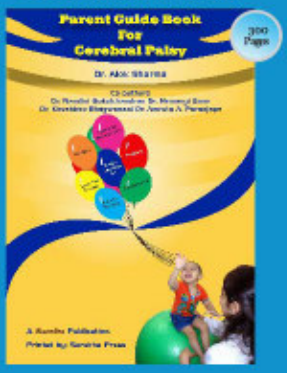


પેશન્ટ અને પેરન્ટ માર્ગદર્શિકા મસ્ક્યુલર ડીસ્ટ્રોફી વિશે

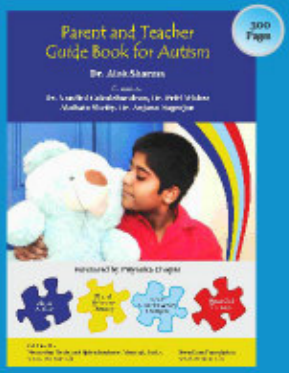
Patient & Parent Guidebook on Muscular Dystrophy



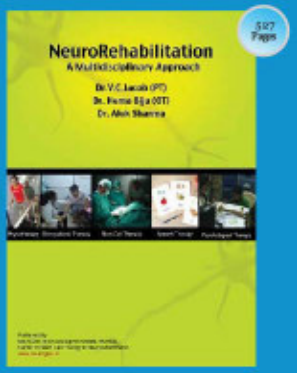
Parent Guide Book For Cerebral Palsy



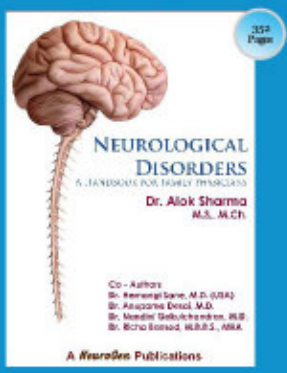
Parent & Teacher Guide Book for Autism



NeuroRehabilitation- A Multidisciplinary Approach



Neurological Disorders A Handbook for Family Physicians



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