Stem Cell Therapy and Neurorehabilitation in Pediatric Neurological Disorders

2nd Edition

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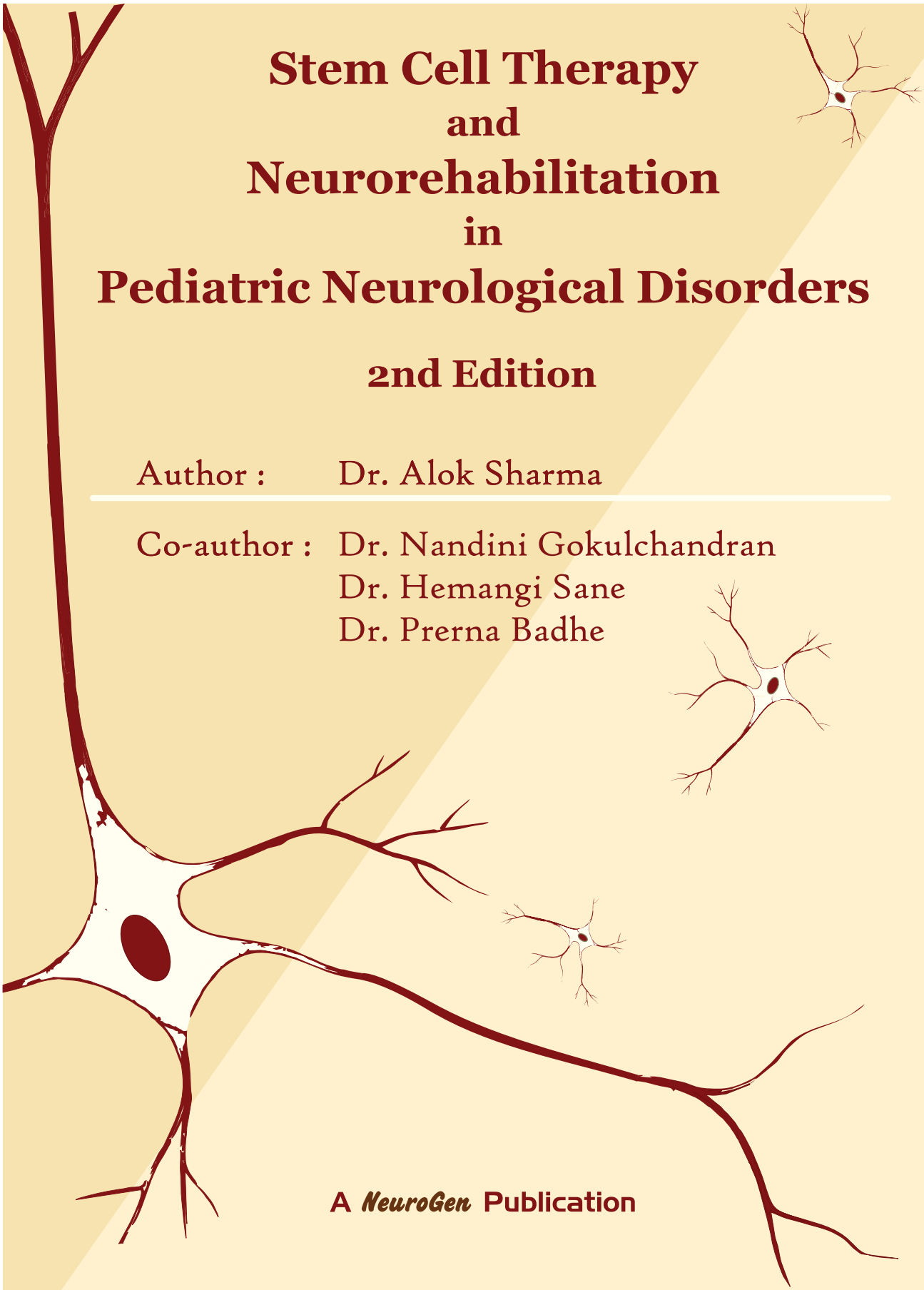

A *NeuroGen* Publication

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2nd Edition

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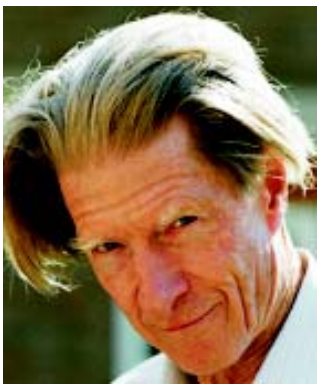
Stem Cell Therapy
"An idea whose time has come"

INTERNATIONAL

2012



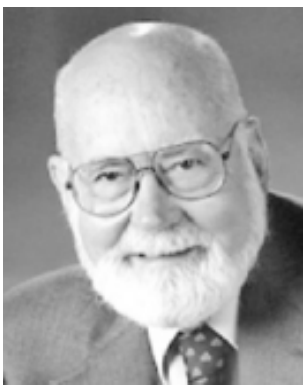
John B. Gurdon

Shinya Yamanaka

2007

Sir Martin Evans

1990



Dr. E. Thomas

Nobel Prize Awarded for Stem Cell Research

Stem Cell Therapy
"An idea whose time has come"

NATIONAL

Prime Minister Narendra Modi visits the Stem cell Institute of Kyoto University Japan and meets with Nobel Prize winner Professor Yamanaka in September 2014.

Pranab Mukherjee's speech at Lok Sabha joint session

President Pranab Mukherjee addressed the joint session of the Lok Sabha at the Central Hall of Parliament in New Delhi on 9th June 2014.

The president shared the Narendra Modi government's agenda for the country. From the economy to the environment, from minorities to terrorism, the President announced a series of programmes on a variety of issues facing the country.

"My government recognises the central role of Science and Technology in raising the quality of life. It will encourage and incentivise private sector investments, both domestic and foreign, in science and technology and in high-end research aimed at nurturing innovation. My government will build world class research centres in the fields of nanotechnology, material sciences, thorium technology, ***brain research, stem cells****, etc. The government will also establish institutes of Technology for Rural Development and a Central University of Himalayan Studies."*

Stem Cell Therapy
"An idea whose time has come"

Scientific Publications on Pediatric Neurodevelopmental Disorders by the Authors

A) AUTISM:

1. Alok Sharma, Nandini Gokulchandran, Hemangi Sane, Anjana Nagrajan, Amruta Paranjape, Pooja Kulkarni, Akshata Shetty, Priti Mishra, Mrudula Kali, Hema Biju, Prerna Badhe. Autologous bone marrow mononuclear cell therapy for autism – an open label proof of concept study. Stem cell international. 2013 (2013), Article ID 623875, 13 pages.
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4. Alok Sharma, Nandini Gokulchandran, Akshata Shetty, Hemangi Sane, Pooja Kulkarni and Prerna Badhe. Autologous Bone Marrow Mononuclear Cells may be Explored as a Novel. Potential Therapeutic Option for Autism. J Clin Case Rep 2013, 3:7.
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brain serve as a new dimension for autism: A case report (2014), Journal of Paediatric Neurology, 12:3.

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C) MUSCULAR DYSTROPHY:

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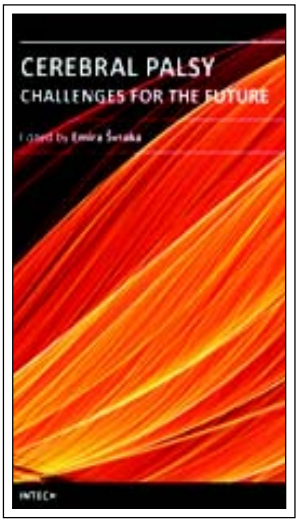

Chapter on "Stem Cell Therapy for Cerebral Palsy" written from NeuroGen, published in an international book- " Cerebral Palsy- Challenges for the Future" (Publisher- Intech)

Chapter 7

Stem Cell Therapy for Cerebral Palsy – A Novel Option

Alok Sharma, Hemangi Sane,
Nandini Gokulchandran, Prerna Badhe,
Pooja Kulkarni and Amruta Paranjape

Additional information is available at the end of the chapter

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1. Introduction

Discovery of stem cells by James Till and Ernest McCulloch in 1961, stands as one of the most remarkable medical-research achievements of the 20th century. This discovery provided a foundation for further breakthroughs in the field of stem cells. Sir Martin J. Evans along with Mario R. Capecchi, and Oliver Smithies were jointly awarded a Nobel Prize in 2007 for their contribution in introducing specific gene modifications in mice by the use of embryonic stem cells. Later in 2012, John B. Gurdon and Shinya Yamanaka were also jointly awarded a Nobel Prize for discovering that mature cells can be reprogrammed to become pluripotent cells. [1]

Ramon y Cajal in 1926 stated "Once the development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centers, the nerve paths are something fixed, ended, and immutable. Everything may die, nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree." [2]. It was a long-standing belief that cells of the central nervous system once damaged cannot be regenerated. The medical science of stem cells has finally made restoration of CNS possible which has changed the old concept of medicine. Not too long ago, this therapy was hamstrung by various controversies, ethical and moral issues. But, tremendous progress of research in this field has finally led to its translation from laboratory to innovative cellular therapies.

A variety of cells including embryonic stem cells, adult stem cells, umbilical cord blood cells and induced pluripotent stem cells have been explored as a therapeutic alternative for treating a broad spectrum of neurologic disorders including stroke, Alzheimer's, Parkinson's, spinal cord injury, cerebral palsy etc. amongst others. It is essential to select suitable cells depending on the nature and status of neurological dysfunctions to achieve optimal therapeutic efficacy. Along with the selection of cells, the route of administration also plays an important role to

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Preface

There are some medical disorders that have remained very difficult to treat over the last many years. Pediatric neurological disorders like autism, cerebral palsy and muscular dystrophy have been some of them. All the advances in imaging, pharmacology and surgical techniques failed to make a significant dent in the quality of lives of these children. However in the recent few years there has been a development in the field of regenerative medicine whereby stem cell therapy has become available to us as a new treatment method . The biggest impact of stem cell therapy has been on the otherwise incurable pediatric neurological disorders. These are new and exciting times for pediatric neurology. With increasing research in this field and greater publications coming out showing the safety and efficacy of stem cell therapy, a quantum shift is happening in our approach to these disorders . We have shifted from hopelessness to hope and from lack of options to the availability of multiple options in all aspects of their care. We can safely say now that *"Stem cell therapy is an idea whose time has come"*

Despite this there is a lack of awareness about stem cell therapy and the clinical conditions it could possibly benefit. We have therefore written this book for pediatricians since they are the primary caregivers to all the children with pediatric neurological disorders. Nowadays with availability of information on the internet, parents of these children obtain a lot of knowledge about newer treatment options and then ask their doctors about it. It's important that pediatricians understand all aspects of this new therapy so that they can counsel and advise the parents appropriately. In this book we share with our pediatric colleagues general information about what stem cell therapy is, the indications where it can be used, a relevant review of literature as well as our own clinical results. We hope that with this book we are able to bring some clarity about different aspects of stem cell therapy in pediatric neurological disorders. From our own clinical experience we can now say with reasonable confidence to the parents of these children that with the availability of stem cell therapy for your children now : *"Aache din aane wale hain".*

– Dr. Alok Sharma

Preface For 2nd Edition

It is not often that one has to bring out a second edition of a book within one year of the first edition. But such are the rapid advances happening in the field of stem cell therapy, that within a year the substantial new data that had become available necessitated a bringing out the second edition. This one year has seen a large number of international and national publications in this field. Our own publications have increased to 41 from the 32 when the first edition was published. A shift in the wind is also occurring, both in the minds of pediatricians as well as other medical doctors. The conversation has shifted from" stem cell therapy does not work", to "maybe stem cell therapy does work."An increasingly large number of pediatricians are recommending stem cell therapy for the various incurable neurological conditions. Standard textbooks of medicine have started incorporating chapters and sections on stem cell therapy.

The first issue of the Indian Journal of Stem Cell Therapy was released recently, (of which Dr Nandini Gokulchandran, a co- author of this book) is the founding editor in chief. The fact that the first issue was release by the Drug Controller General of India in New Delhi is a sign of the regulatory authorities also showing greater openness and acceptance of this form of therapy. Worldwide too there is greater interest in the role of regenerative medicine for various pediatric neurological conditions, earlier considered untreatable. The main focus of stem cell therapy is on autism, cerebral palsy and Ducchenne muscular dystrophy. With increasing objective evidence on PET CT Scans showing biological changes after stem cell therapy, the hundreds of patients who have shown significant clinical results and the large number of publications now available clearly suggests that it is not long before SCT will become a standard of care for these conditions. In the second edition, we have added a separate section on neurorehabilitation, because stem cell therapy works well when combined with an appropriate neurorehabilitation program.

We thank all our pediatrician colleagues for their encouragement and support, as we have worked diligently ,in attempting to provide the best possible care to children with neurological disorders.

– Dr. Alok Sharma

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SECTION A

1. Introduction

Neurodevelopmental and other neurological disorders represent one of the leading causes of disability in children throughout the world. These disorders are currently estimated to affect as many as a billion people worldwide and the number is expected to increase considerably in years to come. Very few of these conditions have a cure and they may worsen over time. These children demonstrate a range of symptoms and functional limitations affecting their daily activities. Neurological conditions also pose an economic burden to the society. Hence, finding a treatment/ cure for these disorders is a goal of increasing urgency.

The devastating nature of neurological disorders is attributed to the longstanding belief that the cells of the brain and central nervous system (CNS) are incapable of regeneration.

In 1928, Ramon Y Cajal stated in his work Degeneration & Regeneration of the nervous system that "In adult centres the nerve paths are something fixed, ended, immutable. Everything may die, nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree."

However, recent progress in regenerative medicine has provided hope that injured CNS can be repaired using stem cells.

Stem cells are unspecialized cells with a capacity of self renewal and differentiation into specialized cells. The main aim of stem cell therapy is axonal regeneration, replacement of damaged neural cells and recovery of lost neural functions. These cells either carry out regeneration of new cells or stimulate the endogenous stem cells to reverse the CNS damage. A number of stem and progenitor cell types have been proposed as therapy for neurological diseases. These include bone marrow stem cells, neural stem cells, embryonic stem cells and umbilical cord blood stem cells. Extensive research has been carried out in this field. Researchers have anticipated that cell therapy may replace the conventional management strategies presently available for disorders such cerebral palsy, autism, brain injury, spinal cord injury, etc in children.

Stem cell therapy has already been translated from bench to bedside. To make it more efficacious some unsolved queries need to be answered such as the ideal source of cells, potent type of cells, optimal route of administration, effective therapeutic

time window and identification of the respondent group of patients. In this book we have made an attempt to address these queries. We have described in detail the mechanism of stem cell therapy in various pediatric neurological disorders.

2. What are Stem Cells?

Stem cells are defined as undifferentiated cells which are capable of proliferation, self maintenance, production of a large number of differentiated, functional progeny, regenerating tissue after injury and flexibility in the use of these options. These cells exhibit a unique property of "plasticity" where in cells isolated from one tissue convert to cells of different tissues by crossing lineage barriers and adopting the expression profile and phenotype of cells that are unique to other tissues.

Types of Stem Cells

Stem cells are categorized based on their potential to differentiate into other types of cells.

1. Totipotent cells: These cells have the ability to differentiate into all possible cell types of the human body including extraembryonic and placental cells.
2. Pluripotent cells: These cells have ability to differentiate into any of the three germ layers viz. endoderm, mesoderm and ectoderm.
3. Multipotent cells: These cells have the ability to differentiate into specialized cells.

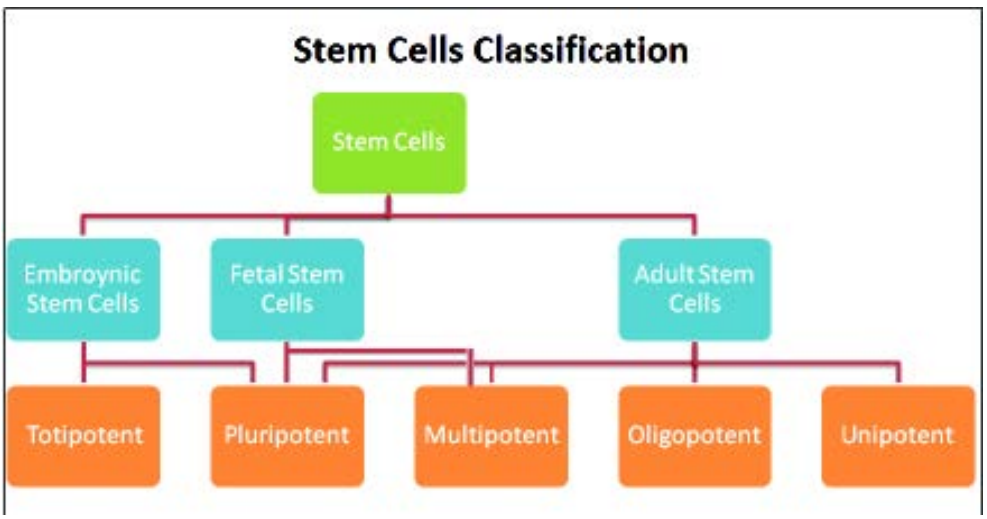

Figure 1: Classification of Stem cells

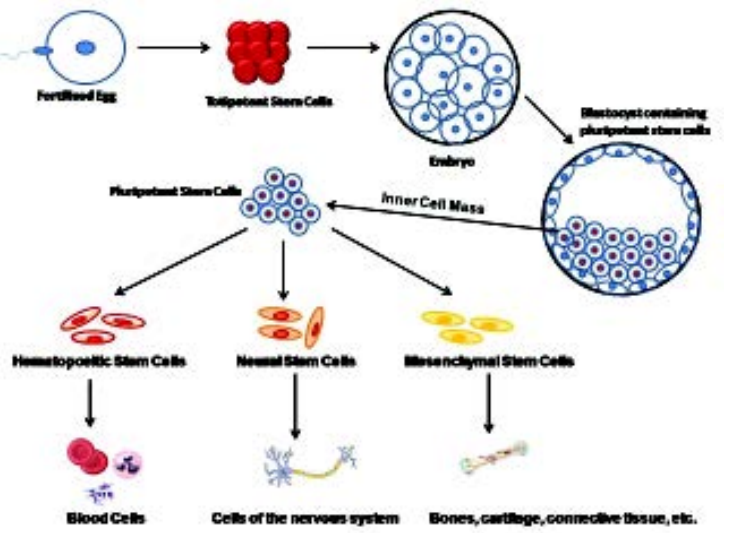

Figure 2: Differentiation of stem cells

4. Oligopotent cells: These cells have the ability to differentiate into a few cells.
5. Unipotent cells: These cells have the ability to produce cells only of their own type, but are capable of self-renewal to be classified as a stem cell.

Stem cells are broadly classified based on their origin, as follows:

1. **Embryonic stem cells (ESCs):** These cells are pluripotent cells derived from a 4-7 day old blastocyst stage embryo. The cells are harvested from the inner cell mass (ICM) of the blastocyst. They can be indefinitely maintained and expanded as pure populations of undifferentiated cells, in culture. Inspite of their clinical potential in tissue repair, these cells have triggered various ethical and moral issues as they involve destruction of human embryos. They also have tumorigenic side effects as ESCs and tumor cells share cellular and molecular phenotypes such as rapid proliferation rate, lack of contact inhibition, a susceptibility to genomic instability, high activity of telomerase, high expression of oncogenes and epigenetic status amongst others. They form teratomas which have the potential to degenerate into malignant teratocarcinomas. The likelihood of development of tumors in children cannot be overlooked as they have many years of life ahead of them for the tumor formation to occur. According to the ICMR, use of these cells fall into the restricted category.
2. **Fetal Stem Cells:** These cells are isolated either from the aborted fetus or from the extra embryonic structures of the fetal origin such as the amniotic fluid and placenta. Fetal blood is a rich source of haemopoietic stem cells (HSC). Non-haemopoietic mesenchymal stem cells (MSC) are also found in the First trimester fetal blood. These cells have better homing capacity, greater multipotentiality and differentiation potential and lower immunogenicity as compared to the adult

stem cells. Although these cells have a greater therapeutic potential they are also susceptible to infections. Studies have demonstrated that these cells are prone to KS-associated herpesvirus (KSHV) infections. As the safety is not yet substantiated, fetal cells are not often used for transplantation. According to the ICMR, use of these cells fall into the restricted category.

3. **Umbilical cord stem cells:** Umbilical cord contains a heterogeneous mixture of stem / progenitor cells at different lineage commitment stages. Cells are isolated either from the cord blood or the Wharton jelly. They consist of embryonic stem cell-like and other pluripotential stem cells, which can give rise to hematopoietic, epithelial, endothelial, and neural tissues. Various banks have evolved to collect and preserve the umbilical cord blood. But the utility of these centers is still questionable. The protocols and guidelines for collection and retrieval of cells are still being standardized. Other disadvantages of use of UCBCs are that the time for platelet engraftment is prolonged in the transplantation of cord blood due to insufficient cell dose. According to the ICMR, use of these cells fall into the permitted category.

4. **Induced pluripotent stem cells (iPSC) :** To circumvent the ethical issues involved in the use of embryonic stem cells, pluripotent cells were generated directly from the patients' own cells. Induced pluripotent stem cells are non-pluripotent adult cells (somatic cells) which have been genetically reprogrammed to form pluripotent cells. But, to initiate the clinical trials involving iPSCs, the reprogramming efficiency and safety has yet to be established.According to the ICMR, use of these cells fall into the restricted category.

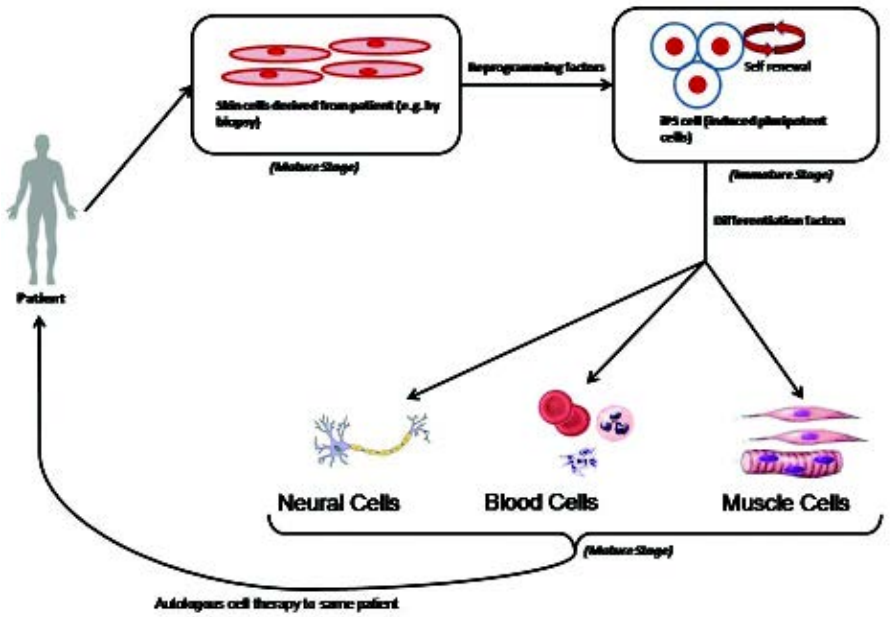

Figure 3: Induced pluripotent stem cells (iPSC)

5. **Adult stem cells:** These cells are multipotent stem cells, isolated from adult tissues. They include hematopoietic stem cells, bone marrow derived stem cells, adipose tissue-derived stem cells, neural stem cells amongst others. Adult stem cells are found in almost all the tissues of the body and help to maintain and repair organs and tissues throughout a person's life. These cells are majorly derived from the bone marrow, brain, skeletal muscle, liver, pancreas, fat, skin and skeletal muscle. According to the ICMR, use of these cells fall into the permitted category.

Major sources of adult stem cells

Bone marrow: Anterior or posterior superior iliac crest is the preferred site for the bone marrow aspiration. If bone marrow cannot be obtained from the iliac crest due to positioning difficulties or obesity, sternum may be used in adults. However, aspiration from sternum poses a great risk of complications.

Bone marrow is a proficient source of autologous cells with distinct regenerative properties, which can be quickly harvested and are thus applicable for both chronic and acute diseases. It is the only known organ in which two or more separate and distinct stem cells and dependent tissue systems not only coexist but functionally cooperate. The mononuclear cell fraction derived from the bone marrow is a heterogeneous population containing differentially matured B-cells, T-cells and monocytes, as well as rare progenitor cells such as hematopoietic stem cells (HSC), mesenchymal stromal cells (MSC), endothelial progenitor cells (EPC) and very small embryonic-like cells (VSEL). The hematopoietic cells are the blood cells which give rise to the myeloid (monocytes and macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets, dendritic cells), and lymphoid lineages (T-cells, B-cells, NK-cells). Bone marrow mesenchymal stem cells (BMMSCs) give rise to mesodermal lineage cells such as osteoblasts, chondrocytes, adipocytes, and muscle cells along with neuroectodermal cells. It has been observed that use of cell mixture is more efficacious than individual subfractionated cells of the bone marrow. They promote angiogenesis, mediate vascular repair, and express several cytoprotective growth factors and cytokines. These cells are also safe and due to its easy availability they are most preferred for cellular therapy. These cells are used for the treatment of various neurological disorders such as autism, cerebral palsy, stroke, Parkinson's, Spinal cord injury, etc along with diabetes, orthopedic conditions, cancers and wound healing.

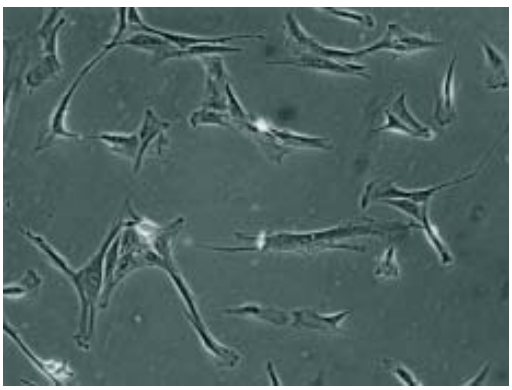

Figure 4: Bone marrow stem cells transforming into neuron like cells.

Adipose tissue: Adipose tissue derived

stem cells (ASCs) are multipotent cells, found abundantly in fat tissue. They can differentiate into several lineages, including adipose cells, chondrocytes, osteoblasts, neuronal cells, endothelial cells, and cardiomyocytes. These cells are obtained either through liposuction or lipectomy. Mesenchymal stem cells make up the majority of the adipose derived stem cells. Due to their plasticity, they are a preferred alternative to the BMSCs. One of the major disadvantages of adipose derived stem cell is that they are not a completely homogeneous cell population in addition to complicated isolating process. Therefore, an expert is required for cell isolation.

Dental pulp: A population of stem cells has been isolated from the human dental pulp known as dental pulp stem cells (DPSCs). They have an ability to regenerate a dentin-pulp-like tissue. DPSCs are a heterogeneous population of cells as they are composed of both mesenchymal and ectodermic cells. These cells are readily obtained (from milk teeth, routine dental procedures such as removal of impacted third molars) and have been shown to possess properties similar to neural stem cells and mesenchymal stem cells. Under appropriate conditions, these cells also undergo neuronal differentiation. One of the disadvantages of DPSCs is that it takes longer to culture mesenchymal stem cells from teeth active tissue. Also, it is difficult to harvest a large quantity of stem cells from teeth.

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3. How is stem cell therapy done?

The process of stem cell therapy is carried out in 3 steps (1) Procurement of stem cells (2) separation, harvesting, enriching &/or expansion and differentiation in the laboratory and (3) transplantation or delivery of the cells. In this chapter, we have discussed each aspect with respect to autologous bone marrow stem cell therapy, in detail. (Others are mentioned in short).

1. Procurement of Stem cells

a) Bone marrow aspiration

The choice of site may be dependent on various factors such as age, weight, marrow distribution, physical status of the patient, physicians experience, etc. However, the most common site is the pelvis. The aspiration is easily done from either posterior

Figure 1: Bone marrow aspiration

or anterior iliac crests. The posterior superior iliac spine is easily accessible and identifiable, however to access this, the patient has to be in the lateral or prone position which can be troublesome and cumbersome. The anterior superior iliac spine can be accessed with the patient lying comfortably in the supine position. In obese patients, the landmarks may be obliterated due to fat distribution.

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

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

The stylet is now removed and a 10 ml or 20 ml syringe, with some heparin in it, is attached and the aspiration is carried out. A total of 100-120 ml is aspirated in adults and 80-100 ml in children is collected. The bone marrow is then transported to the laboratory in a special transporter under sterile conditions for further cell separation.

b) Umbilical Cord Stem Cells

These are procured from the preserved umbilical cord at the time of birth. Nowadays there are many cord banks who collect and store cord blood stem cells. A kit is provided by the banks to the parents or doctors for collection.

2. Cell Separation

Separation of stem cells from its source is one of the most important steps in the process of stem cell therapy. An effective method of cell separation is crucial to gain optimum benefit from the cells. As discussed in the previous chapter, stem cells are primarily obtained from haematopoietic sources such as the bone marrow, peripheral blood and umbilical cord, due to easy accessibility and absence of ethical issues. The protocol for processing these cells is varied.

Harvesting stem cells from peripheral blood.

The most common method of collecting hematopoietic stem cells (HSCs) is by mobilization from the peripheral blood. Since, negligible HSCs are detectable in the

peripheral blood during the steady state, either a hematopoietic growth factor such as granulocyte colony-stimulating factor (GCSF) or chemotherapy (usually cyclophosphamide) with or without granulocyte colony-stimulating factor is necessary to mobilize them.

Most mononuclear cells are collected by peripheral blood apheresis/ leukaphereses. In general, a minimum number of 2x106 CD34 cells per kilogram of recipient weight will ensure engraftment. Hematopoietic stem cells may be positively selected or enriched, ex-vivo using antibodies to CD34 or CD133 or purified by negative selection by using antibodies to remove lymphocytes. In practice, the most common method of purging lymphocytes is via CD34-positive selection.

Harvesting stem cells from bone marrow.

a) Open Method

Bone marrow blood (100-150 mL) aspirated from the iliac bone(generally either anterior or posterior superior iliac spine) and is diluted in Hanks' balanced salt solution (HBSS) at a ratio of 1:1. After centrifugation of samples at 1000 x g for 30 min through a density gradient (Ficoll-Paque Plus, 1.077 g/L; Amersham Biosciences,Piscataway, NJ), the mononuclear cell layer is recovered from the gradient interface and washed with HBSS. The cells are centrifuged at 900 xg for 15 min and resuspended in 1.8 mL of phosphate buffered saline (PBS) at a density of 1.1 x 10^6cells/L.

Figure 2: Stem cell Separation

b) Closed Method

Commercial platforms for harvesting bone marrow concentrates are being engineered to facilitate harvesting in a closed system. Various companies such as Harvest Technologies, Miltenyl Biotec, StemCell Technologies, etc have developed fully automated systems to simplify and accelerate the cell separation.

Harvesting stem cells from Umbilical Cord blood

Currently, there are two types of processing methods used to separate cells from the cord blood, manual and automated. Some companies choose to use manual processing systems while others have moved to automated processing systems.

Manual processing involves allowing the blood to sit for a period of time and then manually extracting cells from the middle of what has "settled" out from the cord blood. There are two potential problems however with manual processing. Manual methods recover only 40%-80% of cells necessary for transplant purposes and can potentially subject the cord blood to potential airborne contaminants.

Automated processing has avoided these potential problems by working in a completely closed system eliminating excess air contamination and, most importantly, allowing for up to 99% recovery of necessary cells for transplantation. In addition, the possibility of human error is reduced. Unfortunately, these advancements make automated processing costly, and those costs are passed on to customers.

3. Transplantation of stem cells

Stem cell transplantation is carried out via various delivery routes such as intravenous, intrathecal, intraarterial, intramuscular, direct injection, etc. Every mode of administration has its pros and cons. Comparative studies need to be carried out to optimize the selection of route of administration to ensure a positive outcome of stem cell transplantation.

Intrathecal delivery

The patient is positioned in the curled up "foetal ball" position to open up the spinous processes. Under local anesthesia, a standard lumbar puncture procedure is performed at the L4-5 level. A 18G Touhy needle is inserted into the sub-arachnoid space. After ascertaining free flow of CSF, an epidural catheter or spinal needle is inserted into the space, far enough to keep 8-10 of the catheter in the space. The stem cells are then injected slowly through the catheter, keeping a close watch on the hemodynamics of

Figure 3: Intrathecal administration of stem cells

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

This method is minimally invasive and is the safest targeted mode of transplantation. In a study carried out by Callera et al, it was demonstrated for the first time that autologous bone marrow CD 34+ cells labelled with magnetic nanoparticles when delivered intrathecally, migrates into the injured site in patients with spinal cord injury.

Intravenous delivery

Intravenous delivery of stem cells is one of the most widely used routes of administration. It is safe, minimally invasive and has no ethical issues involved. Inspite of these advantages, it is not the most efficient method of transplantation. In various studies it has been seen 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.

Intra-arterial injection

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

Figure 4: Intra-arterial Injection of stem cells into the carotid artery

Intraspinal transplantation

Direct implantation into the spinal cord may be done in different ways:-

a) Through a complete laminectomy from one level above to one level below the injury site so that there is sufficient access to the transplantation site.

b) Though a minilaminectomy and exposure of the spinal cord. Two injections are made on either side above the injury site and two injections are made below the injury site.

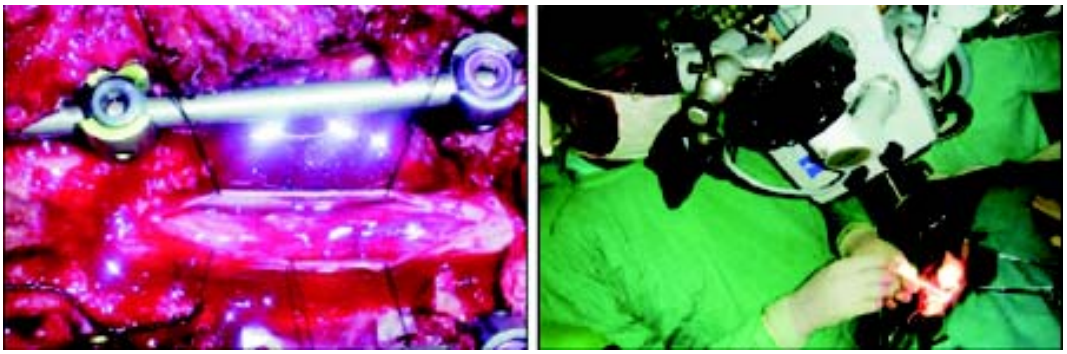

Figure 5: Instraspinal administration of stem cells

Stereotactic implantation into the brain

Cell transplantation for neurological conditions started with stereotactic implantation of fetal cells for Parkinson's disease. There are many stereotactic systems available all over the world however the two most popular ones are the Leksell Stereotactic system and the CRW Stereotactic system. The area where the tissue is to be transplanted is identified on the MRI scan and then using the MRI software the X, Y and Z coordinates are obtained. A small burr hole is drilled into the skull of the patient and the cells are transplanted at the desired location using the X, Y and Z coordinates. The entire procedure is done under local anesthesia. However, the clinical outcome of this method is not significantly different from non transplanted patients. It is also the most invasive method of transplantation and could result in secondary injury.

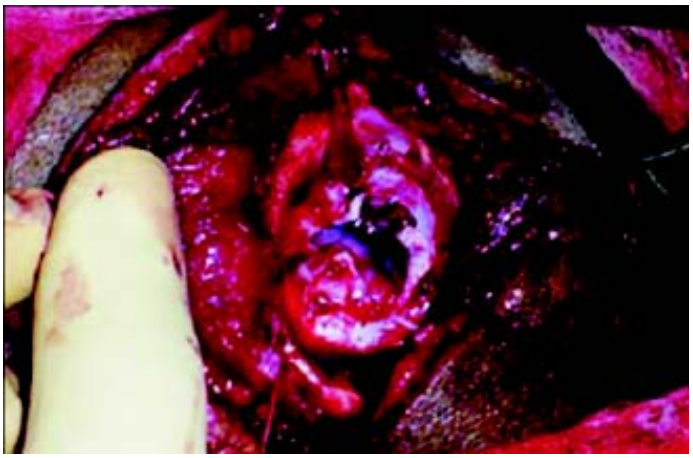

Figure 6: STA-MCA bypass

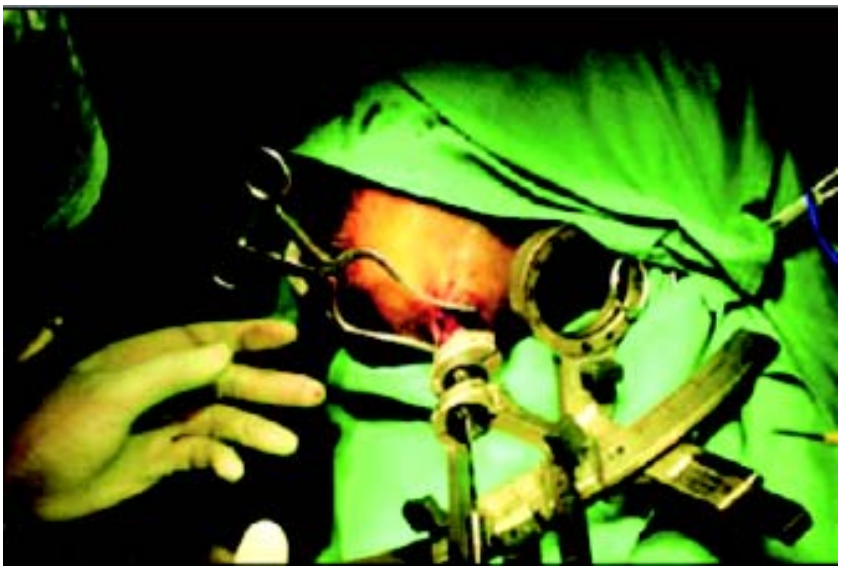

Figure 7: The Leksell Stereotactic frame for direct stem cell implantation into the brain

Intramuscular injection

In certain disorders, especially Muscular dystrophy, cells are also transplanted into the muscles. The points at which they are injected are termed as the "motor points". Motor point is the point at which the main nerve enters the muscle or, in case of deeply placed muscle, at the point where the muscle emerges from under covers of the more superficial ones. At these motor points, the area is cleaned and the cells diluted in CSF are injected with the 26G needle into the muscle at an angle (approx. 45 degrees).The piston/plunger of the syringe is slightly withdrawn to verify that the needle is not inside a blood vessel. Once the needle is removed, the site is immediately sealed with a benzoin seal.

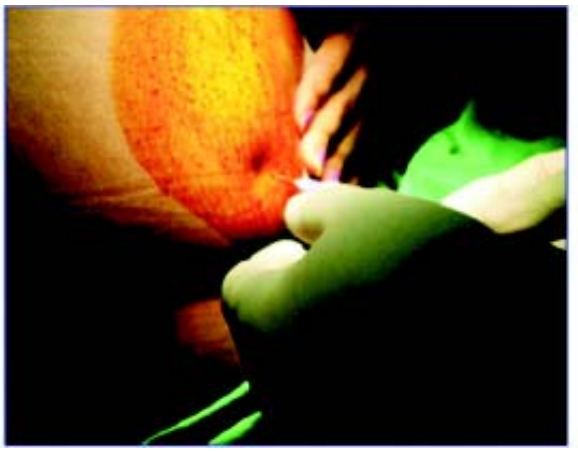

Figure 8: Intramuscular

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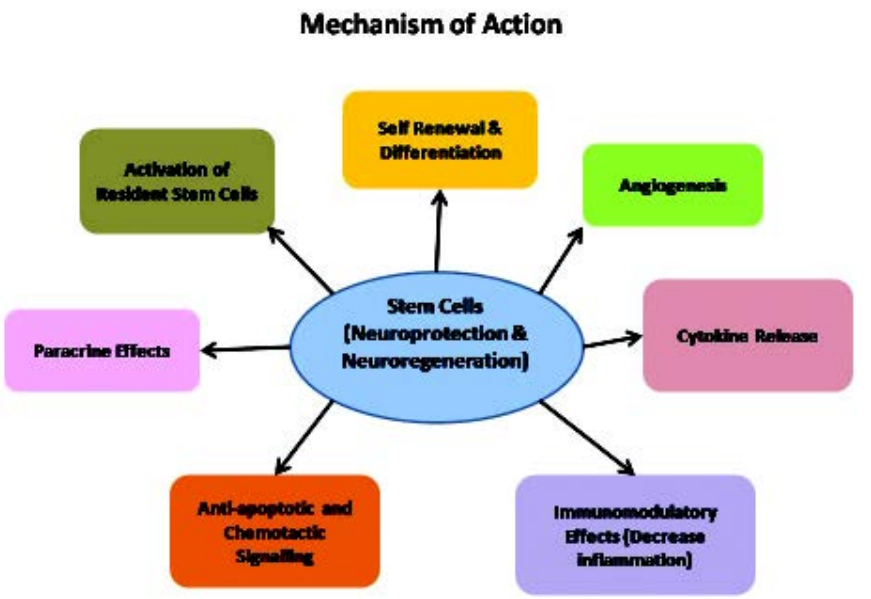
4. How do Stem cells work?

Stem cells are actively involved in the formation of new tissues and thereby can also promote repair and regeneration. Their role, in the normal wear and tear of the body, appears to be assistance of repair and maintenance of normal tissue structure and function. Cell-based therapy could therefore potentially be used to treat a wide array of clinical conditions caused due to cellular damage. The process of deciphering the underlying mechanism of action of stem cells is a continuous process. However, years of experiments and studies have put forward few theories which either individually or in combination carries out the repair of the damaged tissues. Few of the mechanisms have been discussed below.



Plasticity, Pluripotency and Production

Stem cells have remarkable property of plasticity wherein they can cross the lineage boundaries. They can differentiate into cells with function and phenotype other than theirs. In 1998, Ferrari et al. first reported that mouse bone-marrow-derived cells give rise to skeletal muscle cells when transplanted into damaged mouse muscle. Thereafter, transplanted bone marrow cells were reported to generate a wide

spectrum of different cell types, including hepatocytes, endothelial, myocardial, neuronal, and glial cells. Moreover, HSC can produce cardiac myocytes and endothelial cells, functional hepatocytes and epithelial cells of the liver, gut, lung, and skin. Mesenchymal stromal cells (MSC) of the bone marrow can generate brain astrocytes. Enriched stem cells from adult mouse skeletal muscle were shown to produce blood cells. In most of these plasticity studies, genetically marked cells from one organ of an adult mouse apparently gave rise to cell type characteristics of other organs following transplantation, suggesting that even cell types once thought to be terminally differentiated are far more plastic in their developmental potential than previously thought. A critical aspect of the observation of adult stem cell plasticity is that in order for plasticity to occur, cell injury is necessary. This suggests that micro-environmental exposure to the products of injured cells may play a key role in determining the differentiated expression of marrow stem cells.

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

Another mechanism put forward to explain, stem cell switch to a novel phenotype, is a process known as trans-differentiation. Cells may differentiate from one cell type into another within the same tissue or develop into a completely different tissue without acquiring an intermediate recognizable, undifferentiated progenitor state.

Trans-differentiation events are at times considered as misinterpretations caused by cell fusion resulting in nuclear reprogramming and changes in cell fate. Adult stem cells from bone marrow may be able to fuse with cells of the target organ. So far, bone-marrow-derived cells were shown to form fusion heterokaryons with liver, skeletal muscle, cardiac muscle, and neurons. There is evidence that such fused cells become mono-nucleated again, either by nuclear fusion or by elimination of supernumerary nuclei. Fusion and nuclear transfer experiments demonstrated that genes previously silenced during development could be reactivated by cytoplasmic factors modulating the epigenetic mechanisms responsible for the maintenance of a specific state of cell differentiation. Despite the limitation of the low frequency of this event and its dependence of the developmental stage of donor nuclei, cell fusion may be considered as a potential avenue for tissue repair. The physiological purpose of adult cell fusion is speculative. As outlined by Helen Blau, fusion could be a means by which cells 1) deliver healthy genetic material to dying cells (rescue function), 2) supply cells with new genes (repair function), or 3) correct genetically defective cells such as in muscular dystrophy (gene replacement).

Fusion could even be considered a basic mechanism for keeping the adult cell systems intact throughout our lifespan.

In addition to the aforementioned phenomena of cell fate switching, the presence of a rare population of pluripotent primitive stem cells may also explain the acquisition of an unexpected phenotype. Non-hematopoietic cell populations from bone marrow and umbilical cord blood were enriched by in vitro culture and demonstrated to have the potential to differentiate into derivatives of all three germline layers with meso-, endo-, and ectodermal characteristics. Known as multipotent adult progenitor cells (MAPC), these cells contribute to most, if not all, somatic cell lineages, including brain, when injected into a mouse blastocyst. Interestingly, while MAPC express Oct4, a transcription factor required for undifferentiated embryonic stem cells maintenance at levels approaching those of ESC, MAPC do not express two other transcription factors known to play a major role in ESC pluripotency, Nanog and Sox2. This particular expression profile may contribute to the fact that the use of ESC, but not MAPC, carries the risk of generating tumors. Thus, MAPC are a promising source of autologous stem cells in regenerative medicine. Their low tumorigenicity, high regenerative plasticity, and optimal immunological compatibility are essential assets for the successful transplantation of MAPC-derived tissue-committed cells without immune-mediated rejection.

The Paracrine Effect

Exploration of the various cellular mechanisms occurring (both during normal physiology as well as after tissue injury) in the process of stem cell renewal and differentiation, suggests that stem cell treatment or transplantation of stem cells remodels and regenerates injured tissue, improves function, and protects tissue from further insult. These have also led to phase I and II clinical trials regarding stem cell treatment for a variety of surgical diseases. Despite these encouraging advances, the mechanism of this protection is still not well-characterized. As discussed earlier, it was initially hypothesized that immature stem cells differentiated into the phenotype of injured tissue, repopulated the diseased organ with healthy cells, and subsequently improved function. But, recent research indicates that this stem cell-mediated protection may not have resulted from differentiation into the target tissue type. Instead, several lines of evidence suggest that stem cells may mediate their beneficial effects, at least in part, by paracrine mechanisms. The reasons for the above postulations are as follows:

First, studies demonstrate that donor stem cell engraftment and survival after transplantation is only 1-5% which is too few to be relevant therapeutically and influence directly organ function.

Second, stem cells have been shown to confer acute improvement in end organ function less than 72 hr after injury, precluding differentiation as a cause due to time required for meaningful differentiation and regeneration of these donor cells.

Third, and perhaps most importantly, in vitro and in vivo animal studies have revealed that much of the functional improvement and attenuation of injury afforded by stem cells can be replicated by cell free, conditioned media derived from stem cells. Taken together, these indirect and direct data suggest that stem cells may improve injured

organ performance and limit injury not via differentiation but rather via complex paracrine actions rather than an organogenetic role.

Though complete understanding of the mechanism of action of the stem cells is still sometime away, the following effects have been proposed.

Stem cells transplanted into injured tissue express paracrine signaling factors including cytokines and other growth factors, which are involved in orchestrating the stem cell-driven repair process through increasing angiogenesis, decreasing inflammation, preventing apoptosis, releasing chemotactic factors, assisting in extracellular matrix tissue remodeling and activation of resident/satellite cells which is discussed further in details.

Increased Angiogenesis

Stem cells produce local signaling molecules that may improve perfusion and enhance angiogenesis to chronically ischemic tissue. Although the particular growth factors contributing to this neovascular effect remain to be defined, the list includes vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and basic fibroblast growth factor (FGF2). VEGF is a strong promoter of angiogenesis. Chen et al. have recently shown that treatment with bone marrow stromal cells enhances angiogenesis by increasing endogenous levels of VEGF and VEGFR2. They previously demonstrated that administration of recombinant human VEGF165 to rats 48 hours after stroke significantly increased angiogenesis in the penumbra and improved functional recovery.

Hepatic Growth Factor (HGF) exerts beneficial effects on neovascularization and tissue remodeling, while FGF2 is involved intimately with endothelial cell proliferation and may be a more potent angiogenic factor than VEGF.

When exposed to either insult or stress, mesenchymal stem cells (MSC) in cell culture and in vivo significantly increase release of VEGF, HGF, and FGF2, which may improve regional blood flow as well as promote autocrine self survival. Increased perfusion due to the production of stem cell angiogenic growth factor has also been associated with improved end organ function. VEGF overexpressing bone marrow stem cells also demonstrates protection of injured tissue.

Thus, VEGF, HGF, and FGF2 may be important paracrine signaling molecules in stem cell-mediated angiogenesis, protection, and survival.

Decreased Inflammation

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

Anti-Apoptotic and Chemotactic Signaling

Stem cells in a third pathway promote salvage of tenuous or malfunctioning cell types at the infarct border zone. Injection of MSC into a cryo-induced infarct reduces myocardial scar width 10 weeks later. MSCs appear to activate an anti-apoptosis signaling system at the infarct border zone which effectively protects ischemia-threatened cell types from apoptosis. Furthermore, expression profiling of adult progenitor cells reveals characteristic expression of genes associated with enhanced DNA repair, upregulated anti-oxidant enzymes, and increased detoxifier systems. HGF has been observed to improve cell growth and to reduce cell apoptosis.

Evidence also exists that both endogenous and exogenous stem cells are able to "home" or migrate into the area of injury from the site of injection or infusion. MSC in the bone marrow can be mobilized, target the areas of infarction, and differentiate into target tissue type. Granulocyte colony-stimulating factor (G-CSF) has been studied widely and promotes the mobilization of bone marrow-derived stem cells in the setting of acute injury. This homing mechanism may also depend on expression of stromal cell-derived factor 1 (SDF-1), monocyte chemo-attractant protein-3 (MCP-3), stem cell factor (SCF), and / or IL-8.

Beneficial Remodeling of the Extracellular Matrix

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

Activation of Neighboring Resident Stem Cells

Finally, exogenous stem cell transplantation may activate neighboring resident tissue stem cells. Recent work demonstrates the existence of endogenous, stem cell-like populations in adult hearts, liver, brain, and kidney. These resident stem cells may possess growth factor receptors that can be activated to induce their migration and proliferation and promote both the restoration of dead tissue and the improved function in damaged tissue. Mesenchymal stem cells have also released HGF and IGF-1 in response to injury which when transplanted into ischemic myocardial tissue may activate subsequently the resident cardiac stem cells.

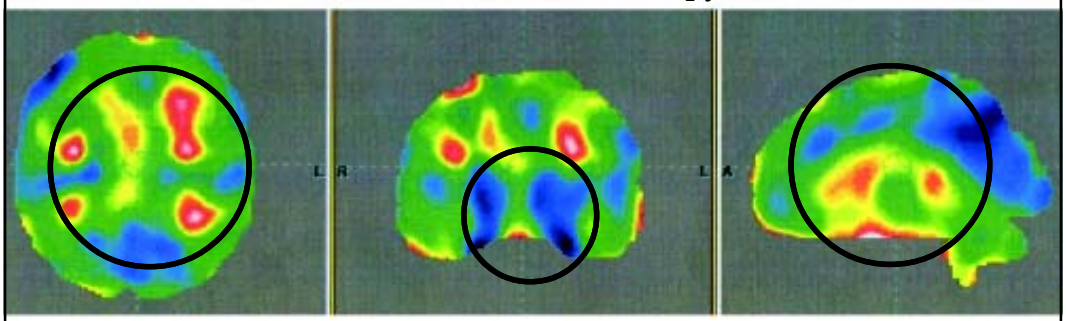
To sum up, although the definitive mechanisms for protection via stem cells remains unclear, stem cells mediate enhanced angiogenesis, suppression of inflammation, and improved function via paracrine actions on injured cells, neighboring resident stem cells, the extracellular matrix, and the infarct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

Remyelination

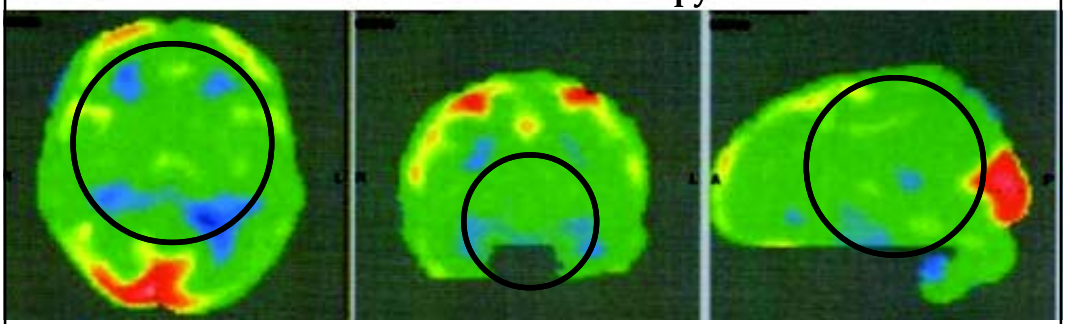
Remyelination involves reinvesting demyelinated axons with new myelin sheaths. Previous attempts aimed at regenerating myelin-forming cells have been successful but limited by the multifocal nature of the lesions and the inability to produce large numbers of myelin- producing cells in culture. Stem cell-based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

How Stem Cells Work in Autism

Before Stem Cell Therapy



After Stem Cell Therapy

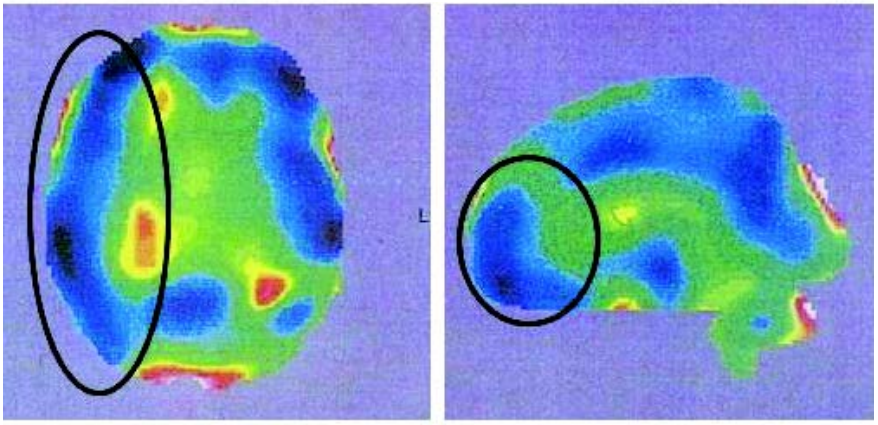


The above figure is a comparison of PET CT scans done before and after stem cell therapy. The red and the yellow areas denote hypermetabolism which have reduced to green which denotes near normal metabolism.

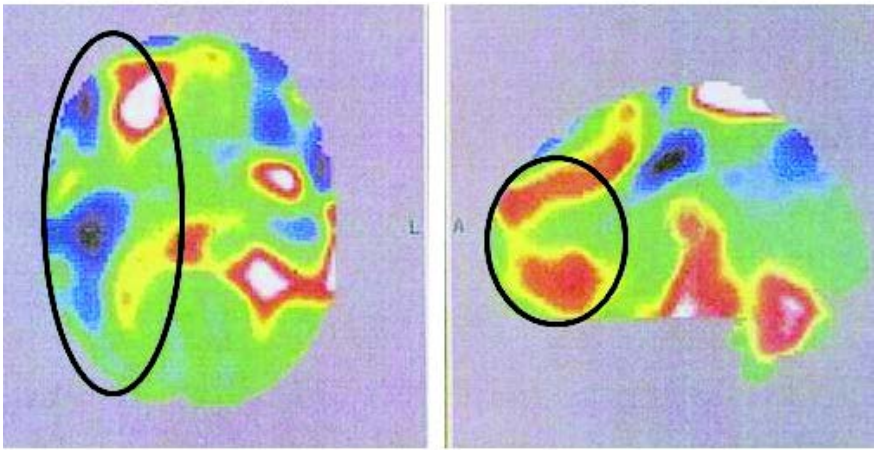
In autism, stem cells carry out the repair process by promoting angiogenesis, reversing the hypoperfusion by increasing the oxygen supply and balancing inflammation. These mechanisms may help in increasing the metabolic activity of the brain which can be seen in the PET CT scans.

How Stem Cells Work in Cerebral Palsy

Before Stem Cell Therapy



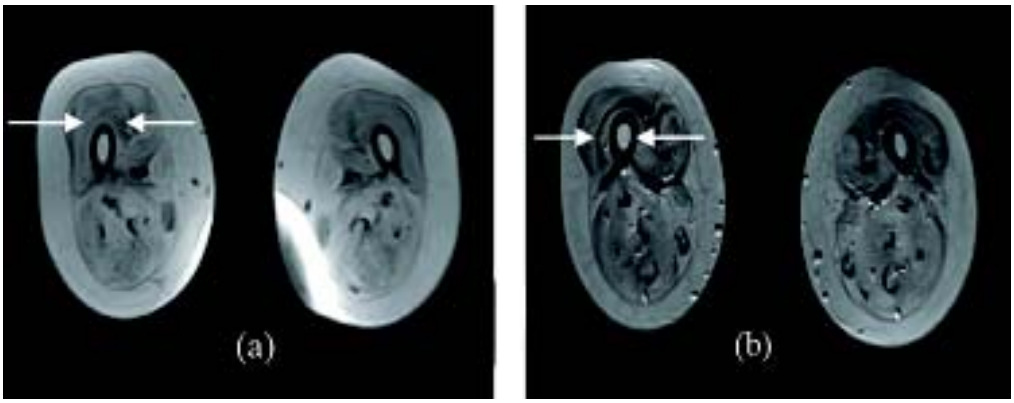
After Stem Cell Therapy



The above figure is a comparison of PET CT scans done before and after stem cell therapy. Post stem cell therapy there is reduction in the blue and the black areas which denote severely damaged areas and more green/red areas are seen indicating reduction in damage and improved brain function.

In Cerebral Palsy, stem cells reverse the brain damage by increasing the blood and oxygen supply through angiogenesis. They stimulate the endogenous cells and halt further cell death.

How Stem Cells Work in Muscular Dystrophy



Before Stem Cell Therapy **After Stem Cell Therapy**

The above figure is a comparison of MRI of vastus medialis and vastus lateralis of a patient with DMD done before and after stem cell therapy. The white arrows in (b) denote muscle regeneration

In Muscular dystrophy, the injected stem cells migrate to the damaged areas and differentiate into new cells. Through paracrine mechanism, they also stimulate the existing satellite cells and halt further degeneration of the muscles.

Recent studies have shown that remyelination can be accomplished by supplying demyelinated regions with cells like Schwann cells, oligodendrocyte lineage cells lines, olfactory ensheathing cells (OECs), embryonic stem cells and neural stem cells, and Adult bone marrow derived stem cells. The remyelinating effect of these cells may be via one or more mechanisms, including: the stem cells act as an immunomodulator by producing soluble factors; they carry out direct cell replacement by differentiating into neural and glial cells in the lesion; and they indirectly promote neural and glial differentiation of endogenous cells. Interactions with viable axons and supportive astrocytic responses are required for endogenous immature cells to fulfill their potential remyelinating capacity.

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

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5. Stem Cell Transplantation in Autism

Autism spectrum disorders (ASD) are pervasive developmental disorders characterized by impairments or delays in social interaction, communication and language, as well as by repetitive routines and behaviors. In a report by the Surgeon General, autism is described as a severe, chronic developmental disorder, which results in significant lifelong disability. It also states that autism has roots in both structural and functional brain abnormalities with genetic predispositions. They are called spectrum disorders because of the wide range and severity of symptoms. The prevalence of autism has increased radically over the few decades. In United States of America the cases have increased from 4 per 10,000 in 1989 to 67 cases per 10,000 in 2000. Currently the figure has exponentially increased to 1 in 68 children in USA and 1 in 250 in India.

Autism spectrum disorder is associated with known genetic causes in 10-15% of cases. The most common causes include fragile X syndrome (about 3%), tuberous sclerosis (about 2%), and various cytogenetic abnormal findings such as maternal duplication of 15q1-q13 (roughly 2%), and deletions and duplications of 16p11 (about 1%).

Like other complex neurodevelopmental disorders, ASD is thought to be the final common pathway of multiple etiological and neuropathological mechanisms, thus, complicating the search for autism-specific biological markers. As there are no definitive biological markers, diagnosis relies on the recognition of an array of behavioral symptoms that vary from case to case, that are increasingly heterogeneous and which overlap with those of other childhood neuropsychiatric disorders.

Pathophysiology:

Brain hypoperfusion and immune dysfunctions have been characterized as the two main brain pathologic alterations in autism cases.

Research on animal brain to study the etiology of autism has shown that a major dysfunction of the autistic brain resides in neural mechanisms of the structures in the medial temporal lobe, and, perhaps, more specifically the amygdaloid complex. Distinct patterns of memory losses and socioemotional abnormalities emerge as a result of extent of damage to the medial temporal lobe structures.

Functional brain imaging, such as positron emission tomography (PET), single photon emission computed tomography (SPECT) and functional MRI (fMRI) have added a new perspective to the study of normal and pathological brain functions. These imaging studies have shown bilateral hypoperfusion of the temporal lobes in autistic children. In addition, activation studies, using perceptive and cognitive paradigms, have also shown an abnormal pattern of cortical activation in autistic patients. This suggests that different connections between particular cortical regions could exist in autism. Further to this, Brain SPECT has established a positive correlationship between regional cerebral flow and development quotient (intelligence quotient) in the left laterotemporal and both dorso-medio-lateral frontal areas, and a negative one in the cerebellar vermis area. This goes to show that cerebral blood flow decrease in the temporal and frontal areas relates to the brain mechanism of autism as well as to intelligence levels.

Clinical symptoms

As with overall autism, symptom presentation is ambiguous among the very young. Children diagnosed with ASD suffer from problems with sensory integration, speech, and basic functions like toilet training, getting dressed, eating meals, brushing teeth, etc.

Many medical conditions can also accompany these symptoms, such as digestive problems, severe allergies, inability to detoxify, very high rate of infection, and vision problems. Some children with ASD display violent or self-harmful behaviors. IQs in children with this disorder range from superior to severely mentally retarded.

Conventional therapies

Autism, similar to other neurodevelopmental disorders, is incurable and requires chronic management. Since, it has become a prevalent dilemma in the present society; interventions to improve the quality of life of people with autism have increased considerably. But, the fact remains that individuals with ASD are among the most difficult and costly to treat.

Currently, the treatments available for autism can be divided into behavioral, nutritional and medical, there being no standard approach.

Recent data has shown evidence that early intensive behavioral intervention has improved outcomes.These interventions are designed to facilitate development and learning, promoting socialization, self awareness, reducing maladaptive behaviors and educating and supporting families. Nutritional interventions restrict allergy-associated dietary components, as well as to supplement minerals or vitamins which may be lacking. Autistic children tend to have problems with digestion, including food sensitivity - particularly to casein and gluten in dairy and wheat products. Medical interventions usually treat specific activities associated with autism. For example, serotonin reuptake inhibitors (SSRI's) such as fluoxetine, fluvoxamine, sertraline, and

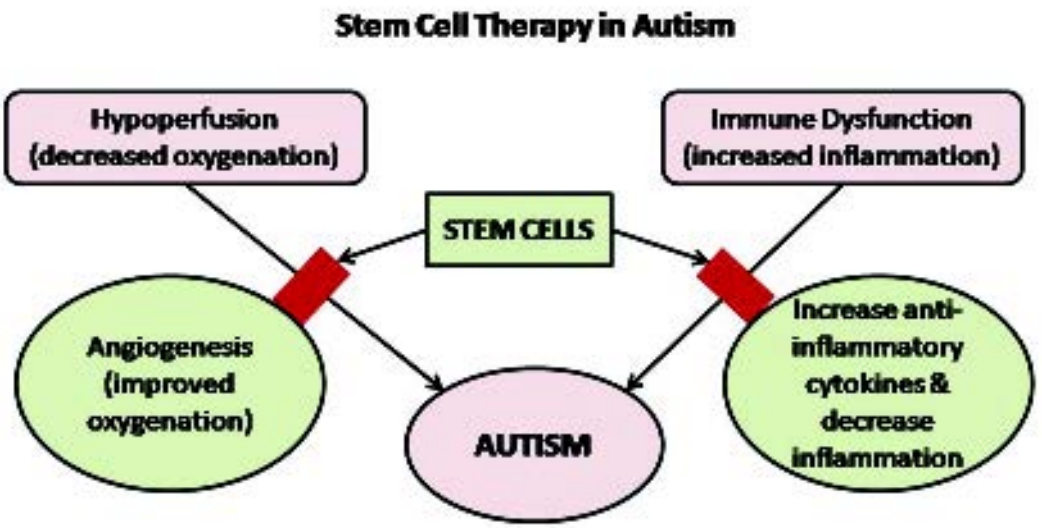
clomipramine, are used for treatment of anxiety and depression. Some studies have shown that SSRI's also have the added benefit of increasing social interaction and inhibiting repetitive behavior. Typical antipsychotic drugs such as thioridazine, fluphenazine, chlorpromazine, and haloperidol have been showed to decrease behavioral abnormalities in autism. Atypical antipsychotics such as risperidone, olanzapine and ziprasidone have also demonstrated beneficial effect at ameliorating behavioral problems. Autism associated seizures are mainly treated by administration of anticonvulsants such as carbamazepine, lamotrigine, topiramate, and valproic acid. Attention deficient/hyperactivity is treated by agents such as methylphenidate.

Other treatments include psychiatric care, neurodevelopmental therapies, and treatment for co-occurring medical conditions.

Other upcoming treatments include, Hyperbaric Oxygen therapy (HBOT), Relationship Development Intervention (RDI),Water Therapy or Aquatic Therapy, Floortime or Developmental Individual Difference Relationship Model (DIR Model), Hippotherapy ,The Handle Method, Neurofeedback, etc.

Summary of current clinical evidence of the role of stem cells in Autism

Though, autism is a very complex neurodevelopmental disorder, different studies have also tried understanding the basic pathophysiology of autism or, in simple terms, why autism develops and what happens in the brain. It is understood now, that the neural hypoperfusion and immune dysregulation are the two key pathologies associated with Autism. There is reduced blood flow supply to certain specific areas of the brain (mesial temporal and cerebellum), which in turn could be the cause of reduced functioning in this area. This coupled with an overall imbalance in the activity of the brain, is possibly responsible for the manifestations associated with autism. Based on the above understanding, many scientists all over the world, such as, Ichim



et al from USA and Siniscalco from Italy (in various scientific reviews and publications) have strongly emphasized the potential of stem cells for the treatment of autism. These proposals are in view of the stem cells having strong angiogenic potential which could facilitate counteractive processes of improving perfusion by angiogenesis and balancing inflammation by immune regulation would exhibit beneficial clinical effects in patients with autism. Other contributing effects of the stem cells, which have been proposed are, strong immunosuppressive activities as well as paracrine effects to stimulate neuronal function via growth factors, such as BDNF, VEGF,NGF AND PDGF.

Worldwide published scientific evidence on Stem Cell Therapy in Autism:

The first ever clinical study published in the world to give clinical evidence of the role of stem cells in autism, came out in August, 2013 from the NeuroGen Brain and Spine Institute, Mumbai, India. This is an open label proof of concept study of autologous bone marrow mononuclear cells (BMMNCs) intrathecal transplantation in 32 patients with autism followed by multidisciplinary therapies. All patients were followed up for 26 months (mean 12.7).The outcome measures used were Childhood Autism Rating Scale(CARS), Indian Scale for Autism Assessment(ISAA), Clinical Global Impression (CGI), and Functional Independence Measure(FIM/Wee-FIM) scales. Positron Emission Tomography-Computed Tomography (PET-CT) scan recorded objective changes. It was found that out of 32 patients, a total of 29 (91%) patients improved on total ISAA scores and 20 patients (62%) showed decreased severity on CGI-I. On CGI-II 96% of patients showed global improvement. The efficacy was measured on CGI-III efficacy index. Few adverse events were reported, including seizures in three patients, but these were reversible and easily controlled with medications. The encouraging result of this leading clinical study provides future directions for application of cellular therapy in autism.

The second study to be published was by Shenzhen Beike Bio-Technology Co., China, which studied the safety and efficacy of human umbilical cord mesenchymal stem cells (hUC-MSCs) and human cord blood mononuclear cells (hCB-MNCs) transplantation in patients with autism. This study comprised of 37 subjects diagnosed with autism ,divided into three groups: CBMNC group (14 subjects, received CBMNC transplantation and rehabilitation therapy),combination group (9 subjects, received both CBMNC and UCMSC transplantation and rehabilitation therapy), and control group (14 subjects, received only rehabilitation therapy). Transplantations included four stem cell infusions through intravenous and intrathecal injections once a week. Treatment safety was evaluated with laboratory examinations and clinical assessment of adverse effects. They used the Childhood Autism Rating Scale (CARS), Clinical Global Impression (CGI) scale and Aberrant Behavior Checklist (ABC) to assess the therapeutic efficacy at baseline (pre-treatment) and following treatment. They did not find any significant safety issues related to the treatment and no observed severe

adverse effects. Statistically significant differences were shown on CARS, ABC scores and CGI evaluation in the two treatment groups compared to the control at 24 weeks post treatment ($p < 0.05$).They concluded that transplantation of CBMNCs demonstrated efficacy compared to the control group; however, the combination of CBMNCs and UCMSCs showed larger therapeutic effects than the CBMNC transplantation alone.

Recently, in October 2014, Bradstreet et al, Ukraine published their study using fetal stem cells in autism. The study was carried out on 45 children with autism. On follow up after 6 months and 12 months, there was a significant change in Autism Treatment Evaluation Checklist (ATEC) test and Aberrant Behavior Checklist (ABC) scores. Improvement was also seen in behavior, eye contact, appetite, etc

Other ongoing clinical trials worth mentioning, on similar lines, are being carried out, in Mexico, Greece and Ukraine.

A detailed analysis of the improvements seen after stem cell therapy:

Improvements in Autistic Children after Stem Cell Therapy can be broadly classified as:

A) **Clinical/Neurological improvements:**

Presented are the details of the improvements seen in 150 children with autism who underwent stem cell therapy. Out of these 90% showed clinical improvements.

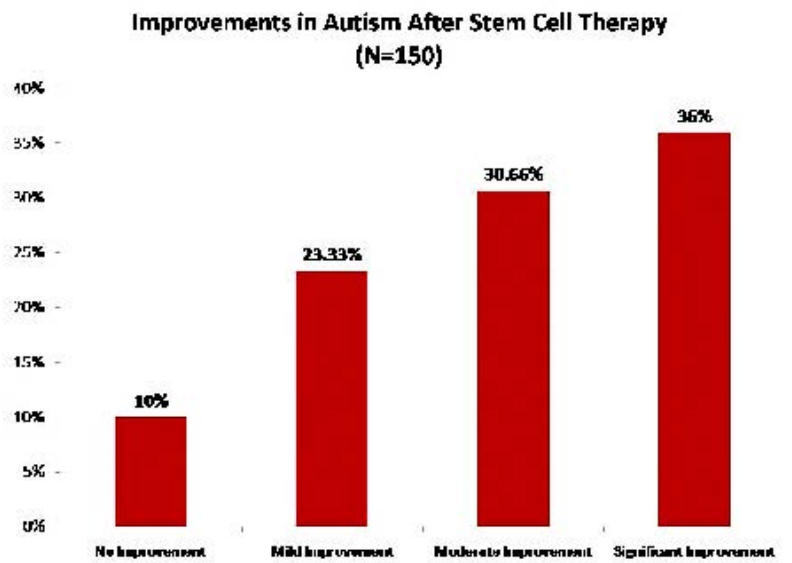


Figure 1: Graph representing improvements in autism after stem cell therapy

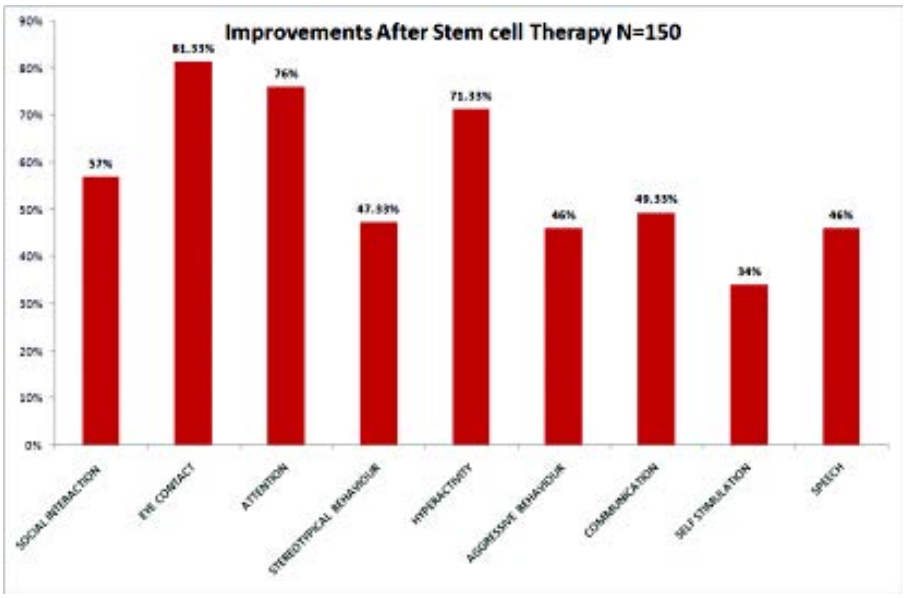


Figure 2: Graph representing symptomatic improvements in autism after stem cell therapy

Improvements in Children with autism after Stem Cell Therapy can be broadly classified as:

A) Clinical/Neurological improvements:

These were reduction in abnormal stereotypical behavior, reduction in self stimulatory behavior, improvement in eye contact, attention span, speech, communication skills and social interactions (Graph 2).

Hyperactivity, eye contact and attention span:

Hyperactivity is one symptom, which improves most visibly. In 71.33% children, it was found that hyperactivity reduced significantly. This was, generally accompanied by improved eye contact along with improved attention span. Eye contact improved in 81.33% while attention span improved in 76%. Children could now sit at one place for a longer time and respond to commands better. This overall resulted in enhanced school performance as well as understanding and cognition. It is also worth mentioning here that in those children who were on medications for hyperactivity, it was possible to reduce the dose of the medicines. This was done by the child's previous physician/ pediatrician. There was no consequent increase in hyperactivity.

Behavior:

Almost 47% of the children showed reduction in stereotypical behavior. While 34% showed reduction in self stimulatory behavior, equal number showed reduction or stopping of self injurious behavior. Violent behavior and aggression also reduced in 46%.

Speech and Communication:

After stem cell therapy, it was observed that communication improved in 49.33% of the children. This was both verbal as well as non verbal. Speech and language communication skills improved in 46%. One child with autism, who was almost non verbal and was extremely hyperactive, once he calmed down after stem cell therapy, started gesturing his needs. He also started verbalizing in bisyllables and small sentences. His overall communication about his needs as well as his emotions to his parents and sister improved remarkably.

Social interaction:

Along with a reduction in hyperactivity, attention to surroundings and awareness about surroundings also increased. This lead to improved social interaction, along with an increase in initiative for different activities, which hitherto, was not observed in these children. Overall, 57% of the children improved in their social interaction skills.

B) Improvements in the Objective Assessment scales:

Changes on Objective Assessment scales:

All the children were scored on the ISAA (Indian Scale for Assessment of Autism) scale which quantifies the severity of autistic symptoms and enables the measurement of associated disability. The score was noted before and 6 months after stem cell therapy. There was a significant improvement in the scores after the stem cell therapy. There were some patients who also showed a dramatic change on the severity category.

Another scale used for monitoring the children is the Clinical Global Impression (CGI) scale. This is used as a clinical research tool to measure the severity of the illness along with the efficacy and response of the intervention/treatment in patients with autism. This scale also revealed improvement, when performed before and after the stem cell therapy, in terms of, the severity of illness and efficacy index. Thus, this indicated that the treatment was efficacious.

C) Objective improvements on SPECT/PET CT Scan Brain:

- Most of the children with autism, have grossly normal brain morphology on MRI Scans of the Brain. However SPECT/PET CT Scan of the brain ,which shows abnormalities in brain perfusion/metabolism is now emerging as a useful imaging technique to identify the areas which are affected as well as the severity of the damage.
- These imaging were done before the stem cell therapy and 6 months after the therapy. The clinical improvements as well as changes on the assessment scales,

are also objectively corroborated by changes seen on the SPECT /PET CT scan of the brain.

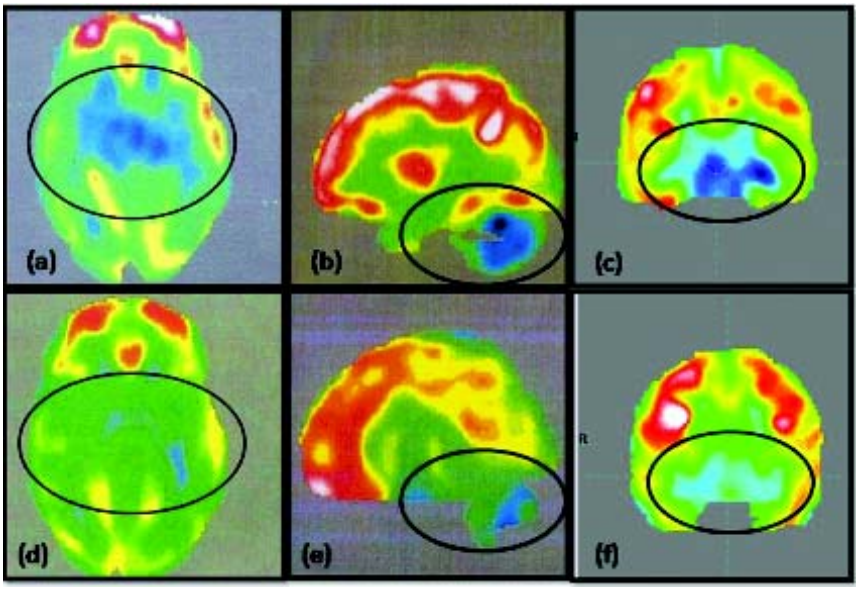


Fig 4: (a), (b), (c) PET-CT scan brain performed before stem cell therapy: Blue areas denoting reduced metabolism. (d), (e), (f) PET CT scan brain performed 6 months after Stem cell therapy showing improved metabolism in the areas of basal ganglia, mesial temporal structures and cerebellum as outlined by the circles

Adverse Events / Complications:

a) None of the children had neurological worsening or clinical deterioration.

b) There are some minor post procedure effects, such as headache or nausea, which occur in some patients but which settles in 2-3 days. This is part of the procedure of injecting into the spinal fluid. Its called a spinal headache.

c) Some temporary increase in hyperactivity may occur which settles over a period of time.

d) Epilepsy is the only significant adverse event that can occur. However we have noticed that it does not occur in patients who are already on anticonvulsant medications and also does not occur in those children who have a normal EEG before the treatment. However in those children whose EEG; show abnormal epileptic activity and who are not on anti epileptic medications seizures can occur. To prevent this it is recommended that an EEG be done before the stem cell therapy. If it is normal then there is nothing to worry about. If it is abnormal then it is recommended that antiepileptic medications be started before the stem cell therapy and be continued for a 6 month period. Those already on antiepileptic drugs should continue these as before and after the stem cell therapy. With this strategy the possibility of seizures or an increase in seizures is almost completely

eliminated. We noticed this in 3 of the 6 children who had abnormal EEGs but were not on medications. However after following the above there has been no incidence of epilepsy in any of the children.

Conclusion :

Based on published literature and our own clinical experience we consider that Stem cell therapy is a safe and effective treatment option for children with Autism. Clinical improvements are seen in over 90% of those treated and include improvements in hyperactivity, communication, emotional responses, social relationships, behavior, speech, attention, eye contact and sensory problems. These clinical improvements are collaborated with objective improvements seen on PET CT Scans of the brain.

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6. Stem Cell Transplantation in Cerebral Palsy

Cerebral palsy (CP) is a non progressive encephalopathy with clinical syndrome of restricted movement and posture with numerous possible etiologies. Its development could be attributed to prenatal, perinatal or post natal factors. Evidence suggests that prenatal factors result in 70-80% of cases of cerebral palsy. Cerebral palsy (CP) is known to affect 2/1000 live-born children. The symptoms of CP vary in terms of severity. The main symptoms include muscle spasticity, muscle weakness, uncontrolled movements, impaired mobility, speech impairment and/or challenges in eating, dressing, bathing, etc depending on the area of the brain affected. Movement dysfunction is often accompanied by visual impairment, hearing loss, osteoporosis, learning disabilities, cognition impairment, behavioral issues and seizures. Risk factors for cerebral palsy include prenatal anemia, improper nutrition, infections, premature delivery, etc. Hypoxia and ischemia are also major risk factors prenatally and during delivery.

The conventional treatments available currently for CP are physical and behavioral therapy, Hyperbaric oxygen therapy (HBOT), Botulinum A toxin injection, surgical treatments, assistive devices, and management of associated conditions.

The prevalence of CP is increasing due to decrease in mortality of low birth weight infants and increase in the rate of CP in these children. Hence, establishing a standard therapeutic approach is the focus of researchers and clinicians all over the world. Although the available treatment options are helpful in managing the symptoms to some extent, none of them repair the damaged brain.

Pathophysiology of brain damage in cerebral palsy

Hypoxic ischemia is the most common cause of damage

Hypoxic ischemia is a common cause of damage to the fetal and neonatal brain leading to cerebral palsy and associated disabilities in children. The neuropathology underlying cerebral palsy mainly includes periventricular leukomalcia (PVL). PVL consists of diffuse injury in deep cerebral white matter, with or without focal necrosis and/or loss of pre-myelinating oligodendrocytes (pre-OLs), astrogliosis and microglial

infiltration. The vulnerability of these cells to damage depends on type of cells and stage of development at which the damage occurs. Oligodendrocytes (OLs) develop through a well-established lineage of OL progenitors to pre OLs to immature OLs to mature OLs. Loss of pre OLs in hypoxic ischemia may lead to deficiency of mature OLs resulting in myelination disturbance which leads to neuronal dysfunctions.

Microglial activation- a secondary effect to ischaemia : adding insult to injury!

The activated microglia secretes various cytokines, such as tumor necrosis factor alpha (TNF-α), interferon gamma (INF-γ), Interleukin -1 beta (IL-1β) and superoxide radicals, exerting a toxic effect on neurons and oligodendrocytes.

Connecting the pathophysiology of cerebral palsy and stem cells:

Stem cells stimulate the repair process by homing to the injured sites of the brain and carrying out regeneration. Injury to the brain at and around the time of birth, leads to the damage of the stem cells in the brain. This leads to loss of the inherent regenerative potential or resources (the neuronal progenitors or stem cell niches in the growing brain) of the brain. Stem cell therapy, hence, restores the lost cells and helps form newer cells and connecting cells. It may also support their survival by introducing other cell types able to restore missing enzymes to an otherwise deficient environment. Stem cells also reduce the levels of harmful chemicals, such as TNF-α, IL-1γ, IL-1β, IL-6 raised due to activation of cells forming a scar tissue in the brain, enhancing the endogenous brain repair. These cells also secrete neurotrophic factors and growth factors such as connective tissue growth factor, fibroblast growth factor 2 and 7, interleukins, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and basic fibroblast growth factor (bFGF) which are responsible for cell multiplication, protection of brain cells and angiogenesis/formation of new blood vessels, retrieving the lost tissue functions.

Recent advances in stem cell therapy provide the hope of developing more effective interventions in treating CP. Research has shown that bone-marrow-derived cells could develop into neural tissue. Woodbury et al. showed that adult rat and human bone marrow stromal cells can be induced to differentiate into neurons.

Various experimental studies have demonstrated that cell transplantation in the CP models lead to survival, homing and differentiation of cells into neurons, oligodendrocytes and astrocytes (support cells).

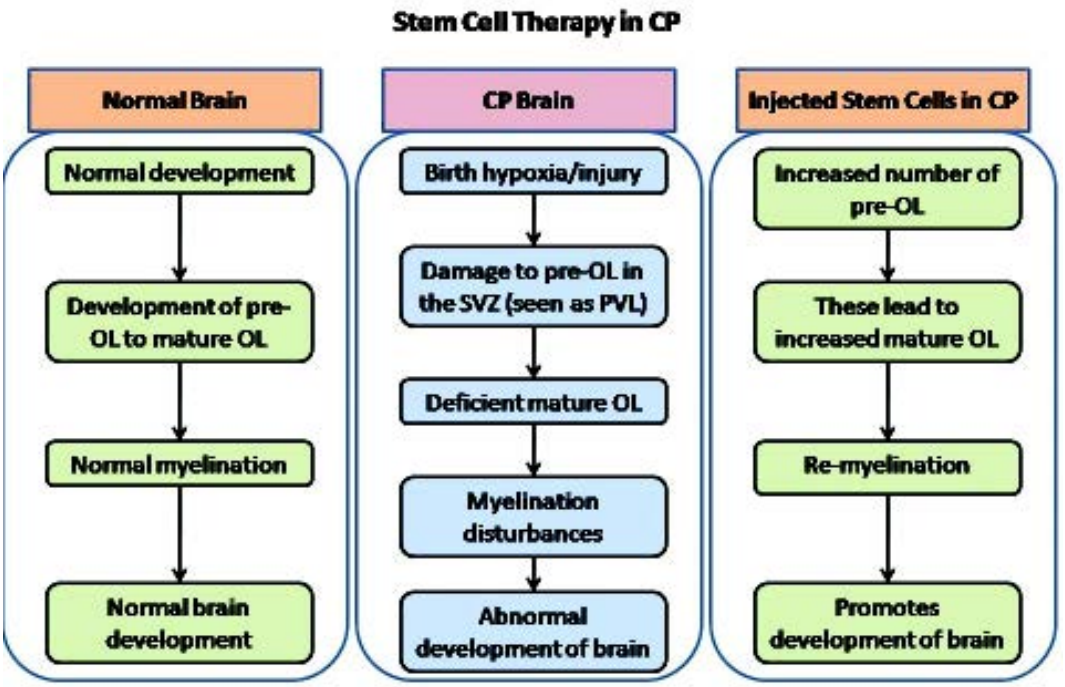
Mueller et al. (2005) demonstrated how human neural stem cells (hNSCs) replace the lost cells in a newborn mouse model of brain damage. Mice received brain parenchymal or intraventricular injections of hNSCs derived from embryonic germ (EG) cells. The stem cells migrated away from the injection site to the site of injury within the striatum, hippocampus, thalamus and white matter tracts and at remote locations in the brain. Subsets of grafted cells expressed neuronal and glial cell markers. It was found that

the complement of striatal neurons in brain-damaged mice was partially restored. Hence, they concluded that human EG cell-derived NSCs can engraft successfully into injured newborn brain, where they can survive and disseminate into the lesioned areas, differentiate into neuronal and glial cells and replace lost neurons.

Summary of current clinical evidence of the role of stem cells in Cerebral Palsy

Over the years, various types of stem cells and cellular elements have been used, via various routes of administration to stimulate neurogenesis in the damaged brain, especially in children. This intervention holds more logical attraction, since adaptive responses would be expected to be permissive in a growing brain.

Seledtsov et al, way back in 2005, carried out a controlled study which included 30 patients with severe forms of cerebral palsy. A cell suspension from immature nervous and haemopoietic tissues was injected into the subarachnoidal space of a recipient through a spinal puncture. One year after the treatment, activity of the major psychomotor functions in treated patients considerably surpassed the normal. Their findings suggested that cell therapy was an effective, safe and immunologically justified method of therapy for patients with cerebral palsy.



Similar route of stem cell transplantation (intrathecal) in 125 severely brain injured patients with cerebral palsy is a study done at the centre of immunotherapy, reported neurological improvement in 85% of the cases.

Recent work in the field of stem cells is seeing an increasing trend towards the use of either:

a) Allogenic/autologous cord blood derived cells

b) Autologous bone marrow derived cells.

The favoured route of transplantation, is biased towards safety, viz. either intravenous or intrathecal as opposed to direct stereotactic injection into the brain.

Ramirez et al presented their data based on parental observations and completed questionnaires concerning the responses of cerebral palsy children to the umbilical cord blood stem cells. Eight children (3-12 years of age) diagnosed with cerebral palsy underwent transplants with 1.5 million stem/progenitor cells (CD34+ and CD133+) which were purified and expanded from the American Association of Blood Banks (AABB)-certified human umbilical cord blood. According to parent tendered observational reports, none of the children had graft versus host reactions. All the eight children showed some improvement in mobility and/or cognitive function. Six children (75%) showed improvement in muscle tone, hip movement, leg movement, rolling to the side, sitting and standing balance by the end of six months.

The results demonstrated by Sharma et al agree with the above trend. Autologous mononuclear cells administered intrathecally in 20 CP children, with a mean follow up of 15 months ± 1 month, showed improvement in 85% cases. Improvement in muscle tone (15/20) and speech (10/20) as well as significant reduction in seizure frequency (2/20) patients and dystonic movements, improved limb strength (11/ 20) patients were observed. On FIM scale, 3 of them showed improved scores. Lee et al conducted a pilot study, wherein autologous cord blood (CB) cells were infused intravenously in 20 children with cerebral palsy. Out of them 11 were quadriplegics, 6 hemiplegics and 3 diplegics. On follow up after 6 months, diverse neurological domains improved in 5 patients (25%) as assessed with developmental evaluation tools as well as by fractional anisotropy values in brain MRI-DTI. The neurologic improvement occurred significantly in patients with diplegia or hemiplegia rather than quadriplegia.

Li et al carried out intravenous autologous BMSCs transplantation in an 11 year old CP boy. They carried out four infusions. Six months after the treatment he could walk better and his vision had significantly improved. These findings were further supported by electrophysiological examinations.

Hassan et al carried out a study on fifty two Egyptian patients with cerebral palsy who were divided into: group I (26 patients who underwent stem cell transplantation) and group II (26 patients who did not undergo stem cell transplantation). These

patients underwent intrathecal autologous bone marrow derived stem cell transplantation. On follow up of 1 year, statistically significant improvements were noticed in motor, independence and communication skills using Boyd's developmental progress scale and 100 points scale.

In a Chinese study, Yang et al carried out UC-MSC transplantation by intravenous infusion and intrathecal injections in twenty-five patients with CP. Six months after the transplantation, 22 of 25 cases subjectively had improvement in motor function. All patients objectively had improvement in scores of GMFM and BSS post-treatment.

Chen et al, assessed neural stem cell-like (NSC-like) cells derived from autologous marrow mesenchymal stem cells as a novel treatment for patients with moderate-to-severe cerebral palsy. 60 cerebral palsy patients were included in this study. (30 control group, 30 treatment group)

On a 6 month follow up, the GMFM scores in the transplantation group were significantly higher. All the 60 patients survived, and none of the patients experienced serious adverse events or complications. They concluded, that NSC-like cells are safe and effective for the treatment of motor deficits related to cerebral palsy.

Luan et al, treated 45 CP children by injecting neural progenitor cells (NPCs) derived from fetal tissue into the lateral ventricle. After 1 year, the developmental level in gross motor, fine motor, and cognition of the treatment group was significantly higher compared to the control group. No delayed complications of this therapy were noted.

Min et al, administered allogeneic umbilical cord blood (UCB) cells potentiated with recombinant human erythropoietin (rhEPO) in children with CP. In total, 96 subjects completed the study. Compared with the EPO (n = 33) and Control (n = 32) groups, the pUCB (n = 31) group had significantly higher scores on the GMPM and BSID-II Mental and Motor scales at 6 months. DTI revealed significant correlations between the GMPM increment and changes in fractional anisotropy in the pUCB group. 18F-FDG-PET/CT showed differential activation and deactivation patterns between the three groups. UCB cell treatment ameliorated motor and cognitive dysfunction in children with CP accompanied by structural and metabolic changes in the brain.

Chernykh et al, evaluated the safety and efficacy of autologous M2 macrophages in 21 children with severe CP. Mean dose of 0.8?×?10(6)/kg M2 cells were injected via Intradural injection. No cases of mortality, psychomotor worsening, exacerbation of seizures, and long-term comorbidities, including tumors, were observed during a 5-year follow-up. After 3 months, GMFM score increased from 13.7?±?7.8 to 58.6?±?14.6, PDMS-FM score improved from 0.76?±?0.42 to 5.05?±?0.97, and the Ashworth score decreased from 3.8?±?0.21 to 3.3?±?0.24. Along with gross and fine motor function enhancement, an improvement of cognitive activity (from 1.62?±?0.41 to 4.05?±?0.64, according to questionnaire assessment) and reduction of seizure syndrome were registered as well. The neurological improvements did not diminish during the 5-year follow-up period.

Mancías-Guerra C et al conducted a phase I open-label clinical trial to assess the safety of autologous bone marrow-derived total nucleated cell (TNC) intrathecal and intravenous injection after stimulation with granulocyte colony-stimulating factor, in 18 patients with CP. A median of 13.12 × 10(8) TNCs (range, 4.83-53.87) including 10.02 × 10(6) CD34+ cells (range, 1.02-29.9) in a volume of 7 mL (range, 4-10.5) was infused intrathecally. The remaining cells from the bone marrow aspirate were administered intravenously; 6.01 × 10(8) TNCs (range, 1.36-17.85), with 3.39 × 10(6) cells being CD34+. Early adverse effects included headache, vomiting, fever and stiff neck occurred in three patients. No serious complications were documented. An overall 4.7-month increase in developmental age according to the Battelle Developmental Inventory, including all areas of evaluation, was observed (±SD 2.63). No MRI changes at 6 months of follow-up were found

Zali et al, evaluated the safety of autologous bone marrow-derived CD133(+) cell intrathecal injection in 12 Children with cerebral palsy. A significant improvement was observed 6 months after cell transplantation versus baseline according to GMFM, GMFCS, FIM+FAM, Ashworth Scale, and BBS outcomes.

Wang et al, studied the impact of umbilical cord-derived mesenchymal stromal cell (UCMSC) transplantation on the motor functions of identical twins with cerebral palsy (CP) and analyzed the correlation between its efficacy and hereditary factors. Eight pairs (16 individuals) of identical twins with CP were recruited and received allogenic UCMSC transplantation by means of subarachnoid injection. Significant improvements were seen in the GMFM at the end of the 1st and 6th months after the therapy compared with that before the therapy.

A recent study was also conducted to evaluate the efficacy and safety of human embryonic stem cell (hESC) therapy in patients with CP. Ninety one patients were included and all received hESC therapy in T1, 66 patients returned for T2, 38 patients for T3, and 15 patients for T4. Overall, 30.2% patients achieved GMFCS-E & R score 1 during the study with different number of patients achieving GMFCS score 1 by the end of each treatment phase (T1: 6 [6.6%]; T2: 7 [10.6%]; T3: 11 [28.9%]; and T4: 5 [33.3%]). All patients in up to 2 yr (n?=?10), 2-4 yr (n?=?10), 4-6 yr (n?=?9), and 6-12 yr (n?=?8) age groups except one of the 5 patients in the age group of 12-18 yr transitioned from GMFCS-E & R score 5 to lower scores by end of T1. Most patients transitioned to GMFCS-E & R score 2 (n?=?34) from higher scores by end of T2. Eleven patients achieved GMFCS-E & R score 1 by end of T3. No serious adverse events were observed.

Clinical results of Stem Cell Therapy at NeuroGen BSI:

At Neurogen BSI, we have treated over 300 CP cases. In an analysis of 193 patients with maximum follow up of 5 years, stem cell therapy was found to be safe and effective in 91.71% of the patients. Improvements were in seen in symptoms like oromotor/speech, balance, trunk activity, upper limb activity, lower limb activity, muscle tone, ambulation and activities of Daily Living.

Out of the 193 patients, 13.47% showed significant improvements, 47.15% of patients showed moderate improvements and 31.08 % showed mild improvements.

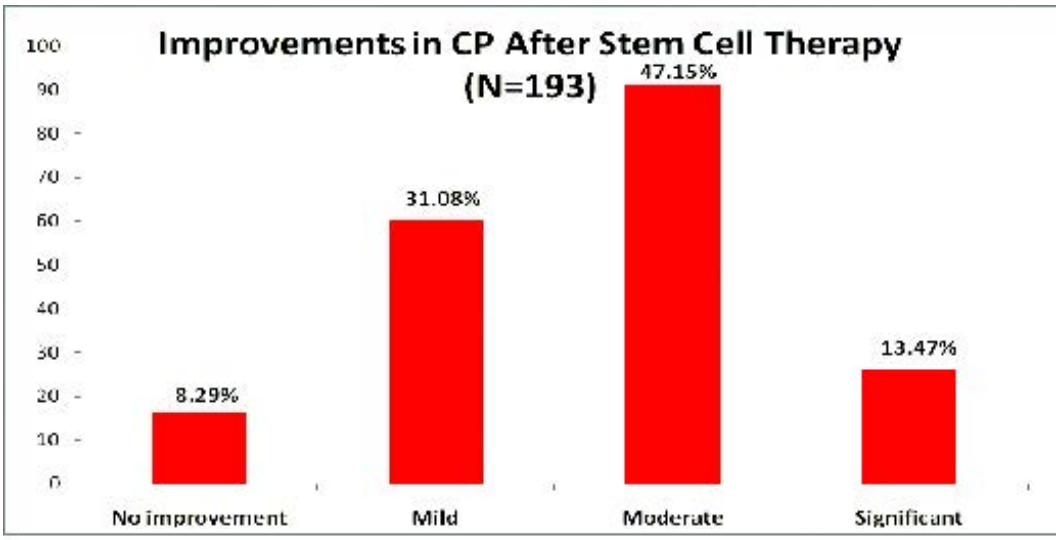


Figure 1: Graph representing improvements in Cerebral Palsy after stem cell therapy

Progressive improvements seen after stem cell therapy :

After stem cell therapy, immediate improvements were observed within a week in muscle tone, involuntary movements of the limbs, head control and drooling.

From 1 week to 3 months of intervention, improvement in voluntary control resulted in initiation of opening and closing of fingers and improved midline orientation. As the tone of the hypertonic muscles reduced, trunk control, sitting balance and gross motor movements of limbs also improved.. Many patients also showed improved oromotor activities.

From 3 months to 6 months of intervention, eye hand coordination was better due to improved head control and gross motor skills. Sitting balance improved further along with initiation of weight shifting while sitting. Maintaining upright position, dynamic trunk balance and weight bearing on legs improved. Initiation of steps while walking with support and/or assistive devices was also seen in patients who were not able to walk previously. Muscle tone and motor control and independence for daily activities improved.

Cognitive skills and understanding improved progressively from one week to six months. Cooperation during therapy sessions was better due to which it was easier for the caregiver to handle the patient.. Cognition improved with respect to awareness,

understanding, response time and command following.

Some patients were followed up even after six months, 1 year, 2 years, 4 years. These patients showed improvement in fine motor activities. Equilibrium reactions developed along with increase in dynamic balance. Speech started improving in the aspects of clarity, fluency and intelligibility. Individuals with monosyllable speech developed bisyllable speech, bisyllable improved to word formation and words improved to phrases. There was also gradual improvement in ambulatory status.

Objective improvements on PET CT Scan Brain:

PET-CT scan was done to monitor improvements in the metabolic activity of the brain. The PET scan measures the 18-FDG uptake which correlates to the glucose metabolism in the brain. The damaged areas of the brain in CP are functioning low and any improvement in the functioning of these areas will lead to an increase in the FDG uptake. Previous studies in patients with CP have shown reduced metabolic activity in various areas of the brain depending on the individual case. A comparative scan performed before and after cell therapy demonstrated increased metabolic activity in frontal, parietal, temporal, basal ganglia, thalamus and cerebellar areas of the brain. The clinical and functional improvements correlated to the changes observed in the PET scan. Improved metabolism in frontal and temporal areas led to improvement in speech and memory. Improvement in basal ganglia led to improved voluntary movement and coordination. Improvement in parietal area led to improved awareness and improvement in cerebellum led to improved balance and fine motor coordination.

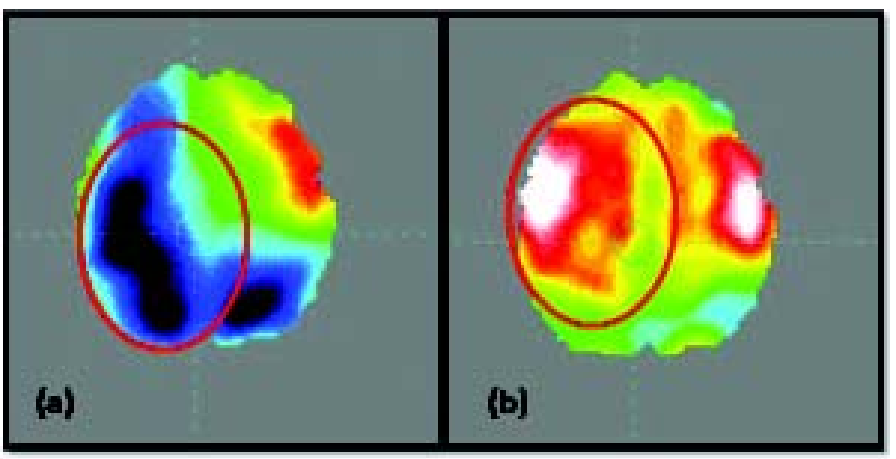


Figure 2: (a) PET CT Scan brain of a cerebral palsy child before Stem Cell Treatment showing blue/black areas representing hypometabolism due to neural damage. (b) PET CT Scan brain of the same child 6 months after Stem Cell Treatment showing reduced blue/ black areas suggesting neurorepair and a positive response to the treatment.

Conclusion

Published international clinical work as well as our own experience clearly establishes the safety and efficacy of stem cell therapy for cerebral palsy. Improvements are seen in over 90% of the patients treated and these include oromotor , speech, balance , trunk activity, upper limb activity, lower limb activity, muscle tone, ambulation and activities of daily living. These clinical improvements are reflected in the objective improvements seen on the PET CT Scans of the brain done before and after the stem cell therapy.

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7. Stem Cell Therapy in Intellectual Disability

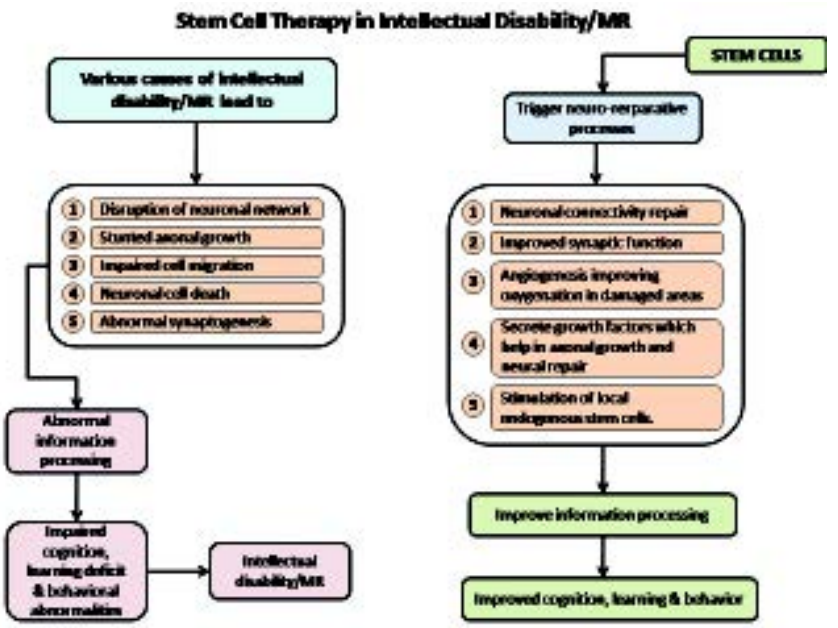
Intellectual disability (ID) in children is a heterogeneous group of disorders with varied causes. It is a developmental disability which first appears in children under the age of 18. It is defined as a level of intellectual functioning (as measured by standard intelligence tests) that is well below average and results in significant limitations in the person's daily living skills (adaptive functioning). Such skills include the ability to produce and understand language (communication); home-living skills; use of community resources; health, safety, leisure, self-care, and social skills; self-direction; functional academic skills (reading, writing, and arithmetic); and job-related skills. In Intellectual disability, the IQ score is below 70-75. About 30% of ID cases are caused by hereditary factors. Intellectual disability may be caused by an inherited genetic abnormality, such as fragile X syndrome. Fragile X, a defect in the chromosome that determines sex, is the most common inherited cause of Intellectual disability. Single-gene defects such as phenylketonuria (PKU) and other inborn errors of metabolism may also cause Intellectual disability if they are not discovered and treated early. An accident or mutation in genetic development may also cause retardation.

The common symptoms presented by children with Intellectual disability are impairment in adaptive functioning, continued infant-like behavior, failure to meet developmental milestones such as sitting, crawling, walking, or talking, in a timely manner, decreased learning ability and ability to think logically, trouble remembering things, failure to meet the intellectual development markers, inability to meet educational demands at school, lack of curiosity and difficulty in solving problems.

With increasing awareness, the prevalence of intellectual disability has risen considerably. Hence, to find a cure for it is the need of the hour. Currently, there is no treatment available for ID. But with correct support and teaching, most individuals can learn to do their daily activities. Management of the patient depends on the level of the child and the associated conditions such as epilepsy, hyperkinesis, behaviour problem and sensory handicaps. But these strategies do not answer the core neurological problems of ID.

Stem Cell Therapy for Intellectual Disability

In case of intellectual disability, any damage to the brain is a permanent and irreversible damage as the neurons of the brain, once damaged, cannot repair themselves on



their own. The underlying neuropathology of intellectual disability includes neuronal death along with disruption in neuronal networks, cell migration, cell multiplication, axon growth, brain plasticity, synaptogenesis, etc. Studies have shown that major defects are recorded in hippocampus and cerebral cortex areas of the brain which further lead to faulty information processing and consecutively affect the cognition and adaptive behavior.

To reverse the damage caused to the central nervous system, only a neurorestorative therapy like stem cell therapy would be beneficial. As discussed in the previous chapters, stem cells have a unique property of migrating towards the damaged areas on administration. They survive, migrate, proliferate and differentiate into the required cell types. They not only replace the dead cells but also stimulate the endogenous cells and prevent further damage. Their paracrine activities such as secretion of growth factors, angiogenesis, neurogenesis, immunomodulation, decreasing inflammation, etc also help in the repair process. This could help repair the disrupted neuronal networks in ID and hence improve the information processing.

Not many clinical studies have been carried out to study the effect of stem cell therapy in ID. But animal studies have shown that administration of stem cells may support the ability for structural brain repair as well as cognitive improvement in models with damaged brain.

Sharma et al published a case report demonstrating the benefits of stem cell therapy in ID. They administered a 13 year old boy with autologous bone marrow mononuclear cells, intrathecally. As a part of the protocol, he was also put on a personalized rehabilitation program. Follow up was done at 3 months and 6 months. No major adverse events were recorded post intervention. In a period of 6 months, he showed improved eye contact, cognition, learning ability, behavior and ability to perform

activities of daily living. His score on Functional Independence Measure increased from 67 to 76. On comparing the pre and post PET CT scan, improvement in metabolic activity of hippocampus, left amygdala and cerebellum was recorded. These changes correlated to the functional outcome.

At Neurogen Brain Spine Institute, 29 patients with intellectual disability were administered with stem cell therapy. On a mean follow up of 6 months, 93.11% patients showed improvements with 41.3% showing moderate improvements, 34.4% showing mild improvements, 17.24% showing significant improvements. On analyzing symptomatically, it was observed that 81.25% cases showed improvement in toilette training, 66.66% showed improved cognition, 58.33% showed improvement in social inhibition and remote memory, 57.14% showed better understanding of relationships and 40.74% showed improved problem solving.

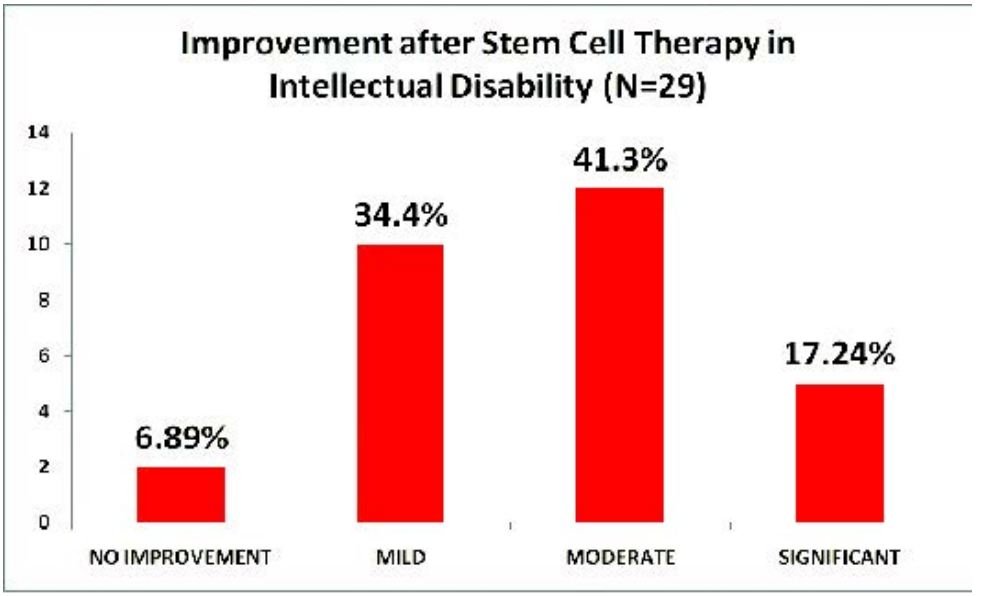
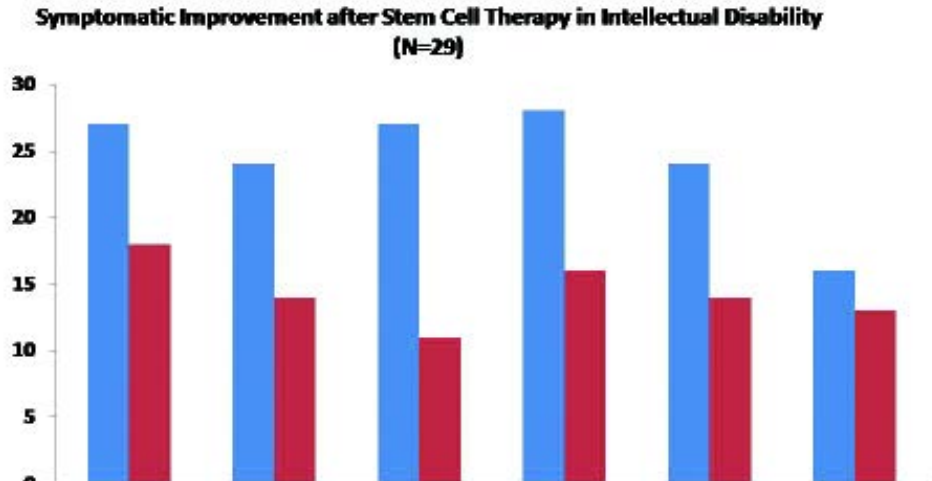


Figure 1: Graph representing improvements in intellectual disability after stem cell therapy



	Cognition	Remote Memory	Problem Solving	Understanding of Relationships	Social Inhibition	Toilette Training
Affected	27	24	27	28	24	16
Improved	18	14	11	16	14	13

Figure 2: Graph representing symptomatic improvements in intellectual disability after stem cell therapy.

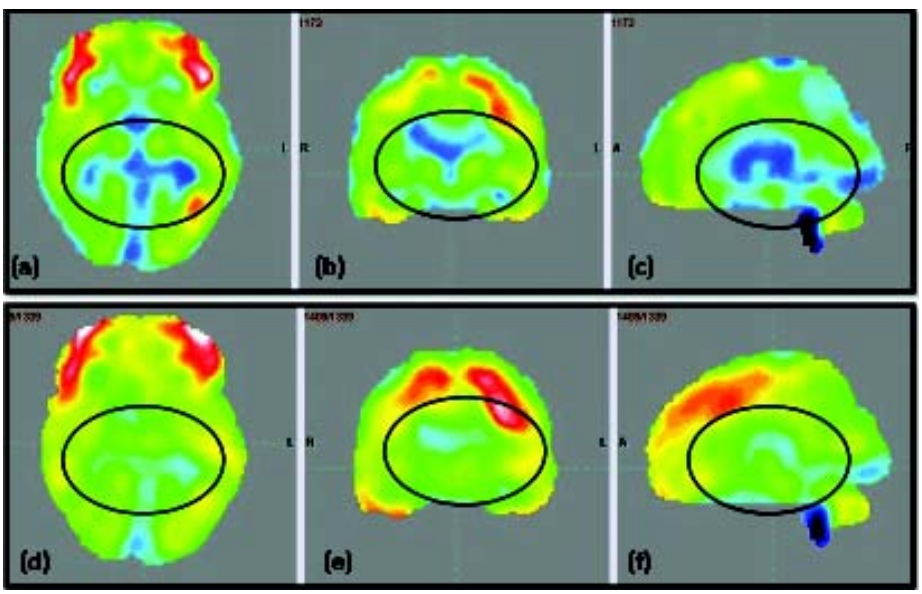


Fig 3: (a), (b), (c) PET CT scan brain of a patient with intellectual disability (mental retardation) before Stem cell therapy showing blue areas with hypometabolism. (d), (e), (f) PET CT scan brain of the same patient performed 6 months after Stem cell therapy showing improvement in metabolic activity involving both hippocampus, left amygdala and left cerebellum denoted by decrease in blue areas.

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8. Stem Cell therapy in Muscular Dystrophy

Muscular dystrophy (MD) is a group of genetic disorders that weaken the muscles. Each type of muscular dystrophy is associated with a distinct genetic mutation. The nature of the gene mutation and location of the chromosome determines the characteristics of the muscular dystrophy and their inheritance. But in general they are characterized by progressive wasting and weakness of the skeletal muscles. Most types of MD are multi-system disorders with manifestations in the heart, endocrine glands, skin, eyes, gastrointestinal and nervous systems.

Muscular dystrophy is broadly classified into nine types including Duchenne, Becker, limb girdle, congenital, facioscapulohumeral, myotonic, oculopharyngeal, distal and Emery-Dreifuss. Out of these Duchenne, Congenital and Emery-Dreifuss muscular dystrophy are commonly observed in children. They are classified based on the gene mutation, age of onset of the symptoms etc.

Duchenne muscular dystrophy (DMD)

DMD is one of the most common childhood forms of muscular dystrophy affecting mainly boys. It is caused due to a mutation in the dystrophin gene, located on the X chromosomes (Xp21) in humans. The protein dystrophin, coded by the dystrophin gene is an important structural component of the muscle providing structural stability to the dystroglycan complex (DGC), located on the cell membrane. Absence of dystrophin allows excess calcium to penetrate the sarcolemma (cell membrane). In a complex cascading system, increased oxidative stress within the cell damages the sarcolemma, and eventually results in the death of the cell. Muscle fibers undergo necrosis and are ultimately replaced with adipose and connective tissue.

The characteristic features of DMD are muscle wasting beginning from the legs and pelvis, then progressing to the shoulder and neck muscles, followed by loss of arm muscles and respiratory muscles. Calf muscle enlargement (pseudohypertrophy) and a positive Gowers' sign are commonly observed. Cardiomyopathy is also common, but the development of congestive heart failure or arrhythmias (irregular heartbeats) is occasional. Affected children usually tire more easily and have less overall strength than their peers.

Common symptoms of DMD are frequent falls, fatigue, weakness of all antigravity muscles, equinnus gait, waddling gait (increased lumbar lordosis), swelling (pseudohypertrophy) of calf muscles.Tightening of achilles tendon and muscles of the thigh impair functionality because the muscle fibers shorten and fibrosis occurs in connective tissue.

Progressive respiratory muscle weakness and/or cardiomyopathy is the cause of mortality in these children. The life span ranges from 17 years to 22 years.

Becker Muscular Dystrophy (BMD)

BMD is a less severe form of Duchenne muscular dystrophy, but with a later, and much slower rate of progression. The genetic defect lies in the same gene/protein (dystrophin), however, there is some amount of protein formed, which makes the severity lesser and progression slower. Noticeable signs of muscular dystrophy also include the lack of pectoral and upper arm muscles, especially when the disease is unnoticed through the early teen years (some men are not diagnosed with BMD until they are in their thirties). Muscle wasting begins in the legs and pelvis (or core), then progresses to the muscles of the shoulders and neck, followed by loss of arm muscles and respiratory muscles. Calf muscle enlargement (pseudohypertrophy) is quite obvious. Cardiomyopathy may occur, but the development of congestive heart failure or arrhythmias (irregular heartbeats) is rare.

Congenital muscular dystrophy (CMD)

Congenital muscular dystrophy is a group of clinically and genetically heterogeneous neuromuscular disorders. It is a slow progressing disorder with onset of symptoms since birth. CMD results from mutations in a variety of different genes, including those encoding the laminin 2 chain, fukutin-related protein. Classification of the CMDs has become increasingly complex, and a wide spectrum of clinical features is now apparent. Patients present at birth, or within the first few months of life, with hypotonia, muscle weakness and often with joint contractures. Serum creatine kinase (CK) levels may also be markedly elevated in some cases. A major distinction between the various forms is the involvement of the central nervous system (CNS) which may include white matter abnormalities, structural changes, mental retardation and involvement of the eyes. Early and severe rigidity of the spine, distal joint laxity, muscle hypertrophy and respiratory insufficiency are also features of note in distinct entities.

Emery- Dreifuss Muscular Dystrophy (EDMD)

Emery-Dreifuss muscular dystrophy (EDMD) is a rare form of dystrophy which is benign in nature. The types are distinguished by their pattern of inheritance: X-linked, autosomal dominant and autosomal recessive. The genes responsible for EDMD encode proteins, emerin and the lamins A and C, which are associated with the nuclear envelope

The onset of the disorder is in the early childhood and its progression is relatively slow. It is characterized by early contractures mostly involving the elbows, ankles, and neck; progressive muscle wasting and weakness beginning in the upper arms and lower legs and progressing to muscles in the shoulders and hips and cardiomyopathy Although the three types have similar signs and symptoms, researchers believe that the features of autosomal dominant Emery-Dreifuss muscular dystrophy are more variable than the other types. A small percentage of people with the autosomal dominant form experience heart problems without any weakness or wasting of skeletal muscles.

Limb Girdle Muscular dystrophy (LGMD),Oculopharyngeal muscular dystrophy (OPMD), Myotonic dystrophy (DM),Facioscapulohumeral muscular dystrophy (FSHD), Distal Muscular dystrophy (DD) are some of the other common types of MD, which though have their routes in childhood, manifest in early or late adulthood.

Diagnosis of Muscular dystrophy

Diagnosis of muscular dystrophy is based upon a clinical assessment (combination of a characteristic clinical presentation), immunohistochemistry tests, muscle biopsy,electrophysiological tests,genetic work up etc.

A typical clinical presentation of slow or late achievements/development of motor milestones, calf pseudohypertrophy and increased level of creatine kinase (CPK) are indicators of high suspicion of muscular dystrophy. An electromyography (EMG) shows electrical activity suggestive of a primary muscle pathology/myopathy.

A muscle biopsy followed by immunohistochemistry or immunoblotting generally confirms muscular dystrophy. It may also be able to indicate the type of MD.

Genetic test (from blood test) confirms the type of muscular dystroph and also demonstrates the various deletions depending on the type of MD such as that of dystrophinopathy, sarcoglycan, dysferlin, etc. The above test, apart from elucidating the nuances of genetic defect, also helps in revealing the possible genetic inheritance pattern.

Conventional treatment

The main aim of the treatment for muscular dystrophy is to control its symptoms and maximize the quality of life of the children making them more independent. Although, there is no permanent cure for muscular dystrophy, physiotherapy, assistive devices such as braces, wheelchair etc, orthopedic management and steroids are currently used for the management of the disorder. These therapies work by strengthening the muscles and increasing strength. They are designed to help prevent or reduce deformities in the joints and the spine and to allow people with muscular dystrophy to remain mobile as long as possible. Prednisone (prednisolone) and deflazacort are the two types of steroids that are mainly used in DMD but their prolonged use can weaken bones and increase fracture risk.

Worldwide scientists, patient and parent groups and pharmaceutical companies, together are working on various molecules and drugs, which could:

a) Facilitate reduction in fibrosis, in the muscles of children and patients with muscular dystrophies

b) Target various antioxidants and scavenging molecules

c) The ultimate horizon/destination - gene therapy and exon skipping. Though, this theoretically could be the answer for genetic disorders, all stakeholders mentioned above, agree that it is possible but needs more research and may take a few years before it becomes a standard therapy.

d) Hence, therapies that can slow the progression of the disease are the focus now!! Therapies that can restore muscle stem cell regeneration are a feasible option. Satellite muscle stem cell regeneration in muscular dystrophy patients and especially in DMD boys is suppressed. This means i) that the boys' muscle cells are weakened and die more quickly than they should, and ii) that they are not replaced adequately. Intermediate therapies, which stimulate muscle regeneration, must be able to address these functions of this disease.

Sacco et al, in their research have quoted "DMD progression, although initiated and driven by dystrophin deficiency, is ultimately a stem cell disease".

Summary of current clinical evidence of the role of various types of stem cells in Muscular Dystrophy in children

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.

In 2012, Sharma et al conducted autologous bone marrow derived mononuclear cell transplantation intrathecally and intramuscularly on 18 year old boy with Duchene muscular dystrophy. After six months of procedure, he showed the significant functional improvements along with improvements in his muscle strength. Clinically, his MRI also showed muscle fiber regeneration with decrease in fatty infiltration.

In 2013, They treated a 9-year-old boy suffering from DMD with serial autologous bone marrow mononuclear cell transplantations followed by multidisciplinary rehabilitation. Brooke-Vignos score was 10 and he was wheelchair bound. Over 36 months, gradual progressive improvement was noticed in muscle strength, ambulation with assistive devices, fine motor movements, Brooke-Vignos score, and functional independence measure score. Nine months after the transplantation, electromyography findings showed development of new normal motor unit potentials of the vastus medialis muscle.

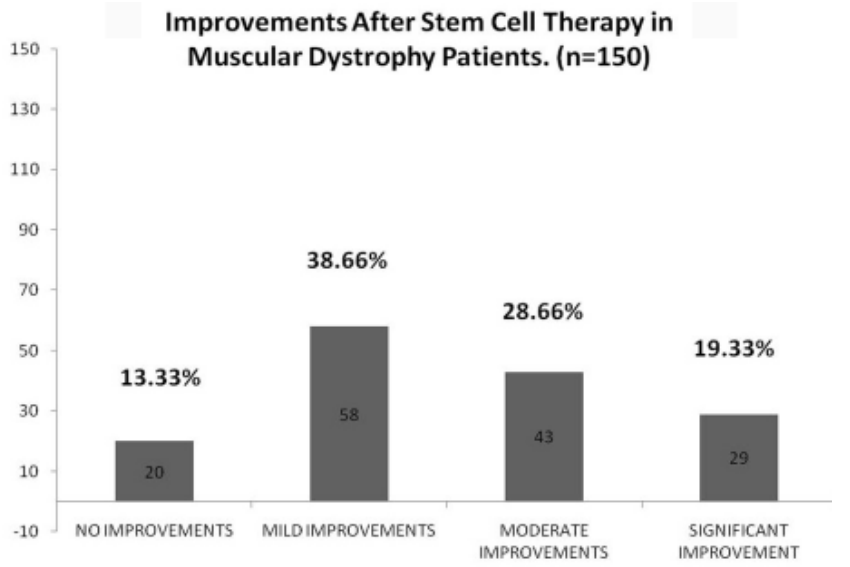

Figure 1: Graph showing improvements in muscular dystrophy patients after stem cell therapy (ref: Sharma et al. Cell Transplantation. 2013 Vol. 22, Supplement 1, pp. S127-S138)

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.

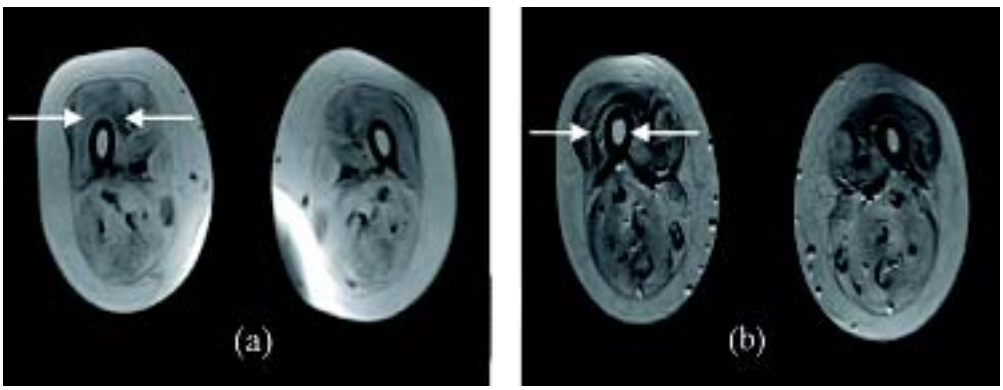

Figure 2: Pre and Post MRI scans. (a) MRI done before stem cell therapy (b) MRI done after stem cell therapy wherein white arrows denote muscle regeneration

At Neurogen Brain and Spine Institute, total of 139 boys detected with DMD were administered autologous bone marrow mononuclear cell intrathecally and intramuscularly. Mean age of the group was 11 years, ranging from 3 to 23 years. Funtional status and muscle strength were assessed using, functional independence measure (FIM) scale, Brooke and Vignos scale and Manual muscle testing. In addition to these outcome measures the time till ambulation was compared with 35 age matched patients that chose not to undergo Stem cell therapy after initial consultation.

Kaplan-Meier Survival Analysis was used to compare the age at loss of ambulation. There was a statistically significant difference in the time till loss of ambulation for children that underwent stem cell therapy from those that did not. The average predicted age at the time till loss of ambulation was 142 months for children that did not undergo stem cell therapy; whereas it was significantly higher,204 months, in children that underwent stem cell therapy. Percentage analysis was performed for the symptomatic improvement in these children. This analysis suggested that majority of the patients had shown improvement or halting of the progression in postural deviations, neck weakness, bed mobility, trunk activity, gross and fine motor function, functional upper limb activity, walking and standing. The pre and post therapy measurements were performed at a median follow up of 6 months.

Outcome measure	**Pre Therapy Mean Score**	**Post Therapy Mean Score**	**Statistical Significance**
Functional Independence Measure	71	76	0.001
Brooke Scale	3.07	3.27	0.076
Vignos Scale	6.5	6.8	0.245

Table 1. Matched pair Wilcoxon Sign Rank test analysis of outcome measures pre and post therapy

Muscle Group	**Pre Therapy Mean Score**	**Post Therapy Mean Score**	**Statistical Significance**
Hip flexors	6	6.69	0.001
Hip Abductors	5.42	6.08	0.001
Hip Adductors	4.21	5	0.001
Knee Flexion	9.1	9.48	0.004
Knee Extension	5.26	5.69	0.003
Shoulder Adduction	5.26	6.02	0.04
Shoulder internal rotation	7.23	7.79	0.001
Biceps	7.96	8.32	0.01
Upper Abdominals	3.8	4.21	0.005

Table 2. Matched pair Wilcoxon Sign Rank test analysis of modified manual muscle testing scale

	Comparison Group	**Intervention Group**	**Test statistics**
Total no. of patients	35	42	-
Percentage of patients currently non- ambulatory	65%	23%	-
Predicted time till loss of Ambulation	142 months	204 months	0.004

Table 3. Kaplan-Meier analysis of time till loss of ambulation for patients with and without stem cell therapy

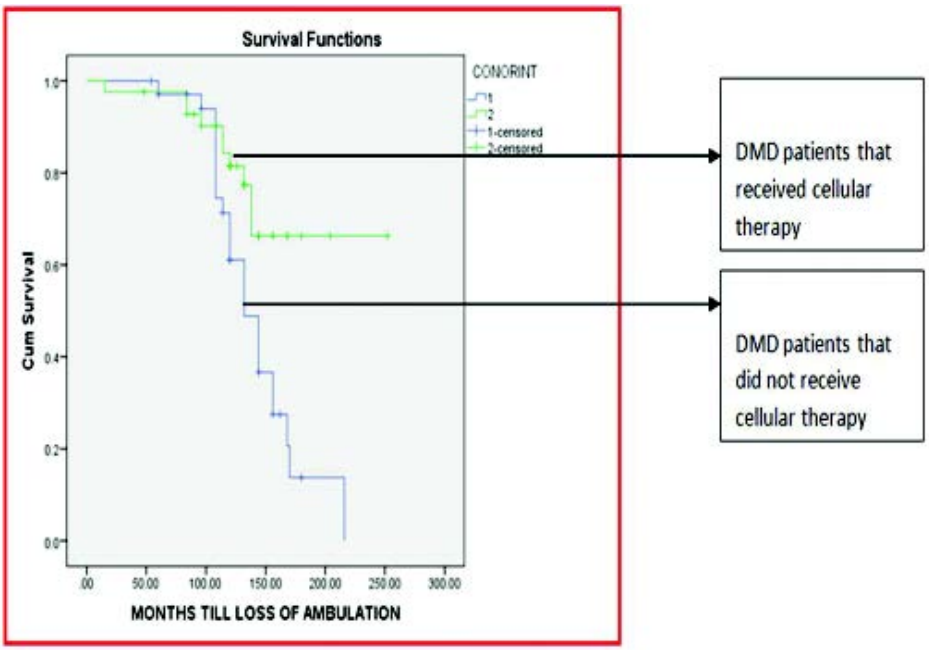

Figure 3: Kaplan-Meier curve analysis of time till loss of ambulation in patients with and without stem cell therapy

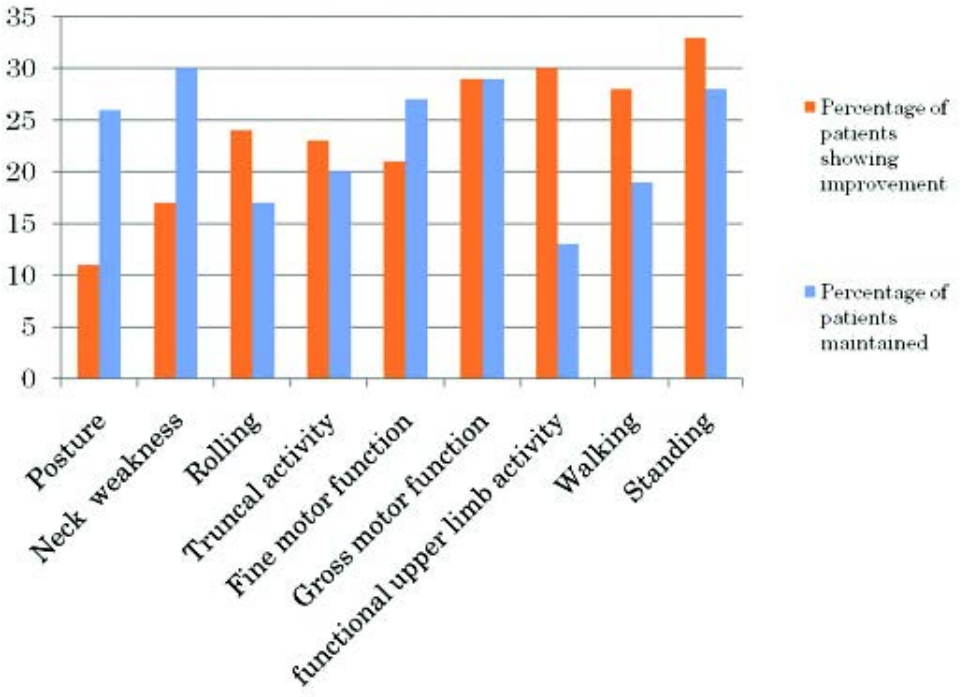

Figure 4: Percentage analysis of symptomatic improvement in the patients with stem cell therapy

Muscle		Percentage of patients with improved muscle strength	Percentage of patients with deteriorated muscle strength	Percentage of patients with muscle strength maintained
Hip	Flexors	29	15	55
	Extensor	37	13	50
	Abduction	32	8	60
	Adduction	41	6	53
Knee	Flexor	29	5	65
	Extensor	29	10	60
Ankle and Foot	Peronei	27	10	63
	Tibialis Anterior	27	10	63
	Tibialis Posterior	26	12	63
	Plantar Flexors	9	3	88
	EHL	14	9	77
	EDL	14	8	78
Shoulder	Deltoids	28	17	55
	Adduction	24	10	65
	Internal Rotation	24	4	72
	External rotation	26	5	69
Elbow	Biceps	19	8	73
	Triceps	26	14	60
Wrist and Fingers	Wrist Flexors	10	4	86
	Wrist Extensors	12	3	86
	Supinators	12	4	85
	Pronators	5	4	91
	Palmar Interossei	12	12	77
	Dorsal Interossei	10	12	78
	Lumbricals	10	5	85
Trunk	Upper abdominals	36	8	56
	Lower abdominals	26	18	56

Table 4. Percentage analysis of modified manual muscle testing scale

Conclusion

Research being done all over the world long with our own large clinical experience shows that stem cell therapy is a viable treatment option for muscular dystrophy and in particular for Duchene muscular dystrophy. Clinical improvements are mostly observed in halting of the progression in postural deviations, neck weakness, bed mobility, trunk activity, gross and fine motor function, functional upper limb activity, walking and standing. Objective Improvements are also seen on muskuloskeletal MRIs of the limbs as well as on EMGs.

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9. Stem Cell Therapy in Spinal Cord Injury

Spinal cord injury is a devastating event that occurs suddenly and whose consequences range from minimal symptomatic pain to a tragic quadriplegia. If cervical spinal damage is severe, quadriplegia results, whereas an injury to the thoracic or lumbar spine leads to paraplegia.

In children, SCI is relatively a rare condition as compared to its prevalence in the adults. Nevertheless, up to 5% of spinal cord injuries occur in children. Diagnosis and treatment of SCI in children is challenging due to their age and behavioral differences. The type of SCI in children are different from that of adults as the anatomy and the mechanics of the spine varies until the child reaches 8-10 yrs of age. The primary causes of injury are birth related injuries, child abuse, falls or motor vehicle collisions. Young children also seem more vulnerable to post infectious or in?ammatory cervical spine issues.

Treatment

The acute management of the child with spinal injury requires rapid restoration of airway, breathing, and circulation. The child should be immobilized supine in a hard collar and on a fracture board. A full spine survey should be performed to eliminate possibilities of fracture and or dislocation. If there are no fractures or dislocation, a CT is performed to rule out an occult fracture, followed by an MRI. Good quality flexion-extension films are also obtained to rule out overt ligamentous instability. Children with severe spinal cord injuries diagnosed within 8 h of injury are administered a 24-hour course of methylprednisolone.

Early surgical intervention is required with definite spinal cord compression and progressive worsening of neurological deficits secondary to a fracture, epidural hematoma or extruded disc causing compression. Delayed or a planned intervention is advised for correction of spinal instability or kyphosis/scoliosis. Reduction of the fracture segments and fixation using spinal instrumentation is then performed according to the type of lesion.

Despite the surgery, many patients are left with neurological deficits, which may recover to some extent with regular rehabilitation.

Summary of current clinical evidence of the role of stem cells in spinal cord injury

Many strategies focusing on neuroprotection or axonal regeneration have been carried out to improve functional recovery after SCI. They work by modifying the injured environment to be beneficial for repair, by replacing lost cells, stimulating and guiding axonal growth or boosting remyelination.

McDonald et al first put forth the concept of use of stem cells for disorders other than haematopoietic. This has paved the way for a whole new area of regenerative medicine in neurological disorders.

Since 1998, this area has burgeoned and innumerable types of stem cells, with equally numerous routes of administering these have been extensively explored. However, before venturing into how stem cell therapy for spinal cord injury has evolved, it is imperative that we understand what is it that we are venturing out to achieve.

This has been very simplistically explained by McDonald as follows:

> ***1) It is not necessary to cure a nervous system injury, and also 2) a disproportionate return of function can result from a small degree of regeneration.***

It is now understood that substantial loss of spinal cord tissue, particularly gray matter, does not preclude near-normal long-tract function. A continuous cross-talk between the laboratory and clinic is mandatory for reaching readily achievable goals that improve quality of life.

Hence, in many of the reports published in various journals all over the world, apart from outcomes of motor and sensory improvement, emphasis has been given on functional improvement and the improvement in the quality of life.

One of the earliest (Rabinovich et al, 2003) stem cell transplants for neurological disorders (spinal cord injury) reported was using minimally manipulated cells from fetal nervous and haemopoietic tissues (gestational age 16-22 weeks). These were implanted subarachnoidally into 15 patients (18-52 years old) suffering from traumatic spinal cord injury (SCI) at cervical or thoracic spine level. Following cell transplantation, six patients showed improvement in their neurological status from A to C grade of SCI, exhibiting incomplete restoration of both motor and sensory function. The status of other five CT-treated patients was reported to be SCI grade B and was characterized by appearance of contracting activity in some muscles and incomplete restoration of sensitivity. The remaining four patients did not exhibit any clinical improvements. No serious complications of CT were noted. The results suggested a clinical relevance of the CT-based approach to treating severe consequences of SCI.

> ***Due to various ethical and medical concerns over embryonic and fetal stem cells, adult stem cells (bone marrow, olfactory ensheathing, etc.) have been tried extensively.***

Olfactory ensheathing cells' are being persistently pursued, though publications of their results have been sporadic.2005, 2008, 2010 and very fresh results (2014) from Prof. Geoffrey Raisman's research, has kept the interest in these cells alive!

In a Chinese language article, Zhou et al, (2004) briefly reported 70 cases following bone-marrow stem cell (BMSC) transplantation. 37 of these were SCI patients. After cell transplantation, the authors reported improved sexual function, sensation and functional improvement in five cases.

Peripheral macrophages have also shown to synthesize nerve growth factor after peripheral nerve damage and eliminate myelin which inhibits neural regrowth. Knoller et al transplanted SCI patients with incubated autologous macrophages. Out of the 8 patients treated in this study, 3 patients showed improvements of motor and sensory functions without any critical complications.

Pioneering and trendsetting paper by Park et al (2005) is one of the earliest reports of intrathecal autologous bone marrow cell transplantation in conjunction with the administration of granulocyte macrophage-colony stimulating factor (GM-CSF). This therapy was carried out in six complete SCI patients. The follow-up periods were from 6 to 18 months, depending on the patients. Sensory and motor recovery was noticed between 3 weeks to 7 months. Four patients showed neurologic improvements in their American Spinal Injury Association Impairment Scale (AIS) grades (from A to C). One patient improved to AIS grade B from A and the last patient remained in AIS grade A. No immediate worsening of neurologic symptoms was found. Radiological changes on MRI were also noticed. Serious complications increasing mortality and morbidity, however, were not found.

Syková et al in two separate publications in the same year (2006) have reported comparative results of intravenous infusion versus intra-arterial infusion of autologous BMMC in SCI. Both the papers reveal that patients receiving intra-arterial transplants show more improvements as compared to those receiving the intravenous transplants. In a novel method, using combination of BM mesenchymal stem cells (MSC) and patient's autoimmune T cells, Moviglia et al (2006) demonstrated the regeneration phenomenon based on the controlled inflammatory activity at the injured site. Both patients showed motor and sensory recovery with no adverse effects.

A series of publications exploring autologous BMSC transplantation either direct injection into the injury site or intrathecal delivery have, from Russia, Brazil, Mexico, Korea, China, India have come out in the last 10 years. These studies mainly address the safety aspects of autologous stem cells being delivered locally, so that the blood brain barrier can be bypassed, perhaps yielding more efficacious results.

Since, direct injection into the spinal cord is a complex process due to the formation of adhesions around the spinal cord as well as shriveling of the cord post injury, injecting BMSCs into CSF through the lumbar puncture, could be a more safe and efficacious procedure.

In 2008, H. Deda et al used autologous bone marrow derived hematopoietic progenitor stem cells to treat 9 patients with chronic complete SCI. Post transplantation all patients' movements and sensations were improved. All patients showed improved ASIA grade.

Another interesting study, by Geffner et al employed the strategy of administering bone marrow stem cells (BMSCs) via multiple routes: directly into the spinal cord, directly into the spinal canal, and intravenous. Comprehensive evaluations demonstrated improvements in ASIA, Barthel (quality of life), Frankel, and Ashworth scoring. Significant changes in bladder function were observed following BMSCs administration.

In 2009, Cristante et al. reported the use of peripheral stem cell delivered intra-arterially in 39 patients of chronic SCI. SSEP evaluation after 30 months of cell transplantation showed improved latency in 66.7% of patient's evaluation.

Pal et al. reported 30 patients with subacute or chronic SCI who received autologous BMSCs intrathecally, and only incomplete SCI patients (16.7%) were seen to have improved functionally without neurological or electrophysiological improvements. While another large-scale clinical trial in India (Kumar et al, 2009), consisting of 297 patients with chronic SCI, treated similarly, reported neurological improvements (32.6%) after a follow up of 3 months.

The proof of concept, of intrathecal stem cells reaching the site of injury came from, Callera et al who carried out a study wherein 10 patients received their own CD34+ cells labeled with nanoparticles via lumbar puncture and 6 patients received magnetic beads without stem cells. On follow up the CSF was assessed for presence of cellular components. MRI done 20 and 35 days after transplantation showed that the magnetically labeled CD34+ cells were visible at the lesion site in 5 patients out of 10. These signals were not visible in the control group.

The advent of 2010 has seen the emergence of newer sources of adult stem cells, mesenchymal stem cells, re-emergence of olfactory ensheathing cells and a combination of stem cells with various drugs.

T. E Ichim et al reported intrathecal administration of allogeneic umbilical cord blood ex-vivo expanded CD34 and umbilical cord matrix Mesenchymal Stem Cells, performed at 5 months, 8 months, and 14 months after spinal cord injury. Cell administration was found to be well tolerated with no adverse effects. Neuropathic pain subsided from intermittent 10/10 to once a week 3/10 VAS. Recovery of muscle, bowel and sexual function was noted, along with a decrease in ASIA score to "D".

O.S Abdelaziz presented a trial of 30 patients having chronic traumatic dorsal spinal cord injury in which 20 patients were administered autologous adult bone marrow mesenchymal stem cell through open surgical intraparenchymal and intralesional injection into the site of cord injury. The treatment was followed by monthly intrathecal injection of stem cells through lumbar or cisternal punctures. Clinical improvement

was observed in 6 out of 20 patients. This study reports that short duration of injury and small cord lesions correlated with good outcome.

Lima et al. carried out a clinical trial in Portugal where in 20 patients who sustained a traumatic SCI underwent OECs transplantation. They found some neurological, functional, electrophysiological and urodynamic improvements in all the patients. In a larger study, Huang et al transplanted 108 SCI patients with OECs. They were divided into group A (n = 79) who were given sufficient rehabilitation and group B (n = 29) with insufficient rehabilitation. On follow up, these patients showed changes in ASIA scale, walking ability, sexual functions. Comparing group A with group B, the increased scores in terms of motor, light touch, and pin prick were remarkably different. 29 out of 31 showed improvement in EMG examinations while 28 showed improvement in PVSEP

Saberi et al enrolled 33 SCI cases to study the safety of intramedullary Schwann cell transplantation. After a 2 year follow up, there were no tumor formations or other adverse events recorded. Similarly in China, Zhou et al injected 6 SCI patients with Schwann cells. On follow-up motor and sensory functions of all the patients improved with improvement in ASIA and FIM. Apart from this, there was improvement in spasticity and bladder bowel function was also observed.

In 2011, Ra et al studied 8 SCI patients who underwent intravenous administration of autologous adipose tissue-derived mesenchymal stem cells and found that hAdMSCs were safe and did not induce tumor development.

In 2012, Park et al carried out a study on 10 SCI patients who underwent intramedullary direct MSCs transplantation into injured spinal cords. 6 of the 10 patients showed motor power improvement of the upper extremities at 6-month follow-up, 3 showed gradual improvements in activities of daily living, and changes on magnetic resonance imaging such as decreases in cavity size and the appearance of fiber-like low signal intensity streaks. They also showed electrophysiological improvement.

Frolov et al injected 20 cases of cervical SCI with autologous hematopoietic stem cells. After 1 year, improved motor and somatosensory evoked potentials were recorded.

Jiang PC et al, enrolled 20 SCI patients in a clinical trial to study the effect of autologous bone marrow-derived mesenchymal stem cell transplantation. Analysis of subsequent treatment results indicated significant improvements in sensory, motor and autonomic nerve function as assessed by the American Spinal Injury Association's impairment scale. Thirty days after transplantation, a total of 15 patients (75%) demonstrated improvement, including four of the eight patients (50%) with grade A SCI, three of the four patients (75%) with grade B injury and all eight patients (100%) with grade C injury.

Bryukhovetskiy AS et al, evaluated the short and long-term effects of the hematopoietic cell therapy in 202 cases of spinal cord injury. Post intervention, the restoration of

neurologic deficit was proved stable and evident in 57.4% of the cases. In 42.6% cases no neurologic improvement was observed. In 50% of the cases the motor restoration began after the first transplantation, which was confirmed in average by 9.9 points improvement in neurologic impairment as compared to the baseline ($P < 0.05$). Repair of the urinary system was observed in 47.7% of the cases. The sensitivity improved from baseline 124.3 points to 138.4 after the first and to 153.5 points after the second transplantations of HSCs and HPs ($P < 0.05$, between the stages of research). The evaluation with ASIA index demonstrated regress of neurologic symptoms in 23 cases. The number of the patients with the signs of locomotive repair was 56.9%. No life threatening Jarocha et al, administered a patient with total SCI at the Th2-3 level with BMNC and MSC transplantations followed with intensive neurorehabilitation treatment. The ASIA score improved from A to C/D (from 112 to 231 points). The sensation level expanded from Th1 to L3-4, and the patient's ability to control the body trunk was fully restored. Bladder filling sensation, bladder control, and anal sensation were also restored. Muscle strength in the left lower extremities improved from plegia to deep paresis (1 on the Lovett scale). The patient's ability to move lower extremities against gravity supported by the movements in quadriceps was restored. The patient gained the ability to stand in a standing frame and was able to walk with the support of hip and knee ortheses. Magnetic resonance imaging (MRI) revealed that at the Th2/Th3 level, where the hemorrhagic necrosis was initially observed, small tissue structures appeared. These results suggested that repeated intrathecal infusions of MSCs might have the potential to produce clinically meaningful improvements for SCI patients.

Al-Zoubi et al, studied the effect of autologous, purified CD34(+) and CD133(+) stem cells in 19 patients with chronic complete spinal cord injuries during a 5-year follow-up period. Purified SCs were directly transplanted into the SCI site. Patients were then monitored and followed for up to 5 years. Ten patients (53%) showed no improvement after 42-60 months (ASIA-A), while seven patients (37%) demonstrated segmental sensory improvement (ASIA-B), and the remaining two patients (10%) had motor improvement (ASIA-C).

Cheng et al, randomly divided 34 cases of thoracolumbar spinal cord injury into three groups: the stem cell transplantation group was given CT-guided CMSC transplantation twice; the rehabilitation group received rehabilitation therapy; and the blank control group did not receive any specific treatment. Seven of the ten patients in the UCMSC group had significant and stable improvement in movement, self-care ability, and muscular tension; five of the fourteen patients (36%) in the rehabilitation group also had certain improvement in these aspects. Urodynamic examination demonstrated that patients in the UCMSC group exhibited an increase in maximum urinary flow rate and maximum bladder capacity, as well as a decrease in residue urine volume and maximum detrusor pressure. The rehabilitation group exhibited decreased maximum bladder capacity, but no perceptible change in maximum urinary flow rate, residue urine volume or maximum detrusor pressure. The study proved that UCMSC transplantation can effectively improve neurological functional recovery

after spinal cord injury, and its efficacy is superior to that of rehabilitation therapy and self-healing.

Hammadi et al, conducted a study on 277 patients suffering from spinal cord injury who underwent intrathecal transplantation of peripheral stem cells. The cells were harvested from the peripheral blood after a treatment with G-CSF and then concentrated to 4~ 6 ml. 43% of the patients improved; ASIA score shifted from A to B in 88 and from A to C in 32. The best results were achieved in patients treated within one year from the injury.

Clinical results of Stem Cell Therapy at NeuroGen BSI:

Sharma et al administered 110 thoracolumbar SCI patients with autologous bone marrow derived mononuclear cells, intrathecally. On a mean follow up of 2 years ± 1 month, overall improvement was seen in 91% of patients, including reduction in spasticity, partial sensory recovery, and improvement in trunk control, postural hypotension, bladder management, mobility, activities of daily living, and functional independence. A statistically significant association of these symptomatic improvements with the cell therapy intervention was established. Some patients showed a shift on the ASIA scale and changes in electrophysiological studies or functional magnetic resonance imaging. No major side effects were noted.

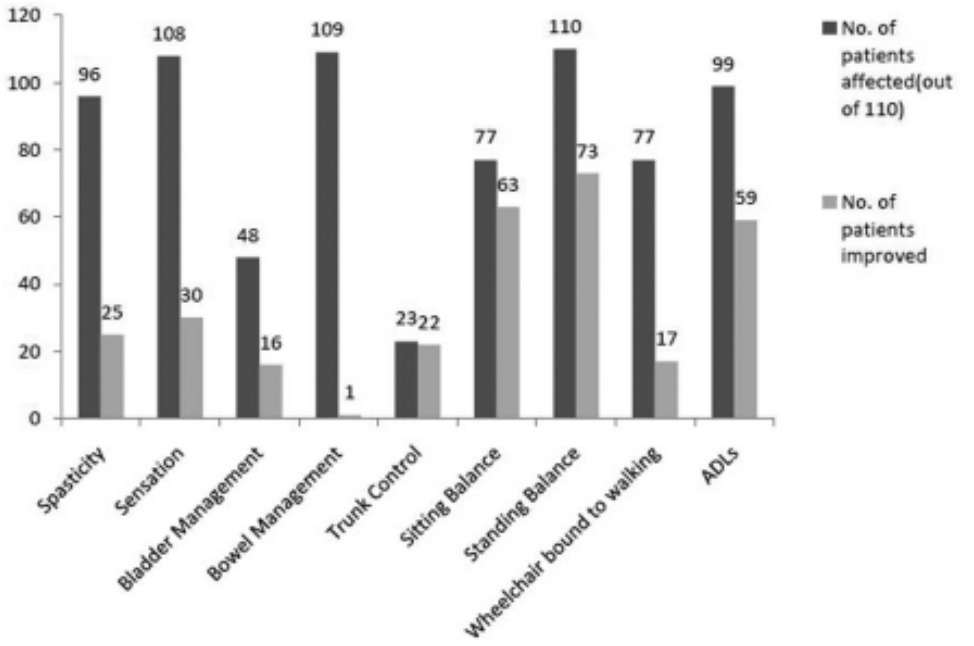

Figure 1: Graph representing improvements in thoracolumbar SCI after stem cell therapy (ref: Sharma et al, Journal of Neurorestoratology. 2013;1:13-22)

In another study, they carried out a detailed analysis of 50 chronic cervical SCI patients who underwent intrathecal administration of autologous bone marrow mononuclear cells followed by neurorehabilitation. On a mean follow up of 2 years ±1 month, 37 out of 50 (74%) showed improvements. Sensation recovery was observed in 26% cases, improved trunk control in 22.4%, spasticity reduction in 20% and bladder sensation recovery in 14.2%. All the 50 cases had improvement in postural hypotension. 12.24% wheelchair bound patients started walking with assistance. Functionally, 20.4% patients showed improved ADLs and 48% showed a positive. No major side effects were noted in the duration of 2 years in both the studies. A better outcome was observed in thoracolumbar injury as compared to the cervical injury suggesting that the level of SCI greatly influences the recovery of the patient. Both studies demonstrated statistically significant clinical and functional outcome.

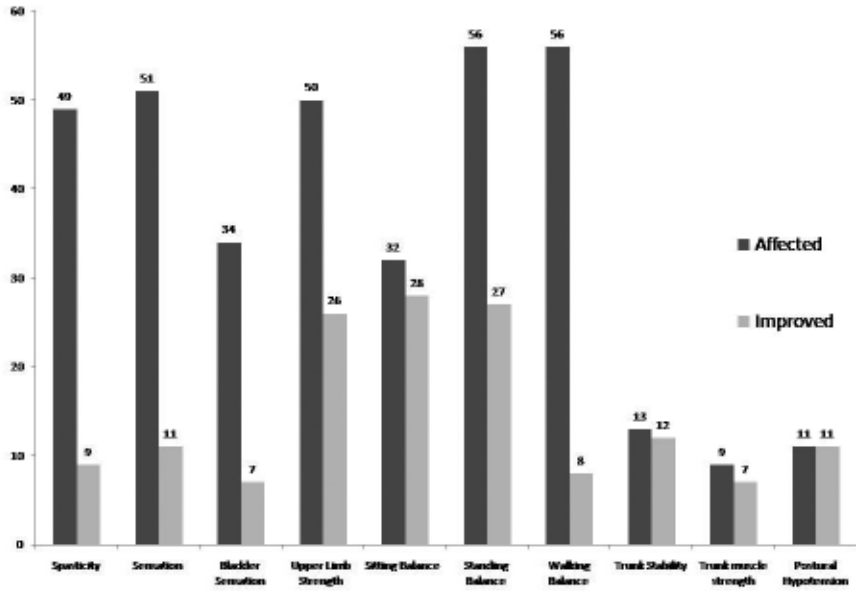

Figure 2: Graph representing improvements in cervical SCI after stem cell therapy. Ref: Sharma et al, J Neurol Disord 2013; 1: 138.

At Neurogen Brain and Spine institute, we analyzed 165 patients with chronic thoracic spinal cord injury to study the effect of stem cell therapy. Changes were recorded in symptoms like muscle tone, lower limb activity, sensory changes, bowel/bladder function, trunk activity, balance, standing, ambulation and activities of daily living. Analysis revealed that out of 165, 94.54% patients showed improvements while 5.45% of showed no improvements in any of the symptoms. Mild improvements were observed in 13.93% of patients, moderate in 55.75% of patients, whereas, 24.84% of patients showed significant improvements

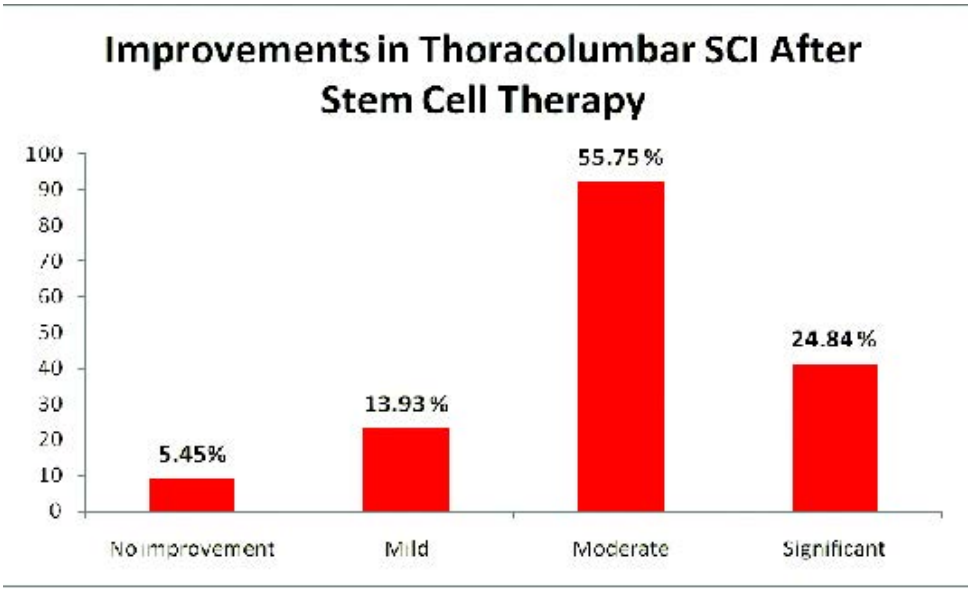

Figure 3: Improvements seen in thoracolumbar SCI after intrathecal administration of autologous BMMNCs.

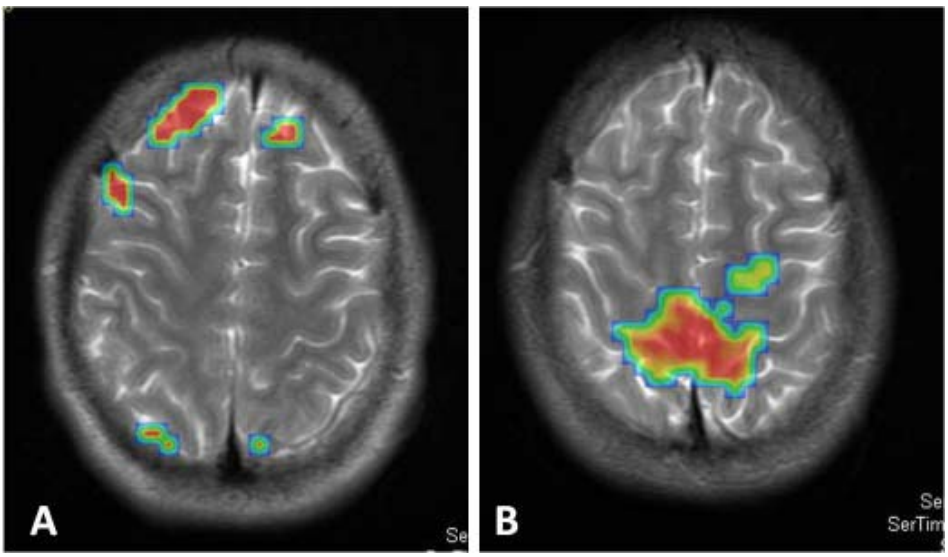

Figure 4: fMRI imaging shows new areas of activation in the brain after stem cell therapy.

Cervical Spinal Cord Injury:

70 patients with diagnosis of cervical spinal cord injury were included in the analysis. Symptomatic analysis was done for the common symptoms observed in these patients and was graded as no change, mild moderate and significant improvements. The symptoms included were muscle tone, upper limb activity, lower limb activity, sensory

changes, bowel/bladder function, trunk activity, balance, standing, ambulation and activities of daily living. Analysis revealed that out of 70 patients, 97.14% patients showed improvements while 2.86% did not show any improvements. Mild improvements were observed in 24.28% of patients, moderate in 54.28% of patients, whereas, 18.57% of patients showed significant improvements.

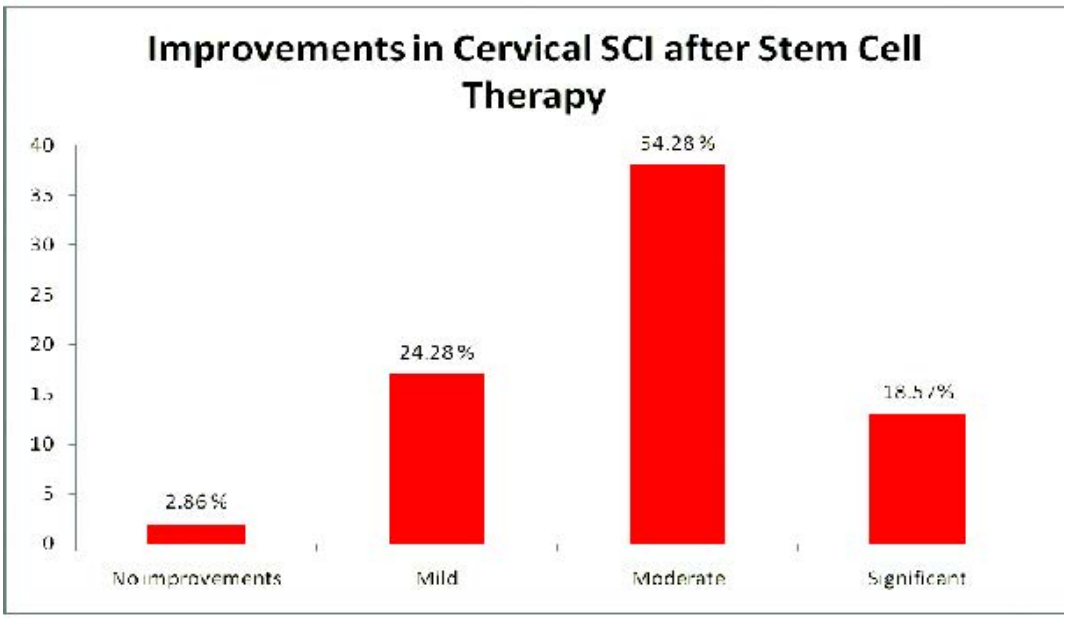

Figure 5: Improvements seen in cervical SCI after intrathecal administration of autologous BMMNCs.

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10. What are the Complications of Stem Cell Therapy?

Stem cell therapy is an exciting research area and it offers potential treatment for several developmental, traumatic and degenerative neurological diseases for which there is currently no cure. A lot was expected from this research and very intensive work has gone behind elucidating the pathways of neuronal development and differentiation. But, like any therapeutic modality, cellular therapy is also associated with some minor and major complications. The occurrence of these complications depends upon the type of cells used and the route of administration. Therefore, we describe the complications as cell related adverse events and procedure related adverse events.

Cell related adverse events:

Cell related adverse events depend on the type of cell, potency of cell, source or origin of cell, cultured or uncultured and cell processing. Here we describe the most studied stem cell types.

i) Embryonic Stem Cells
ii) Adult Stem Cells
iii) Umbilical Cord Stem Cells
iv) Induced Pluripotent Stem Cells

Below are the major cell related adverse events reported with different cell types.

It is important to note that not all the complications are associated with all cell types.

There are some adverse events like teratomas which have been reported only with the use of embryonic stem cells.

(1) Tumorogenecity/ Teratomas

Embryonic Stem Cells

Apart from ethical problems related to human embryonic stem cell derivations, nude mice experiments for various disorders, including brain injury, brought out the problem of teratoma formation after embryonic stem cell transplantation. To achieve human

embryonic stem (ES) cell-based transplantation therapies, allogeneic transplantation models of nonhuman primates have been useful. A model based on cynomolgus ES cells genetically marked with the green fluorescent protein has been described by researchers from Jichi Medical Centre, Japan. Primates provide a close mammalian representation to the humans. The cells were transplanted into the allogeneic fetus because the fetus is supposed to be immunologically premature and does not induce immune responses to transplanted cells. In addition, fetal tissue compartments are rapidly expanding, presumably providing space for engraftment.

However, the researchers found that 3 months after transplantation, a fluorescent teratoma, which was obviously derived from transplanted ES cells, was found in the fetus. Hence, it was understood that, though the transplanted cynomolgus ES cells can engraft in allogenic fetuses, the cells may, however, form a tumor if they "leak" into an improper space, such as the thoracic cavity. Another mammalian model, a rhodopsin-knockout mice, was used to determine whether transplantation of embryonic stem (ES) cells into its subretinal space had a tumorigenic effect.

Mouse ES-cell-derived neural precursor cells carrying the sequence for the green fluorescent protein (GFP) gene were grafted subretinally into the eyes of rhodopsin-/ - mice, whereas control animals underwent sham surgery. Eyes were retrieved after 2, 4, and 8 weeks after cell injection or sham surgery for histologic analysis. Grossmorphologic, histologic, and immunohistochemical analysis of eyes at 2 and 4 weeks after engraftment exhibited no morphologic alterations, whereas neoplasia formation was detected in 50% of the eyes evaluated at 8 weeks after engraftment. Since, the neoplasias expressed differentiation characteristics of the different germ layers, they were considered to be teratomas. The resultant tumor formation affected almost all layers of the eye, including the retina, the vitreous and the choroid. Hence, it has been established in many mammalian models that although ES cells may provide treatment for degenerative disease in the future, their unlimited self renewal and high differentiation potential poses the risk of tumor induction after engraftment. Though clinical studies on use of ES cells in humans are not available, however, cell lines studied shows that human ES lines with submicroscopic genetic abnormalities can display altered growth and differentiation properties suggestive of premalignant change. In other words, a normal karyotype is not necessarily a guarantee of a normal genetic makeup within a cell line. One of the "major challenges to the field" is developing techniques that can detect rare, abnormal cells, particularly if the transformations are not due to changes in gene sequence. Thus, a lot of caution and diligent research will be required before using various human ES cell lines for cell transplantation as a therapeutic option for patients with degenerative disease.

In the literature review, so far, we have not come across any reported complication, such as tumorogenecity, for treatment of neurological diseases using autologous adult stem cells,. None of the published human case reports with autologous bone marrow stem cell transplantation have reported any teratomas.

(2) Seizures

Seizure is one of the possible adverse events of autologous BMMNCs intrathecal transplantation. Earlier bone marrow transplantation in children with leukemia has exhibited epilepsy as adverse event post transplantation. A case series of autologous BMMNCs transplantation in stroke also reported one patient who developed seizures post transplantation. Seizures could be hypothesized to arise post transplantation due to increased production of Brain derived Neurotrophic factor (BDNF), Vascular endothelial growth factor (VEGF) and Nerve growth factor (NGF) by BMMNCs. However the exact mechanism remains unknown. Also these disorders present with seizures as a co-morbidity. Sharma et al, in their study, evaluate seizures as an adverse event of cellular therapy and effect of prophylactic antiepileptic regimen to prevent this adverse event. Children with pediatric neurodevelopmental disorders that underwent cellular therapy were included in the analysis. Seizures were considered as an adverse event if the frequency or intensity of the preexisting seizures increased after cellular therapy or if there were new onset seizures observed. Seizures occured as an adverse event in 6% of the patients, all of them except for one showed an abnormal epileptogenic focus in the EEG. For one patient this investigation was unavailable. Some of these patients also developed new onset of seizures. After starting the prophylactic antiepileptic regimen incidence of seizures as an adverse event reduced to 2% and none of the patients exhibited new onset seizures. In conclusion seizures were observed as an adverse event of cellular therapy, which can be controlled and reduced with the use of prophylactic antiepileptic regimen. Abnormal epileptogenic focus on an EEG is a strong predictor of seizures as an adverse event and an EEG screening of these patients before cellular therapy is recommended.

Table 1. Incidence of Seizures as an adverse event of cell therapy and its prevention by anti-epileptic prophylactic regimen

Population	Without antiepileptic prophylactic regimen		With antiepileptic prophylactic regimen	
	Sample size	Percentage of patients that developed seizures as an adverse event	Sample size	Percentage of patients that developed seizures as an adverse event
Autism	50	3 (6%)	50	0 (0%)
Cerebral Palsy	58	3 (5%)	63	2 (3%)

(3) Immunogenicity:

a) Autologous: Autologous adult stem cells, which are not modified or cultured, have not been associated with any cell related adverse events. Also, there is minimal risk of immunological reactions.

b) Allogenic: These may be associated with immunological reactions.

Hence, as of date, autologous adult stem cells appear to be a relatively safe and reasonably efficacious option for therapeutic use in neurological disorders.

Procedure related adverse events: Procedure related adverse events depend on the route of administration of stem cells. Here are some minor adverse events related to intrathecal administration, as our team is most experienced with this route of administration.

(1) Local Infection either at the bone marrow aspiration site or the CSF injection site or a more severe meningitis is always a possibility after stem cell implantation. However, at the NeuroGen Brain and Spine Institute where over 2000 stem cell implants have been done there has not been any case of local or meningeal infection. None of the other papers reviewed have reported any very serious infection leading to any morbidly or mortality.

(2) Spinal Headache: This is a frequent post treatment symptom which occurs in almost one fourth of all patients (low pressure post spinal headache). Once it comes on, this headache is very severe, but is self limiting and resolves in 3 days. The headache is worse on sitting up. The methods to prevent this are making the patients lie in bed (preferably, head low position) for at least a day after the implantation, drinking lots of fluid, the application of a lumbosacral belt (to act as a binder to raise the intracranial pressure) and the use of analgesics. It is our observation that by keeping the lumbar dressing at the lumbar puncture site on for about 5-6 days the incidence of the spinal headache is reduced.

Giddiness, vomiting and neck pain are some other occasionally occurring adverse events. But these are usually always self limiting and respond to medical management and rest.

Similarly, other surgical methods, such as intraspinous, intracerebral, intrarterial and intravenous injections have possibilities of side effects or complications, specific to the respective procedures.

It is beyond the scope of this book to describe the adverse events associated with all other types of stem cells, though umbilical cord stem cells may be associated with immunological reactions and infections. Induced Pluripotent Stem Cells (IPSCs) have not reached clinical applications due to associated complications of genomic instability, viral vector infections and mutagenesis.

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11. Ethics and Regulations Involved for Stem Cell Therapy

Stem cell research holds an incredible promise to treat persons with devastating disorders. Human stem cell therapy (HSCT) is a controversial theme in the religious, political, legal, ethical and scientific worlds. It has been riddled with ethical questions, in part because the predominant methods being used to derive or attempt to derive human embryonic stem cells require destruction of the embryo. Although there are ethical issues surrounding the collection and use of somatic (adult) stem cells from aborted fetuses and umbilical cord blood, the most intense controversy to date has been focused on the source of human embryonic stem (hES) cells. However, the ethical issues not only involve the embryos but also the creation of chimeras, oocyte harvesting. Other important ethical issues have arouse involving the informed consent of both donors of gametes and embryos as well as recipients of stem cells and stem cell products. Commercialization of the process and conduction of research have also raised concern.

Ethical issues exist in this field because the science behind human stem cell research is very new and many rules and guidelines regarding this specific area have yet to be created. The public opinion about embryonic stem cell research is divided between those that support the research and those that are highly influenced by religious groups that are against the research. Kiessling and Scott had once quoted "Scientific ignorance is the driving engine of the anti embryonic stem cell movement"

Embryonic Stem Cells

Different religions have different ideas about beginning of life and about the moral status of a blastocyst, of an embryo and of a fetus. Hindus and Buddhists believe that embryonic stem cell therapy is seen as a positive action by them as the embryonic cells used come either from leftovers of in vitro fertilized embryos or from natural abortions, and it is used in behalf of helping diseased and injured people. Even Islamic laws allow fertilization in vitro for infertile couples and those couples can either throw the unused fertilized embryos away or donate them to research, and Islamic scholars are for the donation of unused fertilized embryos to research. While, Roman Catholics are against the use of embryonic stem cells for research. They believe that full moral status is acquired at conception. According to Christian beliefs, a blastocyst

is already a living human being that should not be destroyed on behalf of therapeutic meanings, even when most of the blastocysts come from leftovers of in vitro fertilizations, which otherwise are destroyed, and even when this therapy could represent the cure of many life threatening diseases.

In view of addressing these ethical issues associated with human embryonic stem cell research, professional groups have issued guidelines for the ethical conduct of this research and its management. There are different kinds of ethical committees throughout the world. The private companies have set up Bioethics Committees and most universities have an Institutional Review Board or a Research Ethics Committee and they are a very important part of any research projects and most scientists welcome their recommendations. The committees use the Helsinki Declaration and the Nuremberg Code as guidelines when they decide whether a problem is ethically right to treat with stem cell therapy. The Helsinki Declaration which is developed by The World Medical Association (WMA) "is a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data."

Systematic data regarding these efforts should be collected in order to enhance the likelihood that they meet their ethical goals.

iPS cells (induced pluripotent stem cells)

The countless discussions over the ethical issues of embryonic stem cell research can be avoided with the introduction of iPS cells. These cells do not involve embryos or oocytes. As compared to oocyte donation, there are very few concerns involving risks to the donors as a skin biopsy which is done to obtain somatic cells is relatively non-invasive. No ethical issues are raised either for the donation of materials to derive iPS cells or their derivation. The President's Council (USA) on Bioethics called iPS cells "ethically unproblematic and acceptable for use in humans".

Umbilical Cord stem cells

The ethical issues of cord blood banking remain the same as for any tissue bank for allogenic research or transplantation. This issue has been tackled in the European group on Ethics in Science and New technologies (EGE) Opinion no. 11 on the ethical aspects of tissue banking (21 July 2001). The ethical values highlighted in this opinion are as follows: body integrity, respect of privacy and confidentiality of data, promotion of solidarity, fairness of access to healthcare and information and consent of the donors. The process of umbilical cord blood banking should comprise of a detailed consent which explains the couple or the woman clearly, the prospective new treatments. It should be stressed that these treatments are still at the experimental stage. Tissue bank activities should be principally reserved to non-profit making organizations or public health institutions. All private and public tissue banks should be monitored for quality standards and measures. These guidelines are based on the principle of respect for human dignity and integrity which asserts the principle of

non commercialization of the human body; principle of autonomy or the right to self-determination on the basis of full and correct information; principles of justice and solidarity, as regards to fair access to healthcare services; principle of beneficence, or the obligation to do good, especially in the area of health care; principle of non-maleficence, or the obligation not to harm, including the obligation to protect vulnerable groups and individuals, to respect privacy and confidentiality; and principle of proportionality which implies a balance between means and objectives. There are also a few value conflicts regarding the banking of umbilical cord blood. The values of freedom and free enterprise may conflict with the principles of solidarity and justice, according to which access to healthcare should be on an equitable basis and based on realistic needs, as well as with the principle of protection of vulnerable groups.

Informed Consent

Informed consent is a critical part of any research project. It is the process in which a participant/patient provides consent to participate in a research project after being fully informed of its procedures, benefits and risks. After completely understanding the information about the project, the participant/patient gives full and conscious consent for the physician/scientist to continue with the procedure. The consent is obtained after providing all the information to the patient in comprehensible non-medical terms (preferably in the local language) about the diagnosis; nature of treatment; risks involved, prospectus of success, prognosis if the procedure is not performed and alternative treatment. The three major aspects of the informed consent are information, voluntariness and capacity. In accordance with the observations of the Supreme Court, the National Commission of India stated that all information would imply adequate information to enable the patient to make a balanced and conscious judgement about whether or not to be a part of the trial or treatment.

Current ethical basis for using adult stem cells

The ethical basis of offering stem cell therapy as a treatment option is based on the Paragraph no. 32, World Medical Association Declaration of Helsinki- Ethical Principles for Medical Research Involving Human Subject. This declaration states that "In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physicians judgment if offers hope of saving life, reestablishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published."

Some other aspects of the stem cell therapy ethical debate that need further discussion are as follows:

(1) That there is a need to make a precise distinction between embryonic stem cells and adult stem cells. While stringent regulations for embryonic stem cell research are completely justified the same are not needed for adult stem cell research.

(2) That there is a need to look at the whole issue from the patient's perspective respecting the fact that even small functional improvements can mean a lot to a particular patient.

(3) That there is an ethical ground for offering stem cell therapy as a treatment option based on the Helsinki declaration.

(4) That there is enough published clinical evidence about the efficacy and safety of adult stem cells in neurological disorders and based on this evidence there is no need to continue carrying out trials.

The unfortunate part about the raging ethical debate is that although the main objections are concerning the use of embryonic stem cells, these have resulted in the lack of acceptance and misunderstanding towards other non-embryonic stem cells. It is essential that the medical community, patients and activists realized that stem cells are not one common entity but originate from different sources and that the objections to the use of one source need not come in the way of the use of others. Hence, it is time that we re-evaluated the term "evidence based medicine" and turned to "practice based medicine".

There are two sides to the ethical debate for basing our treatment options on evidence based medicine. (1) One side of the debate is "Is it ethical for doctors to offer treatment options that have not become a standard of care as yet?" (2) The other side of the debate is "Is it ethical to deny patients suffering from disabling diseases, treatments options that are safe and available, whilst we wait many years for the results of multicentric international trial to prove that these treatments work?" Both these questions are answered differently by different people depending on what is at stake for them. The role of regulatory bodies in this field also needs to be re-evaluated. Whereas there is no denying the importance of regulation in all aspects of medical care and research, it is also important for the regulatory bodies all over the world to ensure that regulations do not hinder the evolution of newer treatment options. They also need to realize that in this field that is evolving at a breathtaking speed, regulations made several years ago may no longer be valid in the present and that the regulations need to be modified as more evidence pours in from all across the globe. However, getting a consensus on these issues is not easy.

Regulations for stem cell therapy in India

In India for all these years the regulatory authority for stem cell therapy and research has been the Indian Council of Medical Research (ICMR). They have formulated draft guidelines in the years 2003, 2007 and 2013. These are available at www.icmr.nic.in. Although, these cover many aspects of stem cell therapy and research, briefly speaking they had put the use of embryonic stem cells in the restrictive category and the use of

umbilical cord cells as well as adult stem cells in the permissive category. There is a requirement for the formation of an Institutional Committee for Stem cell research and therapy (ICSCRT). This has now been recently modified to an ICSCR. In any case these are guidelines and they as of now have not yet passed by the Parliament as a legally binding law or bill. In the recent past, the Drug Controller General of India (DCGI) has also taken up responsibility of this field and had put up the proposed new guidelines for public opinion on their website in February 2014. As is obvious from all the above is that there are a lot of grey areas. However, in the next few months/ years we should hopefully see something more definite and progressive happening on the regulatory front that will be in the interest of patient care.

Regulations for stem cell therapy

In the recent years medicine has evolved and novel treatment options have emerged in the form of stem cell therapy. This evolution has brought forth mindboggling possibilities for finding treatments and cures for a variety of degenerative conditions. This sudden evolution of biological means for the treatment of incurable diseases has also raised multiple ethical and moral dilemmas. Therefore various regulatory medical bodies have felt an urgent need to monitor and regulate the research in the field of stem cell therapy. Divers opinions, cultural and religious views have made it challenging to device a single policy to govern stem cell research. Rapid economic growth in many developing nations, especially, in Asia has also experienced a proportionate surge in IT sectors as well as biomedical research. Moreover, with restrictions on stem cell research imposed in the US, a shift of activity in this field has been seen, with the opportunity being explored to its earnest in countries, such as China, India, Japan and Korea. However, an overview of the regulatory procedures in the global players shows that these vary from nonexistent to extremely stifling. Both ends of the spectrum are not conducive for the healthy progress of this highly promising area and we feel there needs to be a discussion so that a middle ground can be reached.

The research in the field of cellular therapies is increasing; however, the regulatory bodies should consider these results while drafting the regulations. The regulations for a 'new drug' follow the steps of evidence based medicine. Cellular therapy poses millions of possibilities to be tested due to variations in the source of cells, types of cells, dose of cells and different routes of administration. If the same regulations as that of drugs are used for cellular therapy and cellular products it will be another decade before we can use cellular therapy as a treatment modality.

Research has progressed to show safety of cellular therapy in various incurable, progressive and fatal diseases. Is it fair that on one hand we claim to protect patients from adverse effects of the therapy using evidence based medicine whereas on the other hand we let them die waiting for the treatment? The regulatory bodies should consider the concept of 'Practice Based Evidence' and not rely only on 'Evidence Based Medicine'. Where evidence based medicine disregards the evidence generated

by individual practitioners, practice based evidence progressed forward through such evidence.

Medical era progressed in the time when the evidence based medicine was not implemented so rigorously. Progress of the medical field was through the individual clinical practitioners who pioneered newer forms of therapy based on their clinical experience and expertise. Most of the surgical practice comes from individual surgical expertise and cannot be tested using multicenter randomized controlled trials. It is not possible to measure all the medical practices on the yardstick of evidence based medicine. Evidence based medicine fails to answer questions like what can be considered as a conclusive evidence for a particular form of treatment?

The more daunting fact of evidence based medicine is the funds required to gather enough information to support the medical practices. The lack of funds for a large scale research trial at the hands of individual medical practitioners has led pharmacological and other industries to drive medical research to suit their business objectives. Practice based evidence could therefore provide faster progress in medicine guided by individual medical experts. Newer treatments must be very carefully and rigorously monitored for its safety. But once the safety of these treatments has been established, regulatory bodies may consider use of these treatments in case of the disease that have no cure. Regulatory bodies while monitoring very closely may also promote such practices to generate larger practice based evidence. This would make such treatments easily available and more affordable and the medical innovation will be by the experts in field of medicine and not driven by commercial gain and exploitation.

Individual medical expertise and experiences are of importance but caution needs to be exercised to cause no harm. The purpose and aim of regularizing and monitoring the medical practices is to protect patients from harm and exploitation. But regulations should also safeguard medical progress. The challenge in front of the regulatory bodies is to protect the vulnerable patients with incurable disorders from the false promises of new experimental therapies but at the same time make such treatments available to them. There is a very little difference between 'Helping the patients with incurable diseases with novel treatments' and 'Exploiting the helplessness of the patients' suffering from incurable diseases' and that is the distinction regulators all over the world need to make while designing the regulatory guidelines.

Current regulatory system in India

The present situation in India with regards to guidelines for stem cell therapy

1) The National guidelines for stem cell research have been formulated by the Indian Council of Medical Research and the Department of Biotechnology in 2013. These guidelines have retained the 2007 classification of stem cell research into 3 categories namely Permissive, Restrictive and Prohibitive research. Human embryonic stem cell derivation and differentiation falls in "restrictive" category,

whereby, these cells can only be used for research purposes. "The prohibitive research" includes any research related to germ line genetic engineering or reproductive cloning of any in vitro culture of the intact human embryo, regardless of the method of its derivation, beyond fourteen 14 days or the formation of the primitive streak, whichever is earlier; transfer of human blastocysts generated by SCNT; or the breeding of parthenogenetic animals,in which human stem cells have been introduced at any stage of development. Adult and umbilical cord blood cells are clubbed under the "permissive" group. It has introduced an additional layer of oversight besides the institutional ethics committee (IEC) in the form of Institutional Committee for Stem Cell Research (IC-SCR) and the National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT). A major recommendation has been to omit the word therapy from the title of the guidelines as compared to the guidelines in 2007. As per National guidelines, every organization (academic or otherwise) interested in working on stem cells, must formulate an Institutional Committee for Stem Cell Research and Therapy (IC-SCR). Members of the Committee must include people with appropriate expertise (representatives of the public and persons with expertise in clinical medicine, developmental biology, stem cell research, molecular biology, assisted reproduction technology, and ethical and legal issues in stem cell research) and this Committee must function at the institutional level. Projects will be approved on the basis of scientific evaluation and ethical conduct. The IC-SCR must also be registered with an NAC-SCRT. The NAC-SCRT is constituted by the Government of India. NAC would be comprised of experts from various fields, who would be responsible for examining the scientific, technical, ethical, legal and social issues in the area of stem cell based research and therapy. It will have around 10 members. A chairman, a deputy chairman, member secretary and nominees from DBT, DST, CSIR, ICMR, DCGI, DAE, and biomedical experts from pharmacology, immunology, cell biology, hematology, genetics, developmental biology, clinical medicine and nursing. Legal expert, social scientist, and a women's representative will also be part of NAC. NAC could also consult outside experts on a case to case basis. Institutions involved in stem cell research and therapy will have to be registered with the NAC through Institutional Committee for Stem Cell Research and Therapy (IC-SCR).

2) The Ministry of Health and Family Welfare, Government of India, established a High Powered Committee in June 2013 to suggest a road map for regulation of stem cells and other cell based therapies being practiced in India. Under the chairmanship of Professor Lalji Singh it submitted a Guidance Document for Regulatory Approvals of Stem Cell and Cell Based Products (SCCPs) in December 2013. This Guidance Document is based on the recommendations of that committee and it is subsidiary to the amendments made in 2013 to the Drugs and Cosmetics Act (DCA), 1940 and the new rules proscribed there under. As per these amendments it has been decided that Government of India, through the DCG (I) and CDSCO, shall regulate all practices related to the use of stem

cells, and other cells, for therapeutic purposes in India. The amendment in DCA also mandates that all stem cells and cell based products that can be used for therapeutic purposes shall be referred as Stem Cell and Cell Based Products (SCCPs) and all activities related to their usage i.e. manufacture/isolation/ collection, storage and transplantation into patients must be done only under a license or permission that would be granted by the DCG(I)/CDSCO.

3) Another important and major development has been the proposal of the Drug Controller General of India DCG(I) to include "stem cells" in the definition of new drugs in the proposed bill titled "Drugs and Cosmetics (Amendment) Bill 2015".

Permissive regulations in other countries

Korea

Korean guidelines make a clear distinction between the levels of manipulation of the cells very clear. The guidelines state, 'Cell therapy product" means a medicinal product manufactured through physical, chemical, and/or biological manipulation, such as in vitro culture of autologous, allogeneic, or xenogeneic cells. However, this definition does not apply to the case where a medical doctor performs minimal manipulation which does not cause safety problems of autologous or allogeneic cells in the course of surgical operation or treatment at a medical center (simple separation, washing, freezing, thawing, and other manipulations, while maintaining biological properties).'

Regulations should be more permissive for cells that are autologous, of adult origin and minimally manipulated than the cells that are allogenic, of embryonic origin or are significantly manipulated.

Korean Food and Drug Association (FKDA) Regulation on review and authorization of biological products, Article 41 not only excludes the minimally manipulated cells from the definition of cell therapy product, but has a fast track review process for the use of cell therapy in life threatening, serious diseases and conditions for which treatment is not possible with existing therapy.

The article 41 states, "(Fast Track Review Process) ? For the following medicinal products, the Commissioner of the KFDA may allow post-marketing submission of some documents required under this Regulation or apply the fast track review process. Medicinal products that may have therapeutic effects against AIDS, cancers, or other life-threatening or serious diseases. 2. Medicinal products of which fast introduction is deemed necessary because treatment is not possible with existing therapies (due to development of resistance or other reasons) 3. Medicinal products that may have preventive or therapeutic effects against bioterror diseases and other pandemic infections."

The Korean setup is much more permissive for stem cell research. The government allows and funds work on human embryonic stem cells. The Bioethics and Safety act

lays down the legal boundaries for permissible area for stem cell research. The early guidelines made by the Ethics Committee of the Stem Cell Research Center in 2003 permitted the use of only spare embryos for hES cell line derivation. They prohibited cloning, inter-species transplantation of reproductive cells that might lead to chimeras, production of embryos for research purposes, and somatic cell nuclear transfer to prevent attempts to engage in reproductive cloning. A further advanced version of the Bioethics and Safety Act enacted in January 2004, and enforced since 2005 as a penal law identifies criminal offenses pertaining to stem cell research. It prohibits human reproductive cloning. The transfer of embryos between two different species, embryo production other than for the purpose of pregnancy and also disallows research on spare embryos that have the embryological primitive streaks appearing in their developmental process. It only allows research on spare embryos for research aimed at curing rare or incurable diseases. The though on surface it appears prohibitive, but in practicality provides a legal platform to allow legitimate researchers to conduct research on human embryonic stem cells, including somatic cell nuclear transfer for the purpose of conducting research aimed at curing currently incurable diseases., if they adhere to the procedures laid down by the act.

In 2006, Dr. Hwang Woo-suk scandal, raised not only ethical issues regarding procurement of the eggs, but also questions regarding scientific ethics & falsifying results brought disrepute to the stem cell " hub" which was to be lead by him. This also, lead to enactments of stricter rules regarding embryo donor for research, which came in the form of Bioethics and safety act 2008. Nevertheless, South Korea continues to pursue research for the purposes of therapeutic cloning, with complete financial and legal backing from the government .

The Korean guidelines have taken into consideration the need for different regulations for minimally manipulated cells and the need for more efficient pathways for the approval of the same. Other regulatory bodies need to keep these two important points in consideration whilst framing their regulations.

Japan

Japanese diet passed and implemented 'Regenerative medicine promotion law' in the last year that revolutionalised the regenerative medicine in Japan. As per the suggestions of this law, The Pharmaceuticals and medical devices agency partially amended Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD act) to create a separate approval system from that of drugs and Ministry of health, labor and welfare (MHLW) passes an act on safety of regenerative medicine was devised to promote marketing of safe regenerative medicine practices.

The Pharmaceuticals and medical devices agency, partial amendment of Pharmaceuticals affairs law, renamed as Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD Act):

The partial amendment in this law created a separate approval channel for the cell based therapies and products. This amendment recommended that the cell based

products may not need to use the phased clinical trials to establish efficacy for marketing approval. The provision was made for a conditional approval for the marketing of these products once the safety and presumed efficacy was established. Investigators could demonstrate efficacy in pilot studies of as few as 10 patients in one study if the change was dramatic enough or a few hundred when the improvement was marginal. At the provisional approval stage the treatment could be approved for commercial use as well as national insurance coverage.

Ministry of health, labor and welfare (MHLW), Japan & Japanese Pharmaceuticals and Medical devices agency (PMDA), act on safety of regenerative medicine:

Although there was a separate channel created for the approval of cell based therapies, the partial amendment of PMD act did not specify the route of approval. Therefore an act of safety of regenerative medicine was devised to make sure the safety of the treatments provided and to ensure that the efficacy was established in the due course. Regenerative medicine products and treatments were categorized as regenerative medicine I (High risk), Regenerative medicine II (Medium risk) and Regenerative medicine III (Low risk) (Figure 1). Each of these classes has a separate approval channel and different approval procedure.

Low risk regenerative medicine products (Class III):

The approval process is by a committee within the institute and by submitting the provisional plans to the department of health and welfare.

The institutional committee is called as, "Certified Committee for Regenerative Medicine" includes experts in the regenerative medicine technologies as well as legal experts and is approved by the ministry of health, labor and welfare.

This committee is similar to the IC-SCR suggested in the Indian guidelines. However, this committee has an authority to conditionally approve the treatment and marketing using the cell based products; unlike IC-SCR which is only restricted for the research in cell based products and therapies.

Medium risk regenerative medicine products (Class II):

The approval process is by a committee outside of the institute and by submitting the provisional plans to the department of health, labour and welfare.

The institutional committee is called as, "Certified Special Committee for Regenerative Medicine" approved by the ministry of health, labor and welfare; which includes experts in the regenerative medicine technologies as well as legal experts with capabilities for specialized investigation and objectivity.

This committee is similar to the IC-SCR suggested in the Indian guidelines but is formed of people outside of the institute but is not a committee on a national level like that of the NAC-SCR. The Japanese guidelines have made a provision for a middle

level regulatory body for faster approval process. This committee has an authority to conditionally approve the treatment and marketing using the cell based products; but the provisional plans are required to be submitted to department of health, Labour and welfare. Once the conditional approval is granted the institute must conduct

High risk regenerative medicine products (Class I):

The approval is through the "Certified Special Committee for Regenerative Medicine" which is from outside of the institute as that in Class II but the Ministry of health, labor and welfare (MHLW) will impose a certain period of restricted implementation. During this period the MHLW will confirm the safety by hearing opinions of the Health Science Council. The Ministry can order change of the plan if there is nonconformity to the standards of safety and the institute will have to adhere to these changes for the conditional market approval.

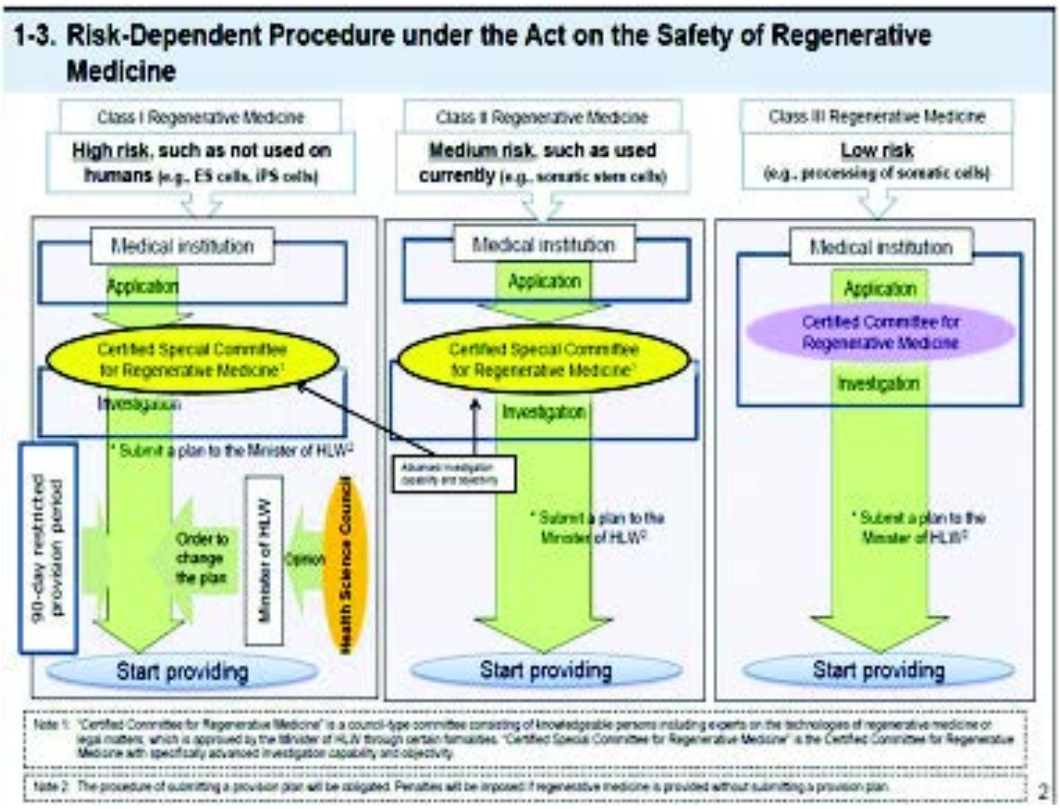

Figure 1: Categorization of regenerative medicine
** Diagram available online at http://www.mhlw.go.jp/english/policy/health-medical/medical-care/dl/150407-01.pdf,*

The publication of the human iPS cell paper by Japanese researchers has renewed the vigour with regards to stem cell research in Japan. The governmental committee revised the guideline for human ES cell research in August 2009. The original guideline

was split into two separate ones: one about derivation of human ES cells and the other about use of human ES cells. The renewed two-level review was abolished and now a protocol only needs an approval of the institutional ethics review committee. Another change in policies in Japan, recently, is pertaining to research that aims to produce germ lineage, which was prohibited till this year.

In May 2010, a new guideline came into effect for germ cell research using human iPS cells and the two existing guidelines for human ES cell research were revised to allow germ cell research using human ES cells. Further guidelines for use of induced pluripotent stem cells and human embryonic stem cells have been drafted by the Ministry of Education, Culture, Sports, Science and Technology (MEXT),allows researchers to use human iPS cells and ES cells under the strict review system included in the original guideline, although the use of human ES cells is not possible until the derivation guideline (which is under control of the MEXT) is amended to enable researchers to establish clinical grade human ES cells.

Thus the Japanese government has been very permissive in promoting the regenerative medicine. The classifications that are made are based on the safety of the cell products and not the efficacy. The approval is granted with proven safety and presumed efficacy, imposing further testing to establish safety satisfying the standards of evidence based medicine. Regulatory bodies from other countries should consider following the Japanese model of regulations for regenerative therapies.

USA

In the US, the National Institutes of Health (NIH) is the central federal body governing stem cell research, but each US state can also decide on its own legislation. The US FDA is responsible for the regulation of cell therapy products. Products derived from stem cells are regulated as biologics under section 351 of the Public Health Act. To assist with regulatory compliance, the FDA has provided general guidance documents via the Centre for Biologics Evaluation and Research (CBER) section of its website (www.fda.gov/cber/guidelines.htm).

US FDA has also recognized the need to make distinction between various cells and cell therapy processes. The United States of America, department of health and human services, Code of federal regulations, food and drug administration, Part 1271: Regulations for Human cells, Tissues, and Cellular and Tissue based products makes a clear distinction about minimally manipulated cells and autologous transplantation from other cell types routed of transplantation. The article 1271 15B (Human cells, Tissues, and Cellular and Tissue based products), stated that 'You are not required to comply with the requirements of this part if you are an establishment that removes Human cells, Tissues and cellular and tissue-based products from an individual and implants such products into the same individual during the same surgical procedure'. This article is suggestive of the distinction between the regulations and implies that the autologous and minimally manipulated cells should not be regulated by the same means as that of the other cell therapy products.

Although president George bush had banned the federal funding for the research on embryonic stem cells and by using embryonic cell lines in 2001, President Barack Obama subsequently lifted this ban. Currently embryonic stem cell research is eligible for federal funding. To obtain federal funding to conduct research using stem cells, a sponsor must submit its application to the NIH. Guidelines for applying to the NIH can be found on the Federal Register (Vol 65, No 166/Friday, August 25, 2000/Notices). Under the auspices of the Obama administration, the National Institutes of Health plans to expand federal funding for stem cell lines that meet following ethical requirements: the embryo used is discarded after IVF; informed consent is obtained from the donors; the couple must not receive compensation (neither financial nor medical benefits) or be coerced or threatened. Older stem cell lines created in the spirit of the new regulations will be considered for federal funding, whereas embryos created solely for research purposes will be excluded .

Our recommendations for designing the guidelines

Based on various international guidelines, white papers and declarations from world medical association we would like to recommend some guiding principles while designing the guidelines in our country for approval and monitoring of stem cell based research as well as therapy.

The recommendations are based on the following documents

1) The regulatory guidelines from different countries like Japan, Korea and United States of America
2) Opinions from white paper of the International society of cellular therapy (ISCT)
3) Helsinki declaration of World Medical Association that guides the ethical principles of human research and
4) Beijing declaration of the International Association of the Neurorestoratology

Recommendations

1. Acceptance of unproven cellular therapies for the treatment of incurable conditions, based on the World Medical Association' declaration of Helsinki.
2. Distinction between legitimate cell therapy medical services and fraudulent services, based on the ISCT White paper.
3. Distinction between clinical trials and medical innovation, based on the ISCT white paper.
4. The basic right of a patient to seek treatment should be respected, based on the ISCT white paper.
5. Distinguishing various centers offering cellular therapy, based on the recommendation of the ISCT white paper.

6. Recognition of the importance of cellular therapy as part of neurorestorative therapies, based on Beijing declaration of the International Association of the Neurorestoratology (IANR).
7. Giving importance to Practice Based Evidence
8. Regulations need to make a distinction between different types of cellular therapies, based on the regulations in countries like Korea, Japan and USA
9. Adapting regulations from countries that have been progressive and more permissive of cellular therapies like Korea, Japan and USA.

Conclusion

In summary what this means in our view is that ethically for conditions for which there is no other treatment option available or all available treatment options have exhausted we can offer stem cell therapy as a treatment option on compassionate grounds. However it is important that all clinical results are documented and published. From a regulatory viewpoint if minimally manipulated autologous adult stem cells, such mononuclear cells, are being used (like we do at NeuroGen BSI) then approval is needed from the Institutional stem cell committee / Ethics Committee. Special informed consent is important before doing this treatment.

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SECTION B

12. How Rehabilitation Augments the Benefits of Stem Cell Therapy

Neurorehabilitation is the clinical subspecialty that is devoted to the restoration and maximization of functions that have been lost due to impairments caused by injury or disease of nervous system. The goal of neurorehabilitation is to help patients with impairments and disabilities and to make them functionally independent, which requires team of rehabilitation specialists, such as nurses, physical therapists, occupational therapists, speech therapist, psychologist and others.

Figure 1: A pediatric Rehabilitation centre

Importance of Rehabilitation:

The rehabilitation team has a role to set short term goals (generally considered to be two to three weeks) and long term goals (longer than 3 weeks) which should be objective, measureable and time limited. Neurorehabilitation team has an

understanding of neural regulation of movement patterns. A framework for typical motor behaviour is necessary to understand how motor behaviour is altered in persons with neurological dysfunction and how plastic properties of nervous system interact to produce change. Motor control is the study of how an individual controls movements already acquired. Neuroplasticity is defined as brain's ability to adapt or use cellular adaptations to learn or relearn functions which are previously lost as result of cellular death by trauma or disease at any age. Neuronal sprouting is thought to be primary mechanism, allowing injured neurons, to reconnect in new ways and allowing intact undamaged neurons to form new connection and to enhance function. Motor learning will continue throughout life as long as environment asks for change and CNS has pliability and desire to learn. The rehabilitation team promotes this learning and facilitates neural plasticity.

The philosophic foundation of rehabilitation team is to promote purposeful activity thereby preventing dysfunction and eliciting maximum adaptation. These goal-oriented activities are meant to be culturally meaningful and important to the needs of patient and their families. Activities include daily life and work skills, exercise, recreation and crafts. Exercise tasks in animal models, have shown that specifically skilled type of exercises lead to increased angiogenesis in damaged cortical areas whereas unskilled activities did not show this positive change. It is believed that in humans too rehabilitation techniques would enhance neuroplastic changes.

How rehabilitation augments the effects of stem cell therapy

The concept of Neuro Regenerative Rehabilitation Therapy (NRRT) at NeuroGen promotes a multidisciplinary and holistic approach to bring about recovery of neural function with a close integration of Neuro regenerative (including stem cell therapy), Neuro protective (medications) and neurorehabilitative therapies (physical / occupational / speech/ psychological). Thus, it combines the best neurobiological repair technologies and neurorestorative techniques. The rehabilitation protocol is then individualized to the specific requirements of each patient emphasizing on functional recovery and independence in ADL. The rehabilitation team sets up goals and the injected stem cells from within the body help in achieving those goals. Studies have shown that exercise induces mobility in the injected stem cells, thereby enhancing the achievable outcomes. Hence, neurorehabilitation appears to work complimentarily with stem cells therapy.

> Studies have suggested that the combination of bone marrow stem cell therapy and exercise training result in significant functional improvement in neurological disorders.

Neurorehabilitation facilitates neural plasticity and improves neural connectivity. It stimulates neurons to function at their optimum capacity. It also activates the local resident stem cells to help repair the damaged areas. Similarly exercise also stimulates the injected stem cells and guides them towards their targeted functions. It helps the regenerated cells to gain maximum function. Neurorehabilitation has also been

postulated to release growth factors, improve oxygenation and increase blood supply. Thus, the synergistic effect of stem cell therapy and neurorehabilitation brings about maximum benefits.

Physical therapy

As an important member of rehabilitation team a, physical therapist has a crucial role to play which includes, bed mobility, ambulation and transfer activities like ,transfers from bed to chair or from chair to commode or from wheelchair to car and so on. Their assessments emphasize measures of voluntary movement, sensory appreciation, ROM, strength, balance, fatigability, mobility, gait and functional status.

Practices in Physical Therapy includes:

1. Therapeutic exercise and re-education.
2. Neurofacilitation techniques.
    i) Proprioceptive neuromuscular facilitation
    ii) Bobath
    iii) Brunnstrom
    iv) Rood
3. Motor skills learning.
4. Task-oriented practice.
5. Forced use.
6. Massed Practice.
7. Biofeedback.
8. Virtual environment training.
9. Musculoskeletal techniques.
10. Electromyogram-triggered neuromuscular stimulation.
11. Orthosis and assistive devices.

Figure 2: Rolling exercise

Figure 3: Standing using assistive devices

Occupational Therapy

Occupational Therapists bring expertise to the rehabilitation team in enhancing the independence and personal satisfaction of patients in their activities of daily living (ADL), community and leisure activities, social integration, and work performance. They play integral part in evaluating the need for a range of assistive devices and training patients to make them independent in eating, dressing, bathing combing and other ADL.

In the patient's home and workplace, the therapist provide grab bars, rails, ramps, environmental controls, computer interfaces, architectural changes such as widening a doorway to allow wheelchair access and emergency remote-control calling systems. Along with the physical and recreational therapist, occupational therapist seek out the environmental, personal, and activity-specific equipment and technologies that enhance the quality of life of patients

Success in retraining during rehabilitation depends on diverse variables that include the characteristics of a task, changing contexts and environments when performing a task, psychological reinforcements including positive contextual factors like motivation, attention, memory for carryover of what is taught and negative contextual factors like environmental distractions, anxiety, sleep deprivation and family support play a significant role.

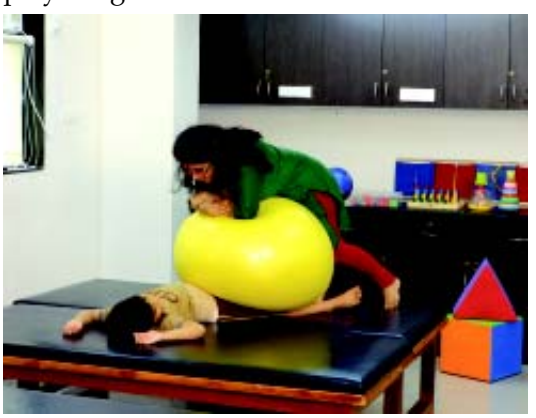

Figure 4: Deep Pressure

Figure 5

Psychology

The word psychology is derived from the Greek words Psyche (which means soul) and logos (which means study). Hence, psychology could be defined as a "study of the soul". However, today it is defined as the scientific study of the behaviour of individuals and their mental processes (American Psychological Association). Neuropsychological testing and evaluation is to identify the pattern of cognitive, behavioural, and emotional strengths and weaknesses and to provide specific treatment recommendations or clarify diagnostic questions. The domains and tests specified

Figure 6: Cognitive rehabilitation

Psychological Counseling:

The purpose of counseling is to broadly empower the client to cope with life situations, to reduce emotional stress, to engage in growth producing activity, to have meaningful interpersonal relationships and to make effective decisions. Counseling increases the control over present circumstances and enhances present and future opportunities.

There are several main broad systems of psychotherapy:

i) **Psychoanalytic:** It encourages the verbalization of all the patient's thoughts, including free associations, fantasies, and dreams, from which the analyst formulates the nature of the unconscious conflicts which are causing the patient's symptoms and character problems.

ii) **Behaviour Therapy:** This focuses on changing maladaptive patterns of behavior to improve emotional responses, cognitions, and interactions with others.

iii) **Cognitive Behavioural Therapy:** Seeks to identify maladaptive cognition, appraisal, beliefs and reactions with the aim of influencing destructive negative emotions and problematic dysfunctional behaviours.

iv) **Psychodynamic:** Primary focus is to reveal the unconscious content of a client's psyche in an effort to alleviate psychic tension.

v) **Existential Therapy:** This is based on the existential belief that human beings are alone in the world. This isolation leads to feelings of meaninglessness, which can be overcome only by creating one's own values and meanings.

vi) **Humanistic:** The task of Humanistic therapy is to create a relational environment where this the self-actualizing tendency might flourish.

vii) **Transpersonal Therapy:** Addresses the client in the context of a spiritual understanding of consciousness.

ix) **Body Psychotherapy:** Addresses problems of the mind as being closely correlated with bodily phenomena, including a person's sexuality, musculature, breathing habits, physiology etc. This therapy may involve massage and other body exercises as well as talking.

Play Therapy, Gestalt Therapy, Rational Emotive Behaviour Therapy, Solution based therapies and Reality Therapy some other forms of psychotherapy.

Speech therapy:

Speech therapy focuses on receptive language, or the ability to understand words spoken and expressive language or the ability to express. It also deals with the mechanics of producing words, such as articulation, fluency and voice. Speech therapy also deals with rehabilitation of language in children who do not speak congenitally due to hearing impairment, mental retardation, autism or attention deficit hyperactivity disorder.

Speech and language therapy is beneficial in neurogenic disorders of non - progressive and progressive origin.

i) **Aphasia:** Aphasia is defined as loss of reception or expression of language as a result of brain stroke. It can be classified as Broca's aphasia (patient presents with intact comprehension with affected expression), Wernicke's (patient presents with affected comprehension with jargon speech), Anomia or nominal aphasia (patient presents with naming difficulties).

   Recovery from aphasia depends on many prognostic factors like age, site and extent of lesion, concomitant problems and time lapsed between the stroke and initiation of therapy. Rehabilitation in aphasia focuses on the following:

   a) Improving auditory comprehension using pointing tasks "point to the spoon".
   b) Encouraging verbal utterances voluntarily.
   c) Improving sentence formation.
   d) Improving naming

   A study done on aphasics concluded that combination of two inout channels - auditory plus visual, auditory plus gestural may facilitate better comprehension and performance by the patient

   Many of the cases of do not improve with traditional speech and language. In such cases, nonverbal modalities can be used to augment or alternate patient's communication. The most commonly used AAC are communication boards, gestures and use of written modality.

   According to Collins (1986), severly aphasic patient may rely more on pictures for basic need that cannot be readily expressed by pointing or natural gesturing (as cited in Davis,2000) (5)

ii) **Dysarthria:** The literal definition of dysarthria is disordered utterance (dys means disordered or abnormal; arthria means to utter distinctly). A more comprehensive definition is that dysarthria is the impaired production of speech because of disturbances in the muscular control of the speech mechanism (as cited in Freed, 2000). Dysarthria can be classified as spastic dysarthria (due to upper motor

neuron lesion), flaccid dysarthria (due to lower motor neuron involvement), ataxic dysarthria (due to cerebellar involvement), hypokinetic and hyperkinetic dysarthria (due to basal ganglionic involvement) and mixed dysarthria.

Common causes of dysarthria are stroke, motor neuron disorder, multiple sclerosis, head injury and Parkinson's disease to name a few.

Most of the patients with dysarthria present with inability to produce sounds clearly, reduced loudness and monotonous or robotic speech. In cases of flaccid and spastic dysarthria, oro - motor structures and functions are restricted.

Treatment of dysarthria depends on the severity of speech problem. Speech and language pathologist aim to improve speech intelligibility (overall clarity of speech) by:

a) PNF (proprioceptive and neuromuscular facilitation).
b) Improving loudness levels.
c) Improving articulatory precision by using exaggerated consonants.

iii) **Apraxia:** According to Darley (1969), apraxia is an articulatory disorder resulting from impairment, as a result of brain damage of the capacity to program the positioning of speech musculature and the sequencing of muscle movement for the volitional production of phonemes. No significant weakness, slowness, or incoordination in reflex and automatic acts is seen (as cited in Freed, 2000). Treatment of apraxia of speech involves phonemic drills, giving proprioceptive and kinesthetic cues to the patients. MIT (melodic intonation therapy) is another technique used (as cited in Freed, 2000).

Darley (1975) stated that the goal of treating apraxia of speech is to help patients relearn the motor sequences needed to produce phonemes accurately.

iv) **Dysphagia:** Dysphagia means disordered swallowing. Swallowing disorders occur in all age groups from newborns to the elderly, and can occur as a result of CVA, presence of tumors and/ or progressive neurologic conditions. Swallowing consists of 4 stages namely oral preparatory, oral, pharyngeal and esophageal stage. Depending upon the stage affected, a swallowing therapist needs to make a judgement on the treatment modality.

A swallowing therapist aims to work on:

a) strengthening the oral and pharyngeal structures for swallowing.
b) modify the bolus in order to facilitate adequate swallowing.
c) recommend postures and maneuvers like chin tuck/ chin down postures according to the nature of disorder. During swallowing therapy, the therapist should ensure airway safety and rule out any silent aspiration. Children with autism, cerebral palsy, hearing impairment or mental retardation present with either absence of speech or deficient speech and language skills as compared to their age. The main aim of the speech therapist

is to bridge the gap between the chronological age and the language age of the child. The speech and language pathologist tries to explore the areas which the child would respond in and facilitate communication within child's impairment. Most widely used techniques for language learning are repetitions, modeling utterances, expanding a topic and role play. However, children with higher grade of severity may have to rely on alternative and augmented communication (AAC) in order to reduce the communicative burden on the caregivers.

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13. Multidisciplinary Rehabilitation in Autism

Autism is defined as a complex neurodevelopmental disability that typically appears during the first three years of life and impacts development in the areas of social interaction, communication skills and behavior. Autism is a result of highly complex interaction between the genes, brain and behavior through the developmental period. Autism is associated with early malfunction of a few structures of brain which are involved in processing social information. Despite the lack of specialized neural systems, children with autism continue to survive in an attempt to fit into the highly social environment.

It is a dysfunction in the neurologial network of the brain manifests into the spectrum of autism. It is a neuro-developmental disorder which leads to difficulties in speech, communication, social interaction, behavior, sensory issue and thinking ability. Children with autism have compromised mental capacities due to subnormal functioning of some areas of their brain. Despite normal physical appearance, their daily functioning is affected. Children with autism have special needs that must be catered to differently. The diagnosis of autism is usually made in early childhood and despite extensive research, the causes of autism haven't been definitively defined as yet.Management of Autism is complex and requires a multidisciplinary team approach.

Role of psychologists in the management of Autism

Bringing up a child with autism can be a challenging process. However, with proper knowledge and information about autism it is possible to make the process easier. As parents you require a lot of patience and perseverance throughout the journey. Every child with autism is unique, and at different ages the challenges also vary. Hence, you must be well equipped beforehand and be aware about the appropriate strategies required for your child. With behavioral issues being one of the major concerns in children with autism, a clinical psychologist/ child psychologist plays an important role in helping you and the child. A psychologist looks at what effect the behavior has on the child and may introduce a behavior management plan accordingly. They will talk through and provide solutions for various problems that you may encounter while parenting your child with autism. Here, we attempt to provide you with some

guidelines which will help you get the best out of your child in the most effective and easy manner.

Behavior Modification

The basics about changing behaviors:

When thinking about the dealing with a behavioral problem it is worth focusing on one area at a time rather than dealing with all at once. Narrowing the behavior down can help to understand why a particular type of behavior is occurring so that you can work out ways of changing or managing it. Trying to tackle several areas at once can make it difficult to achieve any positive changes in any areas. Firstly, list down behaviors of your child that you think are most negative (in a descending order); such as head banging, fighting with other children or refusing to get up in the morning. The least negative behaviors at the bottom of the list should be ignored temporarily or even permanently (for example, refusing to wear anything but red T-shirts).

Certain odd behaviors that are not injurious or harmful to the child or to others, may be looked at as an indication of creative or humorous attempts to adapt (making up silly songs or drawing violent pictures). These should be accepted as part of the child's unique and positive development, even if they seem peculiar to others.

It is important to keep in mind that punishment for a wrong behavior need not necessarily be harmful always. Punishment, if given in a constructive manner could help in increasing the child's awareness about acceptable and unacceptable behaviors. For example: If your child displays aggressive behavior then you could ask him to sit in the corner of the room, or stand facing the wall. You must give him an explanation as to why he was punished and what the acceptable behavior is.

Very often you may tell your child about the behaviors which are unacceptable or what he should not be doing. Instead, make sure you explain to him about the behaviors that are acceptable. For example, saying "Please sit here next to me" instead of "Don't jump around". It is important to maintain a consistent behavior and approach towards the child so that he does not get confused. Maintain well-defined rules which could be bent under some situations (when being rigid towards the child increases temper tantrums or hyperactivity).

The focus of any behavior intervention should always be on the development of new skills to help your child to cope with his environment and to communicate their needs. To make this change lasting the aim is to provide him with other ways of achieving the outcome, previously achieved through difficult behavior.

What are the various strategies for Behavior modification?

Before addressing the specific issues, an understanding about all the available behavioral strategies is necessary. You may use the best suited strategy from the following for your child, in a variety of situations. The strategies used are as given below

1. Positive reinforcement
2. Token Economy
3. Negative Reinforcement
4. Punishment
5. Shaping
6. Chaining
7. Prompting
8. Extinction or planned ignoring
9. Redirection
10. Time out

How can you help your child deal cope with transitions and changes?

- Children with autism yearn for sameness and routine. A change in their routine could be catastrophic. They would try their best to stick to their routine or would throw temper tantrums. It is seen that children with autism work better and learn better with people who are more structured (follow set simple patterns) in their daily routine. The following are a few strategies that may help them accept and adjust to transitions:
- Begin with small changes to their routines and then slowly progress to larger and more number of alterations. This will help them adapt slowly and in a comfortable way.
- Dim the lights of the room, when a new activity is being presented to them as this will help the child focus better and avoid distractions.
- Give prior explanation to your child about the possible transition. Helping them understand why a particular change is taking place would help them be prepared beforehand, rather than having a flaring temper after the change has occurred.
- Make the transition as enjoyable and as stress free as possible because otherwise the child's autistic features will shoot up.

Applied Behaviour Analysis

Applied behaviour analysis (ABA) is a specific form of behaviour modification. It is defined as the process of systematically applying interventions based upon the principles of learning theory. ABA is used to improve socially significant behaviours to a meaningful degree.

ABA is a science which includes general laws about how behaviour works and how learning takes place? It is based on the set of principles that form the basis of behavioural treatments. The principles work on the belief that influencing a response associated with a particular behaviour may cause that behaviour to be shaped and controlled.

This basically means that a behaviour which is rewarded is more likely to be repeated than a behaviour which is not rewarded. ABA is a mixture of psychological and educational techniques which are tailored to meet the needs of each individual child and alter his undesirable behaviours.

ABA is considered an evidence-based "best" practice treatment by the US Surgeon General and by the American Psychological Association. "Evidence based" means that ABA has passed scientific tests of its usefulness, quality, and effectiveness.

Basic principles of Applied Behaviour Analysis:

ABA lies on the principles of behaviourism and more specifically lies on the theory of operant conditioning. It involves giving a child a stimulus (a request) and then provides consequence in terms of either a reinforcer or a punisher. For example, a child if displays socially adaptive behaviour he gets stars, tokens or verbal praise. The consequence of the stimulus is a punisher when he does not display this appropriate behaviour. Punisher could be not giving verbal praise, or with holding the desired toy or activity of the child.

Thus,

- A reinforcer will increase the probability of the response; a Punisher will decrease the likelihood of the response.
- A reinforce and a punishment is different for different child
- Functional assessment of the rein forcers and punishers is essential as it helps in knowing the effectiveness of them on the child and shaping their behaviour.

Advantages of Applied Behaviour Analysis:

Applied Behaviour Analysis is evidence based and it has proved to be an effective intervention in teaching children and adults how to manage their challenging behaviours.

Applied Behaviour Analysis helps to:

- Increase appropriate behaviours
- Teaching new skills
- Regulating self by controlling self stimulatory behaviours
- To generalize the appropriate learned behaviour
- It helps your child learn what "to do" instead of just learning "to stop doing something"
- Improve ability and performance on tasks
- Reinforcement procedures increases on-task behavior or social interactionsand reduce behaviors like self-injury or stereotypical behaviour
- It helps teaching children self-control and self- monitoring procedures to maintain and generalize job-related social skills

Role of Occupational Therapists in management of Autism

The American Occupational Therapy Association (AOTA) defines occupational therapy as a "skilled treatment that helps individuals achieve independence in all facets of their lives. Occupational therapy assists people in developing the 'skills for the job of living' necessary for independent and satisfying lives". As parents and teachers, an independent and satisfying life for your children with autism, must surely be an important goal. Occupational therapists traditionally focus on teaching activities of daily living (ADL) like eating, bathing, grooming, dressing etc. More specifically in autism, occupational therapists with expertise in Sensory/Motor Integration and Skill training, work on optimizing sensory processes, altering behaviors and training for developing gross and fine motor skills, communication, play and social skills. Children on the autism spectrum may benefit from occupational therapy, both at home and at school. Performance of age appropriate meaningful activities depend on the interaction between the people (includes individual's physical, cognitive or emotional ability), the environment (accessibility, structure, safety, and availability of supports to carry out activity) and the nature of the activity itself (complexity, repetitions, size and texture of objects etc.)

What are the Occupational therapy intervention methods and strategies?

The main areas of Occupational therapy intervention include:

- Sensory/ Motor Integration
- Behavior Modification (this has been covered in detail in the section of
- psychological intervention)
- Skill Building (activities of daily living, handwriting, oro-motor skills, etc.)
- Prescribing, providing and training the use of Assistive technology and
- implementation of modifications at home (these have be

Sensory Motor Integration

Before beginning with therapy techniques and strategies, it would be helpful for you if you understand about the normal process and importance of sensory processing and integration. By definition, Sensory integration (SI) is the neurological process that organizes sensation from one's own body and environment to perform an appropriate motor response. There are the commonly known 5 senses of the body, which are hearing, sight, touch, taste and smell.

The Five lesser-known senses which help our body work in harmony with the self and the environment are:

1. **Proprioception and Kinesthesia** - It's the sense that tells about the body's joints and muscle groups, how to react, move smoothly, and tells the body 'where your body is, in space'.

2. **Vestibular or equlibrioception** - It's the sense of balance involved with the inner ear that stabilizes visual fields when the head moves and maintains equilibrium.
3. **Nociception**- Perception of pain
4. **Temporal Sense-** sense of time
5. **Thermoception**- perception of temperature differences.

Sensory integration makes it possible to use our body effectively in response to inputs from the above senses in our environment. Children with autism are believed to have difficulties receiving, assimilating, integrating and processing sensory information. As healthy individuals we unconsciously combine the above senses in order to use information from our environment. Children with autism have trouble learning to do this. Sensory integration therapy is a type of occupational therapy intervention that places a child in a room specifically designed to stimulate and challenge the senses.

Sensory integration therapy is driven by five key principles:

- The child must be able to successfully meet the challenges that are presented through playful activities (Just Right Challenge);
- The child adapts his/her behavior with new and useful strategies in response to the challenges presented (Adaptive Response);
- The child will want to participate because the activities are fun (Active Engagement);
- The child's preferences are used to initiate therapeutic experiences within the session (Child Directed).
- The child has an inner drive that leads him to search for opportunities in the environment that leads to a sense of mastery over the environment (Inner drive)

How does it benefit?

Problems with Sensory Integration may show themselves differently in each child. Activities are specific to a particular sensory system, or a combination based on the child's needs and tolerance. You may use these activities during the day and at home to enhance assimilation, processing and response to a variety of senses. They help in improving awareness, attention/ concentration, decreasing stereotypical (repetitive) behaviors, self-stimulatory behaviors, regulating state of arousal (hyper/hypo-activity), improving eye contact, communication skills, concept formations, planning and execution of motor tasks. These activities help the child's nervous system calm down and become more receptive to learning.

Figure 1: Playing in the Ball pool

Figure 2 Floor painting with one's feet

Figure 3: Wrap with different textures

Figure 4: Clay activities

Figure 5: Deep Pressure

Figure 6: Pulling a theraband

Figure 7: Weight bearing activity

How is sensory integration therapy delivered?

To be effective, sensory activities must be done every day just like medications need to be taken every day in order for them to be effective. Try doing some discrete learning tasks while the child receives soothing pressure. Your child may learn best when he lies across a beanbag chair with another bag placed on top of him (sandwich style). The pressure may calm his nervous system and prepare him for learning. Try slow swinging for 10 to 12 times a minute, during the lesson. Swinging helps stimulate language, encourage eye contact, and improve concentration. Teaching concepts like shapes, colors, numbers, sorting, counting, etc. are best learnt while on a slow swing. To help a fidgety, restless child sit still and attend to his lesson, try a weighted vest. The vest is most effective if the child wears it for 20 minutes and then takes it off for 20 minutes. This prevents habituation. In between study times give a break to your child when he can play with 'fidgets', or can jump 50 times on the trampoline or gym ball. This will satisfy his urge to move or spend his energy and help him focus better on the learning task. You may also ask your child to do a series of physical activities like jumping, running up and down stairs, doing sit ups Conversely, in a low energy, hypo-aroused child with a slow sensory system, learning can occur while doing a drill or while the child jumps on a trampoline, or by using a vibrating chair pad. Creating a visual room can be beneficial. Put in different colored lights, mirrors, colorful rotating discs, radium stickers of planets or stars, disco globes etc. Use them in a variety of ways to improve attention, concentration and eye contact.

Pick the best activity for your child by:

- Choosing activities wherein your child can lead direct or guide the play. This provides the opportunity to initiate a play activity.
- Finding out what works best and spread it across to other avenues. Maintain consistency between home and school to ensure learning, maximize results and confidence.
- Choosing age-appropriate activities, while keeping in mind that there could be a gap between his/her chronological age and developmental age. The best activities accommodate the child's abilities and sensory needs and tolerance levels.
- Involving other family members to participate.
- Designing them in such a way that they do not require an elaborate budget, space,or schedule.

Training For Activities Of Daily Living

One of the earliest life skills that you would teach your child is to perform basic activities of daily living like eating food, washing his/her hands and face, brushing teeth, taking a bath or shower, combing one's hair etc. These are developmental tasks that must be taught one after the other, according to the child's age. While the

average child can learn all of these skills by the time that they are five or six, children with autism often struggle with these tasks. An occupational therapist would work on training your child for all the ADL tasks. The information below may help you train your child at home. These simple and practical methods will help children on the autism spectrum to develop vital self-care skills.

The common techniques used for training these children include:

- Demonstration and Imitation
- Chaining and use of reinforcements
- Picture cards, visual aids (Show them pictures of steps in the activity)
- Prompts, verbal cues, manual hand-over-hand guidance
- Audio- visual aids (cartoon video, nursery rimes like- This is the way I brush my teeth
- Modifying the tasks (to a way in which they may be performed), equipments or the environment
- Helping them cope with the sensory issues (de-sensitization)

A combination of the above techniques can be used to teach all of the following skills like eating, brushing teeth, bathing, dressing and undressing, grooming etc.

Toilet Training

Independent toileting is an important developmental milestone under ADL (activities of daily living) skills. The primary goal of training is to increase independence, social acceptance and reduce the load on family members. Toilet training can be stressful for you as a parent and traumatic for the child. Teaching your child to use the toilet in the right way and at the right time can be a difficult task, whether they have autism or not. But if your child has autism, the process of developing a toilet routine can be much more challenging.

When (at what age) is it appropriate to start with toilet training?

Toileting is a complex task which your child should learn before he/ she enters school at the age of five years. The following skills must be mastered before you can begin with toilet training:

- Dressing and undressing
- Manipulation of fine papers,
- Awareness of bowel and bladder sensation,
- Gross co-ordination and body awareness
- Comfort and tolerance to multiple sensory inputs like noise, textures, temperatures etc.

Achieving bladder and bowel control contributes significantly to a child's self esteem. Ensure parental support and reinforcements during the initial sessions of training.

Role of Speech Therapist in management of Autism

Usually, the first thing a parent says to a professional dealing with autism is "My child does not have speech. Please teach him to talk." In the desperation to see your child verbalize with words and sentences, you fail to connect with him/her. Thus you are unable to notice all the other means of communication. Whether expression comes through spoken language, or picture cards, a communication device, gestures or sign language; it is all communication. Each child has something to say to us. It is our responsibility to listen in a way that ensures that they are heard and understood.

- Keep in mind the basics before getting to in depth training.
- Be emotionally available to your child. Let him know- "I am here for you."
- Do not forget to establish contact with your child before speaking or communicating: Physically move to the child's level. Squat down, kneel and position yourself so that you are face-to-face.
- Establish attention with contact, visual props; ensure that the child is oriented towards you.
- Use gestures meaningfully. Avoid waving in the air while you talk. Use gestures to accentuate the clarity of your communication, not to confuse the child or distract him.
- Do not use complex sentence forms and expressive forms of language. Stick to literal and concrete sentences.

What is the Role of Speech and Language Therapy in Autism?

A Speech and Language Pathologist (SLP) works with children with autism to address the following:

- Helping the child to understand communication
- Facilitating understanding of spoken language and situation expectations
- Giving the child something to talk about
- Giving the child a means of communication
- Giving the child a reason to communicate

The speech therapist works with the child and his/her family to facilitate effective communication among them such that it benefits the overall development of the child. The therapist deals with two categories of children namely, verbal and non-verbal. Diagnostically, there is no clear line of differentiation between verbal and non-verbal individuals with autism. In Verbal autism, children have language abilities which may not necessarily be correct with respect to language rules, grammar or

meaningfulness. Sometimes they may just string words together to form a random sentence. The SLP helps these children convert their vocabulary into effective and meaningful communicative sentences. Non-verbal autism is more challenging to treat. About 10- 15% of people with autism spectrum disorders are truly non-verbal, meaning they don't communicate using spoken words. However, it does not mean that they don't communicate at all. Many do communicate at different levels of complexity using keyboards, assistive devices, picture cards and sign language. Such training may be provided by a SLP.

The SLP also works on their cognition, understanding abilities, verbal repertoire and functional communication. Echolalia i.e. repetition of words or others' sentences is also tackled. During the first 3 years of life the brain is developing, thus it can be easily molded into any form. Hence it is the most important period for acquiring speech and language skills. Children learn languages faster during this period with adequate stimulation and exposure. Managing a child with autism at school or at home is a problem you must definitely be facing.

Management is based on the core concept of a multi-sensory approach [auditory, visual, tactile, sensory, and kinesthetic].

The bottom up process for speech development:

An eight-level hierarchy of supports make it possible to build the foundations for breathing, voice and articulated speech. This hierarchy will help u understand that firstly, no spoken language does not mean no communication and secondly that, a step wise process must be followed to help children on the spectrum find their words.

Level 1- Deep breathing/ exhalation.

Level 2- Voice/ vocal production.

Level 3- Intonation.

Level 4- Starting, maintaining, and stopping sound.

Level 5- Vowel sounds.

Level 6- Consonant sound development.

Level 7- Sequencing words.

Level 8- Purposeful speaking.

A speech and language pathologist will help identify at what level your child is and take him through each of these levels with the help of appropriate techniques. In the following sections we are going to discuss how you could work on your child's speech, communication, social skills and concept learning for children with verbal and non verbal type of communication. Initiating basics at home is a pre-requisite to achieve normal speech and language development.

Role of Physiotherapy in management of Autism

Traditionally 'Autism' is presumed to be a triad of behavioral, sensory and perceptual abnormalities. As soon as a diagnosis of ASD is confirmed the parents are advised to consult a range of rehabilitation professionals like occupational therapist, speech therapist, psychologists and special educators. However management of 'ASD' should not be limited to these. Slowly as the understanding of the disease is growing various studies have identified motor and physical impairment. But in the presence of gross behavioral and sensory manifestations the motor symptoms are often overlooked. Physiotherapist can help in optimal development of motor skills and develop program to address any underlying weakness in both sensory and muscular systems in children with autism. This empowers them to interact better with people and encourage participation which improves child's social skills and quality of life.

What causes motor impairments in ASD?

Although sensory processing deficiencies and behavioral abnormalities are profound in ASD, various motor abnormalities have been identified by various researchers in the last decade. Movement initiated in response to internal or external sensory stimulation requires integration of multiple sensory inputs and organization of the responsive motor outputs. Neuroimaging studies have suggested neural connectivity deficits in ASD, which may contribute to the deficits in the integration and organization of various neuronal responses. ASD shows less activation in cerebellum with relatively more activation in the fronto-striatal region. Evidence also now suggests that aspects of cerebral morphology are different in people with ASD, both volumetric (i.e., cortical thickness, regional area) and geometric (i.e., cortical shape) features. Different morphological features may have varied neuropathological and genetic underpinnings.

What are the potential benefits of physiotherapy for children with ASD?

Although several motor impairments have been identified; the patterns, sources and the causality remains poorly understood. It was believed that the motor symptoms could be corrected when the sensory and perceptual deficits are addressed; but it is intriguing to see the effect of physical intervention on various symptoms in ASD. 15 minutes training with aerobic activity in children with ASD significantly increases the performance in the classroom task. Physical intervention

through aerobic activities and strength training reduces the self stimulatory behavior , repetitive motor behaviors, improved social behavior and classroom performance. In the view of these benefits of physical intervention, physiotherapy has been integrated in the clinical framework for treating children with autism.

Physiotherapy helps to improve postural control to increase stability during fine motor, gross motor, and self-care activities. Improve static balance to improve motor control and attention and decrease impulsivity. Learn to perform the ideation, sequencing, timing and execution components of motor planning. Maximize sensory processing and organization skills to put into controlled motor skills. Lay down the foundations

of gross motor skills to support participation in community and peer activities. Most importantly physical exercise has a calming and relaxing effect. Recently different treatment modalities like aquatic therapy have also been used by physiotherapist for the treatment of ASD. Aquatic therapy helps to improve body awareness, coordination, muscle tone, and to reduce tactile hypersensitivity; it also provides vestibular stimulation and is therefore being explored widely.

To conclude, children of all ages learn through movement and need to master core motor skills in order to maximize their overall potential. Beginning as infants they develop stability so that they can learn to use their hands and feet independently from the rest of the body. They also learn how to manipulate the environment and how to move their bodies within it. They use movement to bond and communicate with others and to explore the world. Limitations in motor skills can lead to difficulty with all areas of development. Physiotherapy can be a beneficial part of a team approach to help children with ASD to be successful and independent as much as possible in school, home and in the community.

Aquatic therapy for the management of Autism

Autism is one of the neurodevelopmental disorders with unknown cause, ununderstood symptoms and therefore inadequate treatment strategies. This chapter will state to you why should your child undergo aquatic therapy? It will state the health benefits of aquatic therapy and what to expect in an aquatic therapy session.

What is aquatic therapy?

The Aquatic Therapy and Rehabilitation Institute defines Aquatic Therapy 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".

Simply put, aquatic therapy means making use of various physical and chemical properties of water for the treatment of various disorders. The most common question that arises in the mind is when we live on land how can being in water help us. That is also the answer to the question because water provides us an alternative environment where the body is more supported and can experience a

larger degree of freedom otherwise unavailable on land. Aquatic therapy is always used in conjunction with land based rehabilitation. Aquatic environment is safe and easy to maintain however it also has an inherent risk of drowning and therefore the therapy must be undertaken by a trained and qualified professional.

Aquatic therapy may consist of individual sessions with therapist and the child, it may also consists of sessions where the family members or care takers are involved or the sessions may also be conducted as group therapy with multiple children and their parents or care takers. Various techniques are used in aquatic therapy. Some of the most commonly used techniques are Halliwick, Bad Ragaz ring method, Watsu, Aai Chi and aquatic exercises.

Why aquatic therapy?

The most important is to understand the benefits provided by aquatic therapy and even simple immersion in water. But before reading about these let's first take a look at what are the difficulties experienced by these children.

Children with autism face range of difficulties and exhibit varied symptoms. Various sensory, motor and cognitive systems are impaired. Children find it particularly challenging to communicate, express, reciprocate socially and integrate the sensory inputs. Till very recently the motor impairments of these were underestimated but in last decade various motor impairments have also been identified.

Behavioral abnormalities start with some of the earliest symptoms being inability to establish or maintain eye contact, lack of interest in forming peer relationships and inability to modulate the emotional responses leading to aggressive behavior or self injurious behavior. Some children seek sameness and may get upset with even slightest change in routine. They lack the language and communication skills. They also show sensory processing abnormalities. The inputs we receive from the environment through all our senses are crucial in forming our motor, sensory and cognitive responses and in turn our social behavior. Children with autism may show hyper-responsiveness to these inputs or hypo-responsiveness or sometimes a combination of both to different sensoryinputs. Hyper responsiveness in turn leads to anxiety, aggression, stereotypical behaviors or repetitive behaviors. Sometime these children may seek more sensory inputs most often they seek deep pressure and vestibular inputs. These sensory processing and integration impairments may lead to lack of normal motor response by the motor systems. The children with autism may also exhibit hypermobility of joints, hypotonia, postural deviations, in-coordination, poor balance and poor fine motor control. Aquatic therapy helps in improving all of these symptoms. Aquatic activities are a fun and enjoyable experience that have many physical, psycho social, cognitive, and recreational benefits. Water activities provide autistic children with proprioceptive and tactile input. Children with Autism have significant sensory difficulties, and are very distractible. These children over or under react to stimuli in their environment and have very strong reactions to certain textures.

Beneficial effects of water immersion:

Mere immersion in water provides multitude of physiological benefits. Compressibility of water is poor; therefore it exerts a pressure on the immersed body from all the directions. This compressive force helps pump the blood from blood vessels back to the heart, increasing the amount of blood that enters the heart. Due to this increase in the volume of received blood heart is able to pump out more blood with every heart beat; increasing the cardiac output. Shoulder or Neck deep immersion increases the cardiac output and also created a larger pressure gradient in the blood pumped out and the blood vessels of brain, thereby increasing the blood supply to the brain. Increased blood supply means that brain receives nutrients much more efficiently and the toxic waste is taken away quickly. Water immersion therefore has a beneficial

effect for memory and cognitive tasks. Inappropriate or exaggerated responses of anxiety to any unpleasant stimuli in children with Autism spectrum disorders are thought to be due to autonomic nervous system dysfunction causing over arousal of sympathetic nervous system and depression of parasympathetic nervous system. Altered autonomic nervous system function is thought to be one of causal factors in Autism Spectrum disorders. Increased blood supply to brain and cardiac systems also leads to activation of the parasympathetic nervous system and suppression of the sympathetic nervous system; after immersion in water. Mere immersion in water therefore helps reduce anxiety, hyperactivity,repetitive motor mannerisms, stereotypical behavioral and inappropriate emotional responses. Water immersion results in calming of the children on spectrum. Buoyancy and upthrust experienced in water provides freedom of movement, which is lacking on land due to poor motor planning and co-ordination and increased risk of fall. Water supports the child but at the same time creates a relatively unstable environment providing vestibular inputs. Viscosity of water combined with hydrostatic pressure provides proprioceptive inputs. These are crucial in addressing the low tone and in-ordination in these children.

Session based therapies are known to provide following benefits:

1. Improve Posture, Coordination, and Body Control: Because water reduces a child's body weight by 90% while also adding resistance, many therapists report improvement in muscle strength, balance, and coordination
2. Improve Sensory Issues: Children with autism tend to over or under react to stimuli in their environment, including light and touch. The warm water and hydrostatic pressure of aquatic therapy help soothe the child in a safe and supportive setting. As a result, many therapists report an improvement in the child's ability to tolerate touch following aquatic therapy
3. Improve Social Skills: Group aquatic therapy has often been used to help in social skill training, promoting engagement and cooperation amongst children. As a result, many therapists note significant improvements in eye contact and self confidence amongst children
4. Improve Cognitive Functions: Aquatic therapy has been k nown to help improve a child's attention span, concentration, impulse control, frustration tolerance and ability to follow instructions

What to expect in a session of aquatic therapy?

An aquatic therapy session can be conducted as an individual session or group therapy session. Group therapy sessions are particularly beneficial for improving the social skills and behavioral abnormalities in these children. A detailed assessment should be duly undertaken before the session. Building a rapport with the child on land before entering into the alien water environment is essential. There are various techniques that a therapist may utilize during these sessions. Some of the common concepts in aquatic therapy are Halliwick therapy which uses a 10 point program to

increase the water adaptability, breath control and movement of the body when immersed in water. Bad Ragaz ring method is essentially used for motor system deficits like low tone, muscle weakness and in-coordination. Aai chi uses various postures and movements in water which provide active relaxation where as Watsu is a technique used for passive relaxation while in water. Various aquatic exercises can be used for building the aerobic endurance. Aquatic therapist will make use of all of these techniques in combination for optimum results.

The time duration for the aquatic program is pre-determined. Ideally an aquatic therapy program for ASD should be for about 2-6 months with a frequency of 1-3 times per week.

In summary the versatility of water allows for a large variety of goals that can be achieved with children on the spectrum. The distinctive characteristics of this condition have to be considered when designing and implementing an aquatic therapy program for this population. It is important to test the skills on land pre and post intervention, to document the clinically relevant changes.

14. Multidisciplinary Rehabilitation in Cerebral Palsy

Cerebral palsy is a movement disorder causing inability to perform movements due to lack of muscle strength, muscle co-ordination or excessive tightness of the muscles. This is because of the brain damage and not because of primary muscle damage. The damage to the brain casues abnormal or absent signals reaching the muscles, which causes weakness or stiffness of the muscles and abnormal movements. Cerebral means pertaining to the brain and palsy means paralysis. It is caused due to poor development or damage to the brain during gestation, at birth or after birth up to 1 year. Although, primarily a movement disorder; it may also lead to impairments in understanding and cognition, learning, intellect, behavior, communication, speech, sensations, perception, hearing and vision; depending upon the areas of the brain damaged.

Cerebral palsy is permanent and affects the children for life. The damage to the brain is neither progressive nor reversible; meaning the damaged part will not get worse nor will it repair completely. The symptoms however may worsen or get better depending upon how the child is taken care of. It is therefore very important to understand what are the symptoms and associated problems with cerebral palsy and how to best manage these so that the difficulties experienced by the child do not increase.

Since the impairment involves multiple body systems a holistic approach in warranted in managing these children, rehabilitative therapies play a great role for functional improvement and to prevent the secondary complications in these children. Therapies make use of brain plasticity to achieve functional goals. The multidisciplinary team may consist of therapists like physiotherapists, occupational therapists, speech therapists, aquatic therapists and psychologists.

Physiotherapy management of Cerebral Palsy

Physiotherapy plays an important role in managing a child with cerebral palsy as soon as the child is diagnosed. Depending on the symptoms, the physical therapy program is planned for every child uniquely. Children with mild cp may not need intervention as extensive as for a child with moderate to severe cp. Physiotherapy helps to improve independence by improving mobility, strengthening the muscles ,

improve the ability to move the parts of the body, prevent joints to become tight or contractures to develop. Exercises help the child to learn how to sit, stand and walk.

Physiotherapy goals differ with the different types of CP:

1. Spastic child:
    - Relax stiff muscles
    - Prevent deformities
    - Encourage movements which prevent spastic body positions
2. Floppy child:
    - Provide support in good position
    - Strengthen muscles.
3. Ataxic child:
    - Improve balance
    - Help walk and stand steady
    - Control unsteady movements
4. Athetoid / dyskinetic child :
    - To control the abnormal or unwanted movements.
    - Control of abnormal posture.
    - Improve co-ordination
    - Smooth execution of voluntary movements.

Physiotherapy treatment aims to:

- Encourage normal movement as much as possible.
- Follow developmental stages.
- Encourage use of both sides of body.
- Improve posture: to maintain correct position while sitting, standing and walking.
- Strengthen muscles: improve the power of the weak muscles.
- Improve range of motion of all the joints i.e. to prevent the joints to develop tightness.
- Exercises to reduce tightness and prevent contractures: due to complications like spasticity and dystonia, these children tend to develop contractures, which can be prevented by corrective exercises and medical management.
- Exercises to improve endurance.
- Chest physiotherapy to reduce secretions to help keep lungs clear and strengthen respiratory muscles

- Improve balance in both sitting and standing
- Teach or develop transitions, example : supine/lying to get up, sit to stand, half kneel to stand etc.
- Teach usage of adaptive devices.

Different therapies used by therapist to treat children with cerebral palsy are:

1. **NDT (neurodevelopment therapy)**: it is a therapeutic approach, which helps in assessment and management of movement problems or dysfunction in children with neurological dysfunction. It aims to maximize child's functional capabilities. It is also known as bobath therapy and was developed in 1940's by Dr and Mrs.Bobath. The treatment aims to makie desired movements more possible and prevent undesired movement. It also helps to achieve normal motor milestones in children with cerebral palsy.
2. **Patterning:** it is a concept based on the theory that typical brain development can be facilitated in the brain injured child by passively repeating the sequential steps of typical development. Failure to normally complete one stage of development impairs the development of subsequent stage. This approach is laborious and also requires multiple sessions every day. Parents and caregivers are trained to carry the procedure at home also.
3. **Constraint-induced therapy**: this therapy aims to improve the use of affected hand in child with hemiplegia (paralysis of one side of the body).The normal hand is plastered for couple of days, to improve the use of affected hand.
4. **Hippotherapy**: it's a technique of horseback riding which has shown improvements in muscle tone, posture and balance.
5. **Spider web therapy**: this techniques involves a number of different elastic cords to specific points on one end of patient's body to different points on the other. This device helps to move the patient move independently while controlling their movement as well as strengthening different parts of the body.

Physiotherapist can guide the parents well as they spend a lot of time with the child. Parents need to get trained, so that home program can be followed effectively. Therapist and parents need to work as a team to obtain the best result in the child. There are several centers where different types of therapies are offered for cerebral palsy. Knowledge about these different therapies will help the parents to carry our exercises of home program.

Parents can use following simple approaches to do therapy at home:

- Exercise the child's limbs using interactive play.
- Set aside times for active play including other members of the family.
- You can encourage your child to move and play by banging pots kept together or slapping hands on the table

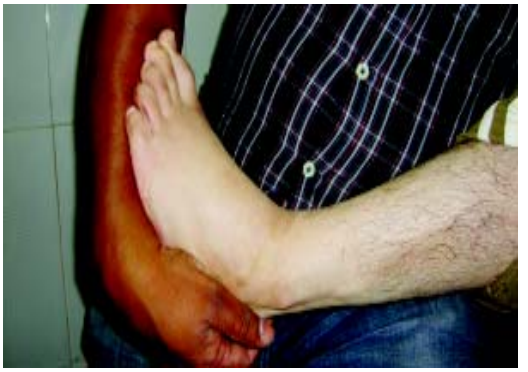


Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

- Child should be encouraged to play with others, especially with children of the same age.
- Encourage activities with the affected side more, for example if your child is hemiplegic, you can encourage him/her to watch TV from the affected side or by talking to them by standing towards their affected side. Below are few simple physical therapy exercises/advice on various position or equipments including diagrams, to help parents or care givers continue therapy at home.

Occupational Therapy management of Cerebral Palsy

Occupational Therapy is a treatment that focuses on helping an individual with cerebral palsy to achieve independence in all areas of their life. An Occupational therapist treats patients with Cerebral Palsy using various neurological treatment approaches aiming for complete neurological integration, bridging developmental gaps, refinement in motor performance, improving learning abilities.

Goals of Occupational Therapy

1. To provide an individual having Cerebral palsy with positive, fun activities that will enable and enhance their physical, cognitive, gross motor and fine motor skills and help them increase their self esteem and give them a sense of accomplishment.
2. Focus on training an individual for skills that are necessary to perform the daily activities. These activities include play, self care activities like dressing grooming, bathing, feeding, fine motor activities like writing and drawing.
3. Focus on the visual motor problems, cognitive and perceptual disabilities.
4. To promote a better upper extremity use and functional independence.
5. Focuses on providing with adaptive devices and adaptive seating devices.
6. Parental counseling is again an important aspect of with regards to optimizing
7. parental support for improving the functional abilities of a child with cerebral palsy.

Different treatment approaches are taken and considered. Since no child is same, intervention for each child is specific and unique related to the strength and limitations of each child.

Therapeutic techniques for various symptoms

Normalizing the Abnormal Tone:

In Cerebral Palsy sometimes the muscle tone is higher than normal or sometimes the muscle tone is lower than normal. Normal tone in the muscle is required to keep the body upright and to perform the movements of upper limbs and legs. Due to this varying and fluctuating tone it is difficult for the child to perform any movements of the trunk and limbs. Hence, reduction of muscle tone is an important treatment goal,

to improve comfort, care, and active function and to prevent future musculoskeletal complications. The most common kind of tone seen in cerebral palsy is spasticity.

Facilitatory Techniques: techniques to increase the muscle tone

- Include heavy joint compression (more than body weight): to facilitate muscle co-contraction (eg: prone on elbows, quadruped, sitting on therapy ball etc).
- Stretch: extending the biceps.
- Tapping: taping over the muscle belly to facilitate a particular muscle with the fingertips.
- Vibration: applied over the muscle belly to facilitate the muscle.
- Fast rocking: over a therapy ball, or in quadruped position to increase the tone.

Inhibitory Techniques: techniques to reduce the muscle tone.

- Neutral warmth: wrapping a child in cotton blanket/ comforter to relax and reduce the abnormal tone.
- Slow/ gentle rocking: over a therapy ball in a slow speed to decrease the tone. Slow stroking: over the paraspinal area from occiput to coccyx in prone position to reduce the tone.
- Slow rolling: on mat.
- Llight joint compression (less than body weight): sitting or lying position, pressure over the joint

Therapeutic Intervention:

- For a Low tone Child: small and heavy joint compression, fasting rocking on chair or therapy ball, fast rolling, weight bearing exercises in prone on forearm, prone on Arm, on all fours, small joint compression of hand etc.
- For a High tone Child: slow movement like slow rocking, slow rolling, slow stroking, tone inhibiting postures like neck and trunk flexion, etc.

Integration of Primitive Reflexes and Development of normal motor patterns

Primitive reflexes develop during the gestation period and usually get integrated to higher levels of development by the CNS. In Cerebral Palsy due the damage to the CNS, there is incomplete integration of primitive reflexes in children with Cerebral Palsy due to which their development is halted.

Facilitating and Developing a Good Postural Control

A child with CP has a poor postural control because of delayed and incomplete motor development, decreased motor control, lack of stability difficulty in anti gravity movements, lack of dissociative movements(individual movement of trunk or extremities) and stereotypical movements with compensatory mechanisms.

Figure 7

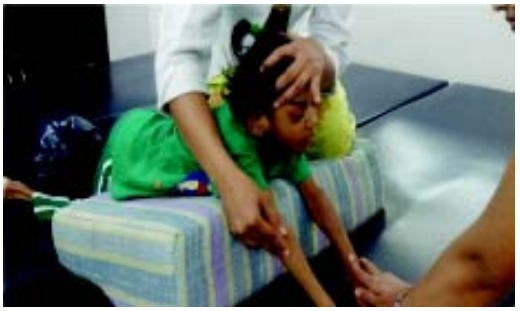


Figure 8

Figure 9

Figure 10

Figure 11

Figure 12

Development of postural control is also affected when there is presence of deficit is the organization of sensory inputs. An efficient postural control is important for performing voluntary skills like eating, dressing, bathing etc.

Occupational Therapists use Neurodevelopmental Treatment Approach which is aimed at facilitating and normalizing the tone of the muscles using various facilitatory and inhibitory mechanisms, reaction and movement patterns and managing the specific reactions to the treatment of equilibrium. Also it is said that children with cerebral palsy have a better postural control in upright position rather than the reclined or tilted position.

Prevention Of Contracture and Deformities

Muscle spasticity is a significant source of functional disability in a child with CP. Due to which secondary complications like development of contractures and deformities of Upper Limb, Lower Limb and Spine, are very common in children with Cerebral Palsy.

Treatment strategies aim at :

- Proper Positioning in Supine, Sidelying, Sitting and Standing
- Passive Range of Motion of all the joints of upper limbs and lower limbs
- Stretching of all the joints of upper limb and lower limb.
- Splinting of Upper Limbs and Lower Limbs

Sensory Integration (SI)

SI (sensory integration) is the ability of the brain to process information to make adaptive response to the environment. Intervention techniques should address the underlying sensory deficit and not the behavior. SI uses all senses but focuses primarily on the Vestibular, Proprioceptive and Tactile Senses. A child's brain organizes sensory stimulation from touch and movement in order to learn and respond successfully to the environment. Occupational therapists use various approaches to help integrate these senses for facilitation of movements and congnitive improvement.

Development of Visual Perceptual Skills

Visual Perception is defined as the total process responsible for the reception (sensory functions) and cognition (specific mental functions).

1. Visual receptive Functions: activities like focusing, dart throwing, playing with marbles.
2. Visual Cognitive Functions
    - Visual Attention
    - Visual memory
    - Visual discrimination / Object (form) perception
    - Visual Imagery

CP children with Visual Perceptual problems demonstrate many problems like in ADLs e.g. difficulty in combing, tying laces, matching clothes or in Play e.g. difficulty in sports, cutting, constructing, doing puzzles.

Intervention focuses on visual perceptual training involving Developmental, Neurophysiologic, Sensory Integration and Compensatory approaches which helps in improving skills that limit function and also compensate for the limitation.

Training for Activities of Daily Living

A child with severe developmental learning delays need training for self care activities

like bathing, upper body and lower body dressing, brushing teeth and feeding themselves, bowel and bladder management, functional mobility sleep and rest.

1) Feeding: Intervention in feeding involves positioning, handling and compensatory strategies. Proper positioning should be emphasized while feeding to promote oral motor functions.

2) Dressing: Learning and participation in dressing is a major step in achieving independence. Even with limited motor and sensory skills dressing can be made easy by motivating the child to actively participate and reducing demands placed on the child.

3) Bathing: Achieving cleanliness is essential for maintaining a good hygiene. Bathing can be made fun and a special bonding time with the mother/ caregiver. Occupational therapist can use bathing therapeutically to enhance motor and sensory skills.

4) Toiletting:Independent toileting is very important for achieving self maintenance. Toilet training can be quiet challenging in a CP child as the child must be temperamentally and physically ready to accept toilet training as well as able to understand the process in order to have any success.

To summarize occupational therapists integrate the physical capabilities of the child into the functional tasks and optimize the outcome by suggesting modified performance or by providing adaptive devices.

Aquatic therapy management of Cerebral Palsy

Aquatic therapy is defined 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" by The Aquatic Therapy and Rehabilitation Institute.

In simple terms aquatic therapy means making use of different properties of water to facilitate functional recovery and independence of children with CP.

Physiological effects of aquatic therapy in Cerebral palsy

Heart and lungs

Water exerts compressive pressure on the blood vessels and pumps up the blood from limbs to the heart. In children with cerebral palsy because of inactivity or muscle weakness or low muscles tone the blood circulation may be sluggish. This causes the blood to be pooled in the lower 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, as the tone of the muscles alters this relaxation is difficult. Incomplete relaxation leads to exhalation of the air from only the upper parts of the lungs and accumulation of air 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.

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. 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 of the muscles. Joint compression combined with increased blood supply help in reducing the tone of the muscles. Viscosity of water helps in strengthening the muscles. Improved circulation helps improve flexibility and pliability of the muscles.

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 nerve signals that are responsible for increased tone of the muscles.

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 in cerebral palsy.

Benefits of aquatic therapy in cerebral palsy

- Sustained reduction in spasticity
- Improved muscle and movement co-ordination
- Improved oromotor control
- Improved respiratory capacity
- Better flexibility of the muscles
- Improved walking patterns
- Improved eye - hand co-ordination

- Improved muscle strength
- Improved cardiovascular endurance
- Regularization of the sleep patterns
- Reduction in the abnormal involuntary movements
- Reduction in the sudden spasms of the muscles

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 small 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 oromotor especially 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.

Therefore aquatic therapy may be preferred in some children or preferred over a certain phases in a child's development. It provides an excellent medium to train the child and improve their motor impairments. It is fun and enjoyable ensuring long term adherence. In adults it helps to maintain various cardio-respiratory health parameters. It is relatively a new form of therapy in India, however it has been an established form of therapy worldwide for decades. It is safe and very effective in improving the quality of life of the children with cerebral palsy. However aquatic therapy alone is not sufficient and must be incorporated in the multidisciplinary rehabilitation program.

Speech therapy management of Cerebral Palsy

The Audiologist and Speech Language Pathologist (ASLP) is responsible for the effective assessment, diagnosis and management of the disorders related to swallowing and feeding, hearing and communication, affecting children with CP. Management by an SLP will vary according to the age of onset of the pathology and age at which the child reports to the SLP, affected domains, severity, pathophysiology, and associated problems. An important guideline is that for the assessment of deficits, the child's chronological age needs to be considered and for treatment planning, his developmental age. It then becomes clear to the caregiver as to at what level the child is, at present and what is the lag between present and the level he needs to achieve within the constraints of his impairment. In all these endeavors, it is important that neither the caregivers nor the professionals lose the sight of the child as a whole. When all the team members and the parents work in coordination, it will result in faster and better progress in all the affected domains of the child's development. The purpose of this endeavor is not to replace sessions with the rehabilitation professionals,

but provide a support to caregivers of children with CP, where such help is not available, or until such sessions can be arranged. It is hoped that this venture is found useful and practical for them. The following section deals with the management of primary disorders- breathing disorders (from the SLP's perspective); swallowing/ feeding disorders; hearing disorders- and secondary disorders overlaid on the primary ones- communication and speech.

Management of breathing disorders for Relaxation and Breathing Exercises

These are meant to relax the muscle tone and reduce rigidity of the respiratory musculature and are to be primarily done by the Physiotherapist. It is essential that these need to be also done by the SLP in consultation with the physiotherapist owing to its relevance in swallowing and speech production. The exercises need to be demonstrated in a clinical set up and then to be implemented in the daily regimen by caregivers.

Since PTists trained in Neurodevelopment Treatment (NDT) principles and treatment can help a great deal in this regard, this exercise regimen has to be planned in coordination with the physiotherapist trained in NDT. NDT is the best treatment approach for enhancing neuromuscular control and breathing capacity which is imperative for the child's general health and also for his later speech development.

Management of hearing impairment (HI)

It is a challenge to work with a child with multiple impairments- CP and HI- and treatment of HI needs to be planned in consultation with the ENT surgeon and the ASLP. Referral to the ENT surgeon is imperative for treatment of conditions that can be medically or surgically treated. Once the best of those options have been tried and the child has irreversible sensorineural hearing loss, then the Audiologist assesses the nature and degree of HI through a battery of audiological tests based on the type and degree of the hearing loss, the child may be fitted with suitable amplification (Hearing Aid fitting) in case of sensorineural and mixed type of hearing impairments. In a child who has HI, fitting with suitable hearing aids can be time consuming and challenging. This just gets all the more challenging when there are multiple impairments that is, CP and HI and even more so if such a child is also having cognitive impairment as may be seen in children with post- Rubella syndrome.

It is crucial that the child is fitted with a hearing aid most suited to his HI for best acceptance. If the hearing status is not a true estimate, there is a risk that the child may be fitted with a hearing aid too powerful which the child would understandably reject, and if it is less powerful it not meet his needs. Hence it is after many sessions and painstaking efforts of an Audiologist that hearing aid fitting may be successfully completed. It is necessary that Hearing Aid trials are done with the child's customized earmoulds. Behind-the-ear (BTE) type hearing aids may be mostly considered as best suited for these children.

In recent times, there is the additional option of cochlear implant (CI) surgery. It is a very important role of an audiologist to do a pre-CI evaluation and determine candidacy for CI surgery. Only when the hearing loss indicates a cochlear loss of a permanent nature and there is not a sufficient degree of improvement with amplification tried with at least 6 months of Hearing Aid fitting, is this surgery considered. After fitting with suitable hearing aids or with CI, the Audiologist & SLP begins with rehabilitation and initiates intensive speech and language therapy.

Management of feeding and swallowing disorders

Oral motor evaluation of the pre speaking child can be best achieved through modified feeding. Love, Hagerman and Tiami (1980) have presented an experimental clinical dysphagia scale wherein 5 feeding tasks are used for assessment:

- Biting
- Sucking
- Swallowing
- Chewing soft food
- Chewing hard food

The children are observed while having assorted foods such as spoon foods, chewables and drinks. Their positioning and any use of adaptive equipment are also observed. Based on the deficits seen, the SLP as the swallowing therapist can plan the therapy. Swallowing therapy is indicated when the actual stages of swallowing, the triggering of swallow reflex and the oral and pharyngeal transit time is worked upon, whilst at all times focusing upon airway safety and ensuring safe swallowing. Hence, this requires the active involvement of the SLP in the capacity of a swallowing therapist. The first priority is to focus on ensuring airway safety. Once safe swallow is ensured, the nutritional and hydrational requirements are considered for which, intensive swallowing therapy is necessitated.

Management of communication disorders in a nonverbal/Minimally verbal child

In assessing communication, it is imperative for the ASLP to do detailed audiological evaluations to rule out hearing impairment and if confirmed, to do the necessary intervention. More about this is given in the section on management of hearing disorders.

With the help of a psychologist, the child's cognitive status needs to be understood and performance IQ or SQ needs to be calculated. These evaluations are imperative for the SLP to assess communication and language development of the children with CP.

Non-verbal communication can be assessed from gestures, facial expressions and vocalisations in response to age- appropriate questions asked, and verbal communication comprising of speech and language needs to be assessed using formaland informal assessment procedures. There are assessment protocols which are designed for nonverbal children like the Picture Test of Receptive Language by Kaul (1999) which tests receptive language uptil 4 years of age. In case of non-verbal children, where it is difficult to gauge their comprehension formally, or as an adjunct to formal methods, an attempt may be made to do so by informal methods. This could be done by attempting to understand their comprehension of humour by telling them funny stories and jokes appropriate to their chronological/ developmental age, and observing whether the child smiles or laughs at the appropriate junctures. The SLP or caregivers could also observe the expression in the child's eyes which may change with the content of speech. This may prove to be an important indicator of verbal comprehension. An effective way to train parents / caregivers can be to demonstrate language therapy sessions by an experienced SLP and train them to emulate the clinician in extra clinical settings and thus be proxy clinicians. Herewith is presented some tips as to language and speech stimulation by caregivers.

Psychological management of cerebral palsy

Education and vocational preparation come into the foreground by school age. During this crucial period, concerns about the physical disability should not distract attention from the emotional and social needs of childhood and adolescence. Disabled youngsters need the same variety of life experiences as all other children, to develop emotional flexibility, personal determination, and social skills. As a child with cerebral palsy grows older, the need for different types of therapies and support services will also change. Psychological interventions for children with cerebral palsy are aimed at obtaining early diagnosis of co-morbidities and therapies.

Diagnosis of psycho-motor and psycho-social development:

- Assessment of the actual development in terms of deficits of fine motor skills, perceptive development, social development and independence
- Assessment of interaction between mother and child aged 0 to 3 years of age
- Assessment of the level of the deficit manifestation in terms of neurological diagnosis

Psychological assessment:

- Cognitive processes: attention span, memory, thinking, intellect
- Assessment of fine motor skills
- Assessment for school maturity
- Assessment of brain functions - gnosis, praxis, speech

- Assessment of the emotional and behavioural state of the child
- Personality assessment

The assessment process differs from an individual to individual and the nature and severity of the case. The assessment process usually lasts for about 45 minutes and if needed then it is held in several sessions. The final medical report includes the test results and other relevant observations made during the examination.

Therapeutic Interventions: Below mentioned are list of therapies for individuals with cerebral palsy:

1. Neuro-cognitive therapy:

This is a new approach to treating individuals with cerebral palsy. It is based upon two proven principles:

i) **Neural Plasticity**: The brain is capable of altering its own structure and functioning to meet the demands of any particular environment. Consequently if the child is provided with an appropriate neurological environment, he will have the best chance of making progress.

ii) **Learning**: Lev Vygotsky proposed that children's learning is a social activity, which is achieved by interaction with more skilled members of society. Counseling and behaviour therapy, for emotional and psychological challenges may be needed at any age, but is often most crucial during adolescence.

2. Cognitive Rehabilitation Therapy (CRT):

Children with cognitive impairments face tremendous levels of uncertainty and frustration, thus in need of additional support. As a parent it is very important that you should learn the best ways to interact with your child as this can immensely beneficial as the child grows up. Cognitive rehabilitation is a program of guided therapy to learn (or relearn) ways to concentrate, remember and solve problems after an illness or injury affecting the brain. It is a structured set of therapeutic activities designed to retrain an individual's ability to think, use judgment and make decisions.

The focus is on improving deficits in memory, attention, perception, learning, planning and judgment. There are many intervention strategies and techniques used to help children reduce, manage or cope with cognitive deficits. The desired outcome of cognitive rehabilitation is an improved quality of life or an improved ability to function in home and community life.

Cognitive rehabilitation techniques are restorative training or re-training the brain in normal function or compensatory ways. This technique teaches the child to make use of tools to help make up for the deficits.

The goal of cognitive rehabilitation is to improve cognitive abilities in order to obtain as much independent functioning as possible. Some of the specific benefits of cognitive

Figure 13

Figure 14

Figure 15

Figure 16

rehabilitation include improvements in the following deficits:

- Attention span
- Memory
- Problem - solving
- Visual - spatial relations
- Learning functional tasks such as feeding, dressing, etc.

3. Behaviour therapy:

This therapy is often used to enhance child's ability and discourage destructive behaviours. As symptoms of cerebral palsy can cause behavioural and emotional problems, many children benefit from counseling or behavior therapy. Behavioural therapy utilizes psychological techniques to improve physical, mental, and communicative skills. The activities used may vary greatly according to age and disability of the child. Some techniques will be used to discourage destructive

behaviour whereas the others to encourage self-sufficiency. Ultimately, a behavioural therapist will act as a coach to the patient and family, by suggesting ways to improve behaviour, as most of the work will be done at home.

Behaviour therapy can complement physical therapy, as employing psychological techniques that encourage the mastery of tasks can promote muscular and motor development. Behavioral therapy can help alleviate depression, mood swings, sadness, loss, anger and frustration by allowing previous negative outcomes to be replaced with a more positive perspective. Praise, positive reinforcement, and small rewards can encourage a child to learn to use weak limbs, overcome speech deficits, and stop negative behaviors like hair pulling, throwing temper tantrum, etc.

Living with a disability, no matter what the severity, can feel like a limitation to the disabled person. It is for this reason that individuals, especially children who are subjected to the limitations of a disability from early on in life, can at times develop negative behavioral traits that may further affect the person's ability to live life fruitfully and independently. It is in such conditions, in which the person's quality of life is being affected or they are affecting the environment around them that behavioural therapy can be so valuable. Even in situations where no such personality traits have surfaced, behavioural therapy is an important part of a child's ongoing therapeutic schedule.

In cases involving behavioural therapy, the treatment is aimed at helping them not only become more independent and productive, but also more able to function in everyday life. For instance, in physical therapy the therapist will help the child to learn to walk with more ease by walking with them, or pick things up with more ease while helping their muscles develop, while in behavioral therapy the therapist might put an object of interest, perhaps a toy or a piece of candy, into a box. They will then request that the child with cerebral palsy to reach into the box with his or her weaker hand. It is the reward aspect of coaching the child to use his or her weaker hand that connects with his or her mind.

4. Counseling or Talk Therapy:

As they get older, children with cerebral palsy will likely feel disliked by their peers, isolated from friendships, embarrassed by body image and/or frustrated with treatment goals. This may be a good time to introduce them to "counseling" or "talk therapy," where they can talk about the things that are bothering them and learn to put them in perspective. It differs from behavioral therapy in that the goals are more along the lines of learning to accept and embrace one's individuality rather than of raw behavior modification.

5. Aversion therapy:

This therapy works on the principle to reward rather than punish negative consequences. This can help enhance self - esteem and the confidence level of the individual. For example, if a child is throwing temper tantrums and isn't cooperative

during the therapy sessions then the parent or there therapist should not shout or get angry at the child. Rather the child should be rewarded if he or she moves in a positive direction for example; in spite of the temper tantrums if he is exercising then he or she should be praised and rewarded.

6. Group Therapy:

Group psychotherapy is a process of psychological influence by verbal and non-verbal techniques in which the psychologist uses the interactions created in specially organized small groups of patients (mainly interactions of emotional character), in order to reduce the patients' body and nervous discomfort and to improve psycho-social functioning. Individuals with physical or cognitive limitations often face real, and sometimes self-imposed, challenges in building relationships. Difficulties in communicating, fitting in or feeling accepted can lead to delays in social, emotional and even physical development. The group therapy is viewed as an important factor for individualization and socialization of children with cerebral palsy. The purpose of this method is to relieve patients and to develop their skills to solve problems as well to overcome noxious personal and behavioural stereotypes. Through group therapy children are able to acquire new knowledge, skills and good behaviour. The group rehabilitation and therapy depends on the specificity and psychological development of children within the group.

Regardless of advancements in technology, a psychologist can have a profound impact on your child's life. Because cerebral palsy can so greatly affect a child's physical ability, the psychological health and development of the child is of least concern. However, a positive state of mind and outlook can lead to an improved quality of life and functioning.

15. Multidisciplinary Rehabilitation in Intellectual Disability

Intelligence is defined as a general mental ability which involves learning, reasoning, problem solving, abstract thinking, comprehension, academic learning and learning from experience. Therefore, Intellectual Disability, formerly known as Mental retardation, involves impairments in all these areas of general mental functions. The most common cause of Intellectual disability can be genetic conditions such as Down syndrome or Fragile X syndrome, complications during pregnancy or at child birth or an illness or injury such as meningitis or head injury. However, in most of the cases, the cause can be unknown as well.

According to the DSM-5 criteria,"Intellectual disability involves impairments of general mental abilities that impact adaptive functioning in three domains, or areas. These domains determine how well an individual copes with everyday tasks:

- The conceptual domain includes skills in language, reading, writing, math, reasoning, knowledge, and memory.
- The social domain refers to empathy, social judgment, interpersonal communication skills, the ability to make and retain friendships, and similar capacities.
- The practical domain centers on self-management in areas such as personal care, job responsibilities, money management, recreation, and organizing school and work tasks."

The symptoms must begin during the developmental period as the disability does not require any specific age and the diagnosis is based on the severity of adaptive functioning rather than IQ scores alone. In the 5th edition of the DSM more emphasis is placed on the clinical evaluation as well as standardized intellectual testing with the severity of impairment on adaptive functioning. An intelligence quotient score of 70 or below is still considered to make a diagnosis of Intellectual Disability, with two standard deviations or more below the population. Based on the severity of the IQ scores, the level of Intellectual disability is categorized into mild (IQ = 55 to 69),

moderate (40 to 54), severe (25 to 39) and profound (below 25).The assessment of Intelligence based on three domains - conceptual, social and practical helps the clinician to make a diagnosis based on the individual's level of functioning in daily life and ease the development of a treatment plan.

Therefore, a multidisciplinary approach of rehabilitation plays a very crucial role in the management of individuals with Intellectual disability. Each discipline contributes to the functioning of the individual with respect to different aspects affected. It consists of Occupational therapy, Psycho social treatment, Speech therapy and Special Education.

1.Occupational Therapy in Intellectual Disability

Occupational therapy interventions for people with Intellectual disabilities mainly aim at improving the functioning of their activities of daily living.

- **ADLS**:Activities such as eating, dressing, bathing, and maintaining personal hygiene are improved with repeated practice. More advanced skills can also be taught such as minor shopping or preparing a meal for him/her. Intervention may also include basic work skills training (behavior norms, work routines), developing and practicing basic cognitive abilities, motor skills. Play intervention may include basic skills such as recognizing rules and agreed upon behavior, choosing suitable play activities to improve attention and concentration, eye hand coordination, motor functioning, visual perceptual skills and sitting tolerance.
- **Social participation**:These are activities related to agreed-upon behavior patterns expected of an individual within a given social system (e.g. community, family or with friends). The intervention within occupational therapy encourages the person to gain skills in the various areas of occupation and thus supports and strengthens social participation.
- **Functional**:Use of assistive technology such as a virtual keyboard, a touch screen, a motorized wheelchair, switch systems, computer programs and internet sites, adapted content amount, or voice output devices can be used to promote a variety of functions related to the individual, the occupation and the environment.
- **Adaptive:**Accessibility and Environmental Modification: Occupational therapy practice relates to the person, the occupation and the environment. The various limitations that characterize the population of people with intellectual disabilities require both general and client-specific environmental modifications to ensure accessibility. The characteristic difficulty in problem-solving, initiative and coping with unfamiliar situations, amplifies the need for accessibility modifications for this population. These accessibility modifications include changes in the environment (as in widening passageways, modifying playgrounds or adding symbol signs), in the equipment (such as adapting seating systems of adapting feeding aids), or of the task (such as changing the complexity of instructions or dividing a task into sub-stages).

- **Rehabilitative:** Rehabilitative approach is used for individuals with impairment to regain maximum functional ability. For ex: use of splints and modified assistive devices for persons with physical disabilities.
- **Leisure:** These are non-obligatory activities that are internally motivated and are performed at times that are not devoted to work, studies, self-care or sleep. Intervention in this area may focus on exposure to varied leisure opportunities, identification and choice of areas of interest, planning leisure time and participation in activities that lead to a perception of capability, pleasure, control and satisfaction.
- **Vocational training**: Vocational training will involve assessing the strengths and skills of the adult areas of interest, identifying abilities and choosing suitable occupations, analyzing occupations and adapting them as needed, and training and retraining them. For ex: structured workshops such as money management, communication skills, and appropriate business attire.

2. Psycho social Treatment in Intellectual Disability

Psycho social treatment involves behavioral intervention and family oriented strategies to deal with the maladaptive behavior of the child. Primary intervention must be for children before and during the preschool years as the child can be taught acceptable behavior at home as well at school. It includes various modes of behavior modification such as positive and negative reinforcement, extinction or punishment. The child at an early age can recognize signs of acceptable behavior through compliments, clapping, smiles and encouragement. This will also improve their social skills and help them be at ease with other children. Challenging behaviors such as anger outbursts or excessive stubborn behavior can be managed with negative reinforcement or punishment. Older children can be taught social skills such as turn taking, sharing, following commands and smiling. Family oriented approach involves encouraging the family to first accept the child with the disability and empowering them with the skill set they need to encourage their child with intellectual disability. Most of the time, it has been seen that there is overprotection from the family due to which the child loses opportunity for learning. Help is always available and the child understands that everything will be taken care of without him putting any effort. It is therefore important from a Psycho education perspective, for the parent to make their child become independent according to his/her ability rather than providing assistance at every level.

Psychosocial intervention can be used in three different contexts:

- Interventions with the individual - Increase social or vocational skills, educative focus with the aim of reducing distress.
- An intervention with the immediate social context - this intervention is used with the immediate family member or caretaker to reduce high levels of expressed emotion.

- Interventions aimed at the wider social context of the person - This includes a focus on housing, leisure or employment. For example, the use of supported employment to improve the social functioning of people with severe intellectual disability.

3. Speech therapy in Intellectual Disability

In order to determine the most appropriate interventions and approaches to communication with an individual with ID, it is necessary to understand the degree of communicative impairment that exists for the individual. Receptive communication is important for individuals with ID in that it constitutes the individual's "understanding" of what it being communicated to them. Repeated listening experience can play a significant role in the perception of synthetic speech on the part of individuals with mild-to-moderate intellectual disabilities. Slowing down both the pace of communication as well as the pace at which new concepts are introduced can also improve receptive communication for individuals with ID. When attempting to communicate, use simple words and sentences, repeat verbal information, supplement with non verbal signs and pictures and check for understanding.

There is a wide range of abilities in expressive communication among individuals with ID: some individuals with severe ID may not produce any intentional expressive communication while others with severe ID are capable of intentional communication and also some, limited, symbolic communication. Levels of expressive communication can be grouped from lowest to highest into the categories of intentional-contact gesture, intentional-distal gesture, single symbol, and combined symbols. When attempting to understand an idea being communicated by an individual with ID, use both closed and open questions, be attentive to the body orientation, facial expression, leading gestures, and eye gaze and offer more suggestions and prompting.

4. Special Education in Intellectual Disability

As vast majority of children with intellectual disability have mild level of intellectual disability, thus, special education for them involves teaching basic academic and learning skills. A special educator can vary the pace or rate of instruction, increase the intensity of instruction by presenting more trials for a given learning task, provide a more highly or structured environment, immediate reinforcement for target behavior or acquisition of skills and a more focused, individualized attention to the child. Basic mathematical calculations can be taught with designs or fingers so that they can use it for minor purchases. Systematic instruction can be used as a practice for teaching mathematics to children with mild intellectual disability. Reading of time in the clock can be emphasized, depending on the ability of the child. Writing can be taught by first holding thick crayons, allowing them to scribble, coloring inside the borders and joining the dots. Identification of words is taught by making them recognize letters repeatedly and then proceeding towards fixation. Identification of fruits is taught from known to unknown (such as Apple that is known, to Banana that is

unknown). Slowly and gradually teaching them parts of body, starting from eyes and nose which also helps them improve their eye contact. Orientation of left and right side of the body can be taught through actions by the special educator. Etiquettes and manners are taught such as greeting the teacher, taking permission, asking for help, sitting with other children to eat, taking turns and standing in queue. Teaching children through direct activity such as making sandwiches, paper folding, sequence activities etc.

16. Multidisciplinary Rehabilitation in Muscular Dystrophy

Muscular dystrophy is a progressive neuromuscular disorder that has manifestations in various body systems like musculoskeletal, neurological, cardio-respiratory and gastro-intestinal. Due to the vast physical manifestations and the progressive and incurable nature of the disease, it also had intricate psychosocial implications. Treatment of these children therefore requires a multidisciplinary team. Along with the medical and surgical management, rehabilitation therapies play a great role. Rehabilitation is also multidisciplinary and different aspects of rehabilitation need to be included in the management plan at different stages of the disease. A multidisciplinary rehabilitation team for muscular dystrophy may include professionals from the fields of physiotherapy, occupational therapy, speech therapy, nutrition management, psychology, aquatic therapy and yoga therapy.

The disease manifestations are significantly different as the disease progresses and it can be divided into 5 stages based on the functional abilities of the children.

- 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)

Physiotherapy management of Muscular dystrophy

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 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.

The exercises prescribed for these children have various physiological benefits in altering the disease progression and secondary complications.

Physiological benefits of exercise

Regular exercise helps to increased density of the bone minerals by improved absorption of calcium and phosphate. There is facilitation of the bone growth due to the tensile and compressive forces on the joint cartilages. The synovial fluid formation and recycling improves helping in joint lubrication and prevention of contractures. Size of existing muscle fibers increases and there is transient increase in the number of muscle fibers. Exercises stimulates local satellite cells bringing about neoagiogenesis in the muscles and formation of new muscle fibers. Low intensity muscular training exercises bring about 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. Thus the musculoskeletal system efficiency and repair improves with exercises. In an immedicate response to exercise blood pressure increases improving the blood supply but the chronic response to exercise is reduction in the peripheral resistance and blood pressure thereby reducing the cardiovascular

effort. There is also positive respiratory benefit which improves aeration and oxygenation of the blood. Exercise improves blood supply to the brain, thereby improving cognitive abilities. Exercise also has antidepressant effects and anxiety.

Basic principles of exercise prescription in muscular dystrophy

Exercise prescription in muscular dystrophy is very different from exercise prescription in the healthy population. The disease primarily affects the muscles and therefore their response to exercise is also very different. Although there is some wear and tear of the muscles while performing daily activities, not using these muscles does not preserve them longer. The muscles unless used appropriately undergo atrophy in addition to the dystrophic 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. Making use of Muscle plasticity to increase Type II fibers to preserve muscle strength
2. Regressive resistive training wherein the resistance is reduced as per the capacities of the dystrophic muscles keeping the repetitions same or increasing the repetitions
3. Facilitating concentric contractions and avoiding eccentric contractions
4. Preventing disuse and fibrosis

Based on these principles various types of exercises prescribed as below

1. Strengthening exercises to improve the strength of the muscles
2. Stretching exercises to improve the length of the muscles and prevent fibrosis and contractures
3. Range of motion exercises to maintain the movement of the muscles throughout the joint range
4. Endurance exercises to improve the musculoskeletal and cardiovascular system endurance.

Stage 1: Pre-symptomatic (0-4 years) (sub 2)

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) (sub 2)

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.

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.

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 cardio-respiratory endurance training exercises

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

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

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

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

In this stage the exercises are mainly passive, weight bearing exercises should be performed depending upon the health of the bones and contractures and deformities. The therapist must check the X-ray of the patient before passive weight bearing to assess the bone porosity. Active exercises of elbow, wrist and hand can be performed in this stage.

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.

muscles

Stretching exercises in muscular dystrophy

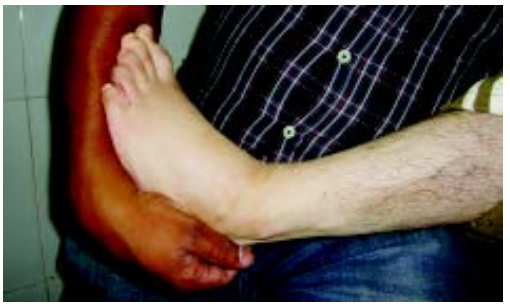


Fig. 1:Passive stretch for calf muscles

Fig. 2 Passive stretch for calf muscles

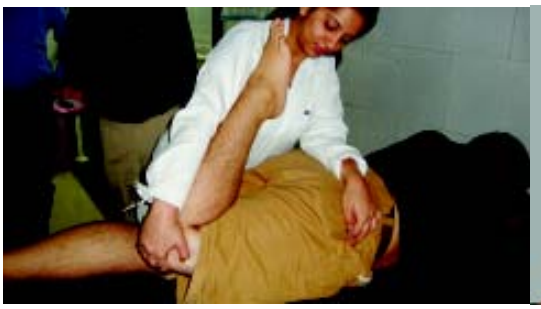


Fig. 3Passive stretching of hip

Fig. 4Passive stretching of hamstrings

Strengthening exercises for muscular dystrophy

Fig. 5 Neck strengthening exercises

Fig. 6 Shoulder strengthening exercises

Fig. 7 Shoulder strengthening exercises

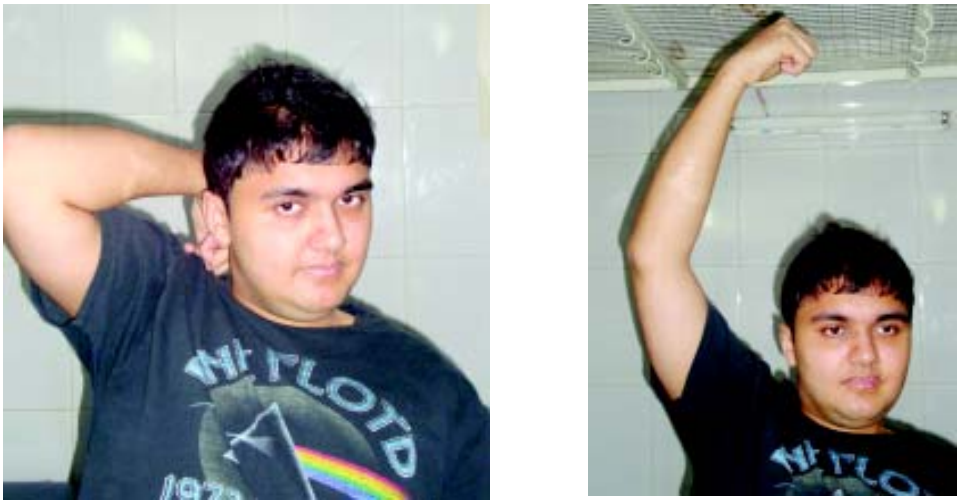


Fig. 8: Elbow exercises

Fig. 9 Wrist Exercise

Fig. 10 Wrist Exercise

Fig. 11: Hip exercises

Fig. 12: Hip exercises

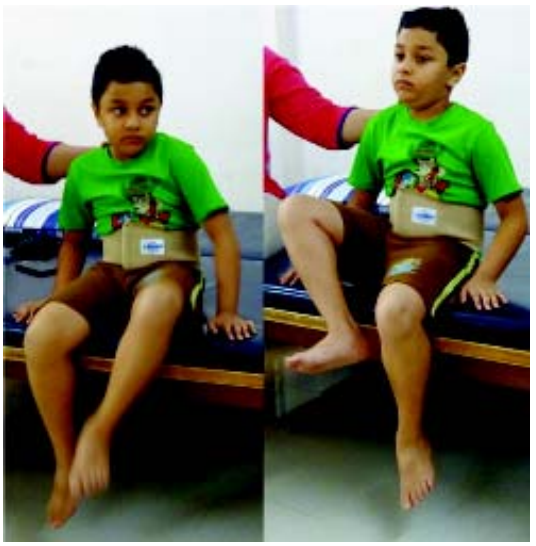


Fig. 13: Knee exercises

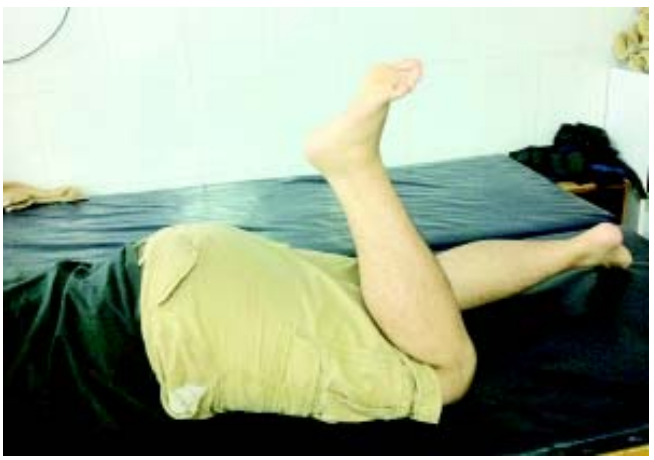


Fig. 14: Knee exercises

Fig. 15: Trunk Strengthening exercises

Fig. 16: Trunk Strengthening exercises

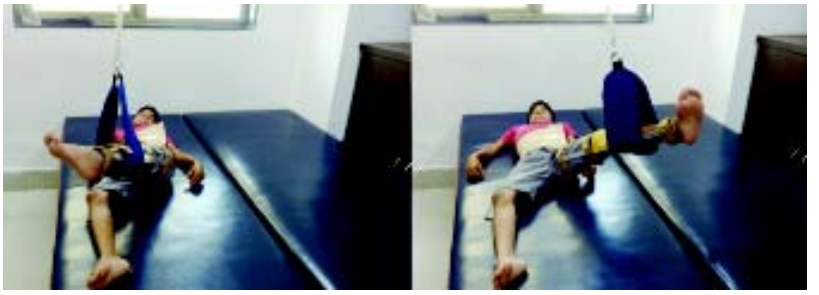


Fig. 17: Suspension exercises

Fig. 18: Suspension exercises

Fig. 19: Balance Training

Fig. 20: Balance Training

Occupational therapy management of muscular dystrophy

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

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.

The desired training effects can be achieved through play activities to improve functional skills as well as facilitate communication

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.

In these stages the child is likely to develop difficulty in managing activities like eating, bathing, grooming, dressing, toileting and transfers. Children can be given various adaptive devices to facilitate these activities and to improve the functional independence.

These children also develop various postural deviations and may require adaptations in the home and school environment to suit their needs. It is also important to take care of the needs of the patients while transporting them. Children are non-ambulatory in this stage and therefore will require wheelchair assistance. Other mobility equipments can be used like scooters for longer distances.

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

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

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

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

While transporting the children several practical issues may arise and need to be managed as per every child's need.

Transport Issues

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

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

Housing and school adaptations

There are many housing adaptations that the therapist can recommend that will make life easier for the person with muscular dystrophy and their care takers, like; Ramps, Bathroom alterations, Extensions, Handrails, Door alterations, Hoists and lifts.

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.

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.

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.

Adaptive devices for eating

Fig 21 : Two handled mug

Fig 22 : Plate Guard 1

Fig 23 : High rimmed eating untensil

Fig 24 : Anti skid mat

Adaptive devices for grooming

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

Adaptive devices for dressing and toiletting

Fig 12-17 : Velro clothing

Fig 12-19 Dressing-aid-stick

Fig 12-22 Commode Chair

Aquatic therapy for muscular dystrophy

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

- Reducing 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.

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.

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

Speech therapy management of muscular dystrophy

As the muscle weakness progresses the weakness of bulbar muscles and hypertrophy of tongue leads to speech and swallow impairment in children with muscular dystrophy. 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

Level I- Pre-symptomatic

Swallowing

It is unlikely that a patient would develop any swallowing or speech difficulties during this phase but some precautions need to be taken.

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

Level II to IV 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.

Various aspects may be involved in this phase that lead to impaired speech and swallowing. Some of these aspects are respiration, phonation, resonance and articulation. A speech therapist would do a detailed assessment for all of these factors and devise an action plan for the management.

Some of the assessment tools are

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.

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.

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

To improve the aspects of speech most important is the breathing exercises. A lot of emphasis should be given on breathing exercises in this phase. Along with the breathing exercises oral motor exercises can also be prescribed.

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].

Level V - Late ambulatory

Speech impairment does not progress as rapidly as that of swallowing impairment in MD. In this phase the clinical presentation may range from mild difficulty to inability to swallow. Due to progressive respiratory muscle weakness the patients may also be required to be kept on a ventilatory support with tracheostomy and may lose useful speech. Similarly for swallowing at this level of functioning the child may have been placed on RT feeds or PEG feeds and may be having very little oral feeds in small amounts of safe consistencies.

Assistive breathing devices and assistive communication devices may be offered in these stages to facilitate communication. Respiratory training may also be continued.

It is important that speech therapy is provided since the early stages of the disease to slow down the progressive deterioration.

Psychological management in muscular dystrophy

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 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.

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:

Hippocampus: Function - Memory

Cerebellum: Function - Automatization

Frontal Lobe: Function - Planning & Organization

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

Strategies to improve common cognitive impairments

- 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.

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.

Psychological counseling and psychiatric intervention when necessary are a very importance aspect of multidisciplinary rehabilitation of Muscular dystrophy. The progressive nature of the disease and unavailability of treatment options makes the disease extremely dynamic in terms of psychological health of the patient. It evolves through different stages of the disease and with each stage the patient requires different support systems and management strategies. Therefore regular visit to the psychologist is recommended to avoid adverse psychological effects of the disease.

Thus rehabilitative management of muscular dystrophy is multidisciplinary team activity, all the team members play a crucial role in improving the quality of life of children with muscular dystrophy.

17. MultidisciplinaryRehabilitation in Spinal Cord Injury

Rehabilitation of the spinal cord injured individuals is by far one of the most challenging fields for the rehabilitation experts. Till today there is very little to claim as a panacea for the spinal cord injury (SCI) or regeneration of the damaged spinal cord. However the researchers all over the world find great hope in stem cell therapy (SCT) and it has been proved beyond doubt that the results with SCT coupled with good comprehensive rehabilitation is better than just giving SCT. Therefore rehabilitation is being given a better facelift by SCT. As everyone knows that the role of all the members of the rehabilitation team is equally important and goes hand in hand with each other. No one can claim that other's role is less important. Perhaps in one case one of the team member's role may be more significant than other's, whereas it may be the other member's role in yet another case. But overall each one has to put in his best foot forward to achieve the desired goal. Therefore it always pays if we can achieve the co-operation and coordination of all the team members. It is not always possible to get everyone together all the time. But a good network of communication between the team would bring in good results.

To help of patient come out of this dreadful situation, it requires effort from a team of members, which is rightly called as a multidisciplinary team.

Multi disciplinary team

An ideal multi disciplinary rehabilitation team should comprise of all of the following members:

1. Physiotherapist
2. Occupational therapist
3. Psychological counselor
4. Care givers

Physiotherapy management of spinal cord injury

Physiotherapy is the discipline of medical sciences where in physical modalities and exercises are used to improve functional abilities and independence of a person.

Physiotherapists have a great role to play in spinal cord injury.

Aims of physiotherapy in spinal cord rehabilitation

Acute stage:

In the acute stage of spinal cord injury rehabilitation the goal of physiotherapy:

It is advisable to involve the patients in planning. However very few patients can make their own decisions and therefore therapist has to explain advantages and disadvantages, often trying out different techniques. Perhaps, it will be more beneficial to show other patients who have experienced the same problems and have solved their problems. Many a times it would be essential to set a trial period, trying out trial calipers/ shoes. Eventually the therapist can take a final decision in prescribing the necessary equipments. Before taking the final decision therapist has to make a thorough evaluation of motor skills, functional skills, home assessment, ADL and opinions of other team members and taking patients' consent.

Following are the most important aspects of training the spinal cord injured patients to achieve maximum functional potential and to avoid secondary complications:

Bed mobility

The most essential need of a SCI patient is some amount of mobility in the bed. The very first thing that he attempts is going on to the side by using upper trunk movements and scapular movements. The therapist can assist him initially by just doing passive rotation and asking him to assist as much as possible. Next, he is asked to do this by himself and the therapist helping only as much as he wants.

When the patient can do by himself, more and more resistance has to be applied. He may use momentum, even weight cuffs may be applied to the hands to increase the momentum and facilitate movements. It also strengthens the muscles. These activities give him awareness that with swift movements of the upper trunk he can initiate lower trunk movements. Rolling can be made easy if he flexes his one hip and knee or both hips are flexed.

Pressure relief

Due to lack of sensation, they don't perceive the discomfort of pressure on certain vulnerable points because of squeezing of the local blood supply and resulting into ischemia over certain area and that will lead into pressure sore. They also do not have the ability to move the part to relieve the pressure. Therefore they have to develop new methods consciously. Patients who have very pointed bony prominences are prone to develop pressure sores than others (e.g. Some have anatomically pointed ischial tuberosities.) Therefore the therapists have to make a protocol for each patient and see as to how often they have to do the pressure relieving measures. After the patient becomes active in wheelchair activities, the chances of getting pressure sore are much less. Therefore careful clinical observations can help a patient to develop a

treatment protocol which he can follow by himself.

Transfers

Moving from one surface to other is a major task for almost all SCI patients and needs special training and effort. They need the support of their strong hands to do that. They have to take extra care that they don't fall on the ground while transferring and also see that they do not hurt themselves.

Wheelchair mobility

As a first step, the paraplegic has to accept, the very concept of using a wheelchair for mobility. This is not an easy thing for a person who was walking and running or driving a vehicle a few days or months back. For him to accept this slow moving mode of mobility is very difficult. Not only that, the stigma attached to the wheelchair is too much. However when he realizes that he is bedridden and that without moving from the bed, life becomes monotonous and a desire could come to him to get into a wheelchair. If he observes another wheelchair bound patient moving around comfortably, he too would consider getting into a wheelchair and attempt moving at least within house. When he observes people even get out of the house in a wheelchair and face other people in the society, slowly he gets a desire to accept a wheelchair for mobility rather than remain in a bedridden condition. This acceptance is the first step towards rehabilitation.

Ambulation:

To Walk or not to Walk?

If you ask any patient this question, he would certainly say that he wants to walk. Initial stage he would say that he cannot accept a wheelchair as a mode of ambulation. However as time passes and he realizes that there is a lot of energy consumption he slowly accepts the fact that wheelchair may be better mode of locomotion. However those who are functionally able to manage with orthosis will never take the idea of a wheelchair. Therapists would like to sell the idea of wheelchair to those patients who have no hip flexors. This is because wheelchair is more practical and energy saving and time saving.

There is a debate on this issue even among the medical personnel. Those who are in favor of ambulation and standing believe there is a physiological benefit for the patient.

i. Most of the body's calcium is found in the bone.

ii. SCI patients have a high calcium washout and incidence of osteoporosis is evidently seen in the bones. This calcium washout is considered to be predisposing factor for formation of bladder stone and ectopic bone formation which are seen in SCI patients.

iii. Weight bearing can increase the bone density.

iv. It is assumed that with ambulation and weight bearing, calcium excretion will be decreased and therefore less osteoporosis, ectopic bone formation and fewer bladder stones.

However there is a counterargument that standing and ambulation alone are not sufficient and more pressure is needed to promote bone growth. Muscle contraction can provide much more compressive force also shearing and torsion forces increase bone density significantly.

Occupational therapy management of Spinal cord injury

The purpose of OT in Spinal Cord Injury is to

1. Evaluate a person's ability and level of functioning in his/her home, at work, and while engaging in leisure activities and hobbies.
2. To provide individualized therapy to retrain people to perform daily living skills using adaptive techniques.
3. To facilitate coping skills that could help a person overcome the effects of SCI.

Role of the Occupational therapist

The occupational therapist is particularly concerned in helping the paraplegic reach the highest level of independence both physically and psychologically that his injury, home, and work environment will allow. The paraplegic with the help of the occupational therapist overcomes difficulties successfully with the use of various aids and adaptive equipment and modifications in the home and place of work environment. A variety of purposeful activities are also used and modified to promote self-esteem by highlighting functional skills and emphasizing the tangible development of a client's physical, social, emotional, sensory and cognitive abilities. OT's unique contribution to occupational performance lies in its use of purposeful activities to promote psychological and physical health and maximum functional independence. As a part of complex rehabilitation, it is applied in solving the problems of occupation (self-care, work and leisure) of patients. It is emphasized that early OT, started immediately after stabilization of patient's functional state, is of great importance.

Occupational Therapy Intervention

The Acute Phase:

When the patient arrives in the hospital he will mostly be confined to bed waiting for or recovering from surgery to stabilize the spine which may be immobilized in traction or in a halo brace or body jacket and prohibited from flexing, extending, and rotating the spine. Occupational therapy begins within the first 48 hours of admission. After the evaluation a daily range of motion program should be started with active and active assisted ROM of all joints within strength, ability,and tolerance level. Positioning should be evaluated and instruction to the staff, patient, and family members should

be given if necessary. Participation in self care activities (eating, combing, and writing) should be encouraged. Discussions regarding further therapy and rehabilitation are initiated to prepare the patient and the family members for discharge.

The Rehabilitation Phase:

The Rehabilitation Phase is also known as the Active or Mobilization phase. In this phase the patient can sit in a wheelchair therefore upright sitting tolerance should be developed. The occupational therapist also works on:-

1. Bed Mobility

Bed mobility skills like rolling, coming to sit from supine, scooting and sitting at edge of bed techniques are taught to the patient. The patient is instructed and assistance is provided until patient is independent. Weight bearing while performing therapeutic activities in different positions like prone on arms, quadriped and kneeling are initiated to improve upper extremity and trunk stability, balance and develop skills for transfers.

2. Upper Extremity Strengthening

The Occupational therapist uses weights/resistance for progressive resistive exercises and resistive activities to strengthen upper extremity muscles. As muscle strength increases, the amount of resistance should be increased to help the patient increase tolerance and endurance. Shoulder exercises should emphasize the shoulder depressors (latissimus dorsi), the flexors, abductors, and extensors (deltoids), and the scapular musculature. The triceps, pectoralis, and latissimus dorsi are required for weight shifts in the wheelchair and for transfers.

3. Endurance Training

The intervention progamme should be graded to increase the amount of resistance that can be tolerated during the activity. As muscle power and endurance increases, increase the amount of time in wheelchair activities which helps patient participate in activities and occupation throughout the day.

4. Self care retraining-

Self-care retraining may commence whilst patient is still in bed, focusing on feeding and grooming. There are many assistive devices/specialized items of equipment that O.T. prescribes to help you achieve greater independence in feeding, grooming, showering, dressing, and bladder and bowel management.

5. Bowel and bladder training

Therapists may assist in independent stimulation and applying a urinary collection device, with or without facilitatory equipment, by suggesting the best possible technique in the best possible position.

6. Environmental Barriers, Home and Work (Job/ School/Play) Barriers assessment and recommendations

Environmental Barriers, Home and Work Barriers are physical impediments that keep patients from functioning optimally in their surroundings. Occupational therapists use the results of tests and measures to identify variety of possible impediments including:

- Safety Hazards (e.g. throw rug, slippery surfaces for patient with help of lower extremity orthosis & walker etc)
- Access problems (e.g. narrow doors, high thresholds & steps, absence of elevators)
- Home & Office design barriers (e.g. excessive distances to negotiate, multi storey environments, sinks, bathrooms, counters and placement of controls or switches)

Occupational therapists after identifying the impediments use the results of tests to suggest modification to the environment to improve functioning in the home, workplace and other settings:

- Construction of ramps or lifts to home.
- Railings and grabs around the house
- Electrical points fixed at a height accessible to patient from wheelchair
- Enlarged doorways and passages for easy access of wheelchairs
- Removal of cabinets from under sinks and platforms in kitchen
- Removal or rearranging furniture that hampers wheelchair access
- Alter thresholds to no more than 3/4" in height
- Position the heights of bed and chair in level with cushion of wheelchair to ensure easy transfers.

7. Domestic retraining

As part of occupational therapy program, patients have the opportunity to practice homemaking activities in a simulated or in the environment the patient will be returning. E.g. cooking in a wheelchair accessible kitchen, where appropriate skills will be taught and opportunities to practice different pieces of equipment that can enhance patient level of independence in this area. Other domestic skills may also be addressed according to your individual need. A number of products are commercially available to facilitate independence in performing home management tasks. Examples of these products include:-

Easy reachers, long-handled dustpans, brooms or vacuum cleaners Trays or trolleys can be utilised to transport items or carry hot items to reduce the risk of burns on lower limbs. A front loading washing machine, and a lowered clothes line or front loading dryer, can facilitate independence in laundry tasks.

8. Vocational rehabilitation

Vocational options are discussed with the patient by the occupational therapist. An

occupation is of varying importance to patients, but most will see it as giving a sense of purpose to their life and will want to return to their former work if at all possible. Early contact with the patient's employer to discuss the feasibility of an eventual return to his previous job is important. If the degree of the patient's disability precludes this some employers are sympathetic and flexible, and will offer a job that will be possible from a wheelchair. If appropriate, a work site assessment may be arranged. An onsite work task analysis performed at the client's workplace as well as examination of the worker and the work environment will provide the therapist valuable insight about the present skills of the patient. However, many patients-find life outside hospital-difficult enough initially, even without the added responsibility of a job, and in these circumstances a period of adjustment at home is advisable before they return to work. If a patient is planning to return to his previous employer, school, or college the occupational therapist should assess the suitability of the premises for wheelchair accessibility. Ideally, if a patient is considering returning to work the therapist assists him by assessing his work abilities in a simulated work environment. In addition the patient will build up his strength and stamina and both he and the staff will have a clearer idea of his employment capabilities. The patient should be taught proper body mechanisms and energy conservation to perform work in a safe manner. The occupational therapists provides referrals for a number of services to provide vocational counselling, rehabilitation and assistance with finding employment in the community.

Psychological rehabilitation of Spinal Cord Injury

Spinal Cord Injury (SCI) leaves a major impression on the person's body and mind. A new spinal cord injury patient usually has many queries regarding his future and at the same time has a sense that things are not going to be the same. A person who had been leading an independent satisfying life becomes immobilized, bowel and bladder incontinence, loss of sexual functioning and becomes dependent on others for every small necessity. The patient not only faces loss of body control but also experience changes in self worth, sense of independence, confidence, and relationship with family and friends.

There are various stages that one goes through post spinal cord injury: 1) shock and denial 2) grieving followed by depression or vice versa 3) anxiety / frustration 4) anger /aggression 5) trying to adapt to the situation. The patients may go through all the above stages or they might not go through the stages given in the above order or they might skip some stages.

Shock and Denial:

When the patients come in terms with what has happened with them they are often not yet ready to acknowledge, the extent or permanence of their disabilities. At the other extreme, patients sometimes build denial systems based on unrealistically high hopes. Clear communication, emphasizing realistic expectations before introducing

treatment, may prevent some of these responses. They should be provided with information on obtaining recommended future.

Greif andMourning:

Working through grief and loss is the way people adjust to losses they have sustained. This adjustment requires emotionally "letting go" of something that was valued but can't be replaced. It is only after letting go that the person is free to reinvest their emotions into new things. However, letting go can be difficult, complex, and require a great deal of time.

Tasks of Mourning:

Four tasks of mourning that a person needs to successfully work through while grieving.

1. Accepting the Reality of the Loss:

Patients and families struggle long and hard with this reality. For some, the struggle and disbelief continues for years and some never do accept the reality of their loss and will forever be in mourning. Their emotional energy goes to fighting against the reality of the spinal cord injury/disease instead of concentrating on strengthening and using the remaining intact muscles and nerves. Those who do accept this reality, even a part of it, can then move forward to the next step.

2. Experiencing the Emotional Pain Associated with the Loss:

Emotional pain is a reflection that something which has been valued or treasured has been lost. The emotions are often very strong and difficult to manage. Anger, sadness, hopelessness, fear and a sense of injustice are very common. Those individuals who do not successfully handle this task in the grief process may, over the long term, lose motivation and interest in most or all activities, withdraw from friends and family, become bitter and resentful, stay depressed, develop poor personal hygiene or eating habits, seriously abuse drugs and alcohol or deteriorate physically. Those persons successful at this step can move forward to the next.

3. Adjustment to the Environment despite Spinal Cord Injury:

Adjustment means effectively learning to deal with the world despite the changes caused by the spinal cord injury/disease. A person may need to learn new skills because he cannot perform his old job.

4. Withdrawing Emotional Investment:

The final stage of mourning involves the actual "letting go" of life as it used to be before the spinal cord injury/disease and investing energies elsewhere. Perhaps the person learns to participate in an activity that he did prior to hospitalization but now does it in a different manner; or the person who was very "body" oriented learns to use the "mind" more for stimulation, satisfaction, and productivity.

4. Anxiety:

A panic like reaction of initial recognition of the enormity of the traumatic event takes place as the patient is relatively unaware. As, the patient comes into terms with the injury and the consequences the level of anxiety eventually subsides.

Depression:

Depression is a common illness and it can affect anyone. However, it is more common among SCI patients as about 1 in 5 people. Estimated rate of depression among people with SCI ranges from 11% to 37%. Krause, et al suggests that 48% of patients with SCI in 1997 had clinical symptoms of depression at a year or more after injury. Another study showed that 60% of Portuguese patients with spinal cord injury have depressive symptoms.

Suicide:

In Denmark, a suicide rate is 5 times higher than a general population and it is not related to the severity of the injury. Suicidal tendencies are higher during the initial days after spinal cord injury.

Independence:

Causes of depression after spinal cord injury and found that social support and recent stressful events can be used to identify patients at a high risk of depression but that they are less likely to become depressed if they are independent. Adjustment to spinal cord injury and quality of life can be adversely affected by inadequate home facilities that make a person more dependent. Expectations of independence decline steadily with increasing age. In some patients, there are secondary gains in their dependent state, though they may not be consciously aware of this.

Body Image:

Many spinal cord injury patients value the fact that they look "normal" except for the wheelchair. The magnitude of disability may be "invisible." Patients sometimes report that people stare at them more. Their sense of "being different" and social discomfort increases. Spinal cord injury patients may not integrate disability into their self-concept for some time.

Adjustment:

Affective internalization, of the functional implications, of the disability along with behavioural adaptation to newly perceived life situation. True adjustment and adaptation begins after discharge from rehabilitation.

Family Issues:

Spinal Cord Injury is a life altering event not only for the person but also for family member. Family member also suffer from the various stages that a person goes through

post spinal cord injury. Findings suggest that the spouse of a person with spinal cord injury usually suffers from emotional stress that is comparable to or greater than those of injured partner. The spouse has to now take on overall charge of the patient, himself or herself and other family members. They normally have to juggle out time for everything. This leaves the caregiver at a higher risk of physical and mental stress, burnout, anger, fatigue and resentment.

Individualised Psychotherapy

Hope is a potentially important coping strategy for both the person and family with spinal cord injury. Goal-directed hope based on realistic perceptions of life, focusing on progress, positive interpretation of events, and goal setting are important in helping people and families cope with spinal cord injury. The psychologist can help the team of therapists to understand the patient's stage of adjustment, and provide consultation on behavioural management approaches. Emotional responses dealt with by psychotherapy include a range of ego defences, most commonly repression and denial. Typically, as denial decreases over time, depression, anxiety, and anger increase. How these emotions are expressed depends largely on the patient's pre-morbid personality style. Psychotherapy can help via reinforcing adaptive coping skills and teaching new coping strategies. The psychologist may also work with the interdisciplinary team to develop behavioural modification programs, based on learning theory, to decrease these behaviours. Contingency management and behavioural "contracting" are, most frequently used in rehabilitation setting. Approaches emphasizing positive reinforcement to "shape" desired behaviours are particularly effective. Cognitive therapy is used to help the client overcome the negative and distorted view of himself or herself or people around him or her.

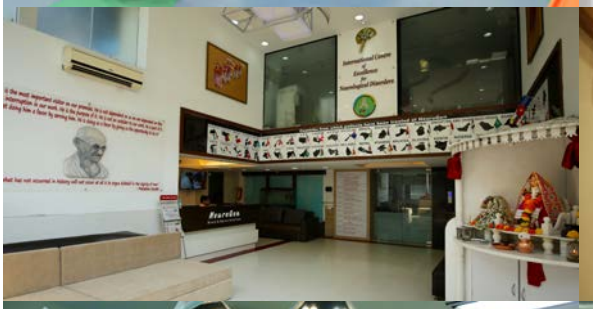
Group Therapy:

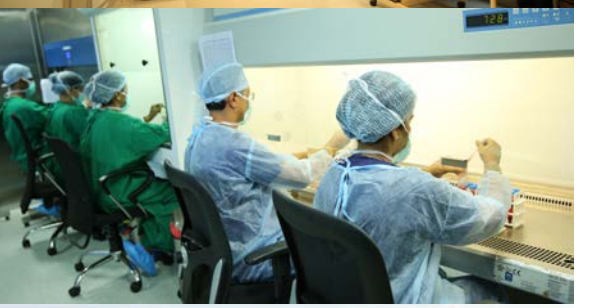
Psychological treatment of spinal cord injury often includes group psychotherapy, which is an excellent method to both maximize patient learning and efficiently use therapist time. Patient groups can provide emotional support, peer role models; teach new coping skills, and decrease social discomfort. Likewise, multiple-family group psychotherapy is a powerful and effective tool for facilitating family adjustment to spinal cord injury. Family members experience similar emotional responses to the patient and similarly benefit from

psychological intervention. If not included in the team effort, a well-meaning family member could inadvertently sabotage the independence-oriented rehabilitation approach, or be too psychologically

NeuroGen Brain & Spine Institute





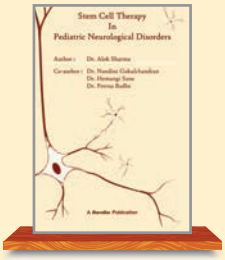



The NeuroGen Brain & Spine Institute is an International center of excellence for Neurological disorders. Founded by Dr. Alok Sharma it Is India's First dedicated Hospital for Stem Cell Therapy and Comprehensive Neurorehabilitation. Located adjacent to the Arabian sea on the scenic Palm beach road in Navi Mumbai, this center has a multidisciplinary team of expert and experienced medical professionals that provide holistic care using the latest technological advances in the world. It has treated over 7500 patients from 65 different countries. The care offered here is very professional yet very caring.

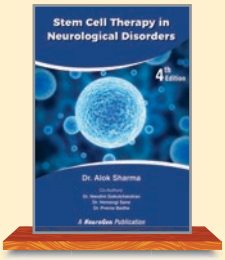
A separate pediatric neurorehabilitation facility and other play areas makes it very child friendly. The institute is very scientific and academic in its approach and to date has published 86 scientific papers in international and national journals. 15 books have also been published and chapters contributed to several international textbooks. NeuroGen also has many international tie ups with leading organizations from America and other countries for research and treatment collaborations. The institute is very quality conscious and has several certifications (1. ISO 9001:2015, 2. GLP & 3. GMP certification). Despite all the international partnerships and treatments offered to patients from all over the world the institute is very socially conscious and through the Stemcare foundation financially supports patients from the lower socioeconomic strata to be able to avail of the treatments that are needed. Its a policy of the institute that no patient should be deprived of any treatment due to financial reasons. NeuroGen doctors conduct free medical camps all over the country. Conferences, workshops and CME's are regularly conducted to impart knowledge to doctors, therapists as well as patient families. Cutting edge research, pioneering new treatments, the best medical professionals, comprehensive treatment facilities all under one roof and a caring holistic approach and make the NeuroGen Brain and Spine institute a unique and special facility for patients with Neurological problems.

Other books published by NeuroGen Brain and Spine Institute

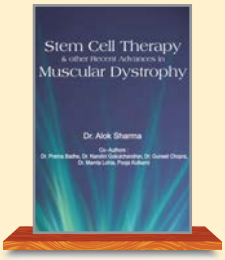
Stem Cell Therapy In Pediatric Neurological Disorders 2nd Edition



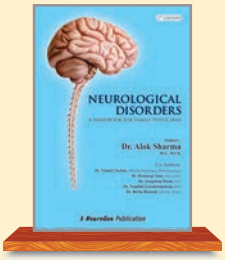
Stem Cell Therapy in Neurological Disorders 4th Edition



Stem Cell Therapy & Other Recent Advances in Muscular Dystrophy



Neurological Disorders A Handbook for Family Physicians 2nd Edition



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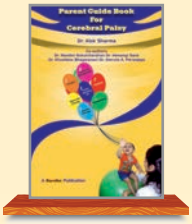
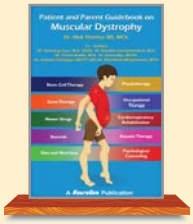


Patient & Parent Guidebook on Muscular Dystrophy



પેશન્ટ અને પેરન્ટ માર્ગદર્શિકા મસ્ક્યુલર ડિસ્ટ્રોફી વિશે

NeuroRehabilitation- A Multidisciplinary Approach

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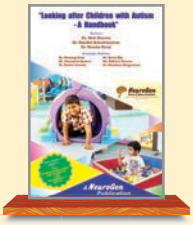

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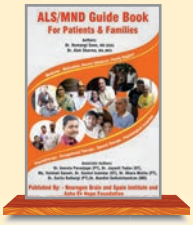

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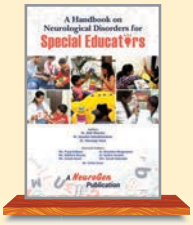

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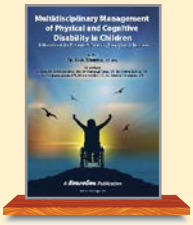

Neurogen Brain and Spine Institute offers a comprehensive NeuroRegenerative Rehabilitation programme for patients suffering from incurable neurological disorders. The aim is to provide these patients a relief from their symptoms & physical disabilities, using the safest & most effective available treatments & technologies from the field of neurosciences and regenerative medicine in a professional, scientific as well as holistic & caring manner.

Published By

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