

Stem-cell therapy for neurologic diseases

Shilpa Sharma, Devendra K Gupta

Abstract

With the advent of research on stem cell therapy for various diseases, an important need was felt in the field of neurological diseases. While congenital lesion may not be amenable to stem cell therapy completely, there is a scope of partial improvement in the lesions and halt in further progression. Neuro degenerative lesions like Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis have shown improvement with stem cell therapy. This article reviews the available literature and summarizes the current evidence in the various neurologic diseases amenable to stem cell therapy, the plausible mechanism of action, ethical concerns with insights into the future of stem cell therapy.

Key words: Neurologic diseases, stem cells, treatment modalities

INTRODUCTION

Ongoing research on stem cell therapy for various diseases has motivated the search for a cure in the arena of neurological diseases. This is one field where medicine has little hope for recovery and the patient might be incapacitated for life, waiting for some miraculous cure. Various basic scientists have been working on the role of stem cells in different neurological diseases hoping to find a breakthrough. Here we review the available literature, current evidence in various neurologic diseases amenable to stem cell therapy, try to explain the plausible mechanism of action and discuss the ethical concerns with insights into the future of stem cell treatment.

WHAT CAN STEM CELL OFFER?

The neurological diseases may be grossly classified as congenital or acquired lesions. The acquired lesions may result from hypoxic, traumatic injury, and infective or degenerative lesions. While the neurological deficits from congenital lesions may not be completely amenable to any

sort of medical therapy, stem cells may offer a regeneration of neurons from the place where the growth has halted. Neurodegenerative disorders like Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis may be halted or slowed in progression by the use of stem cells. Scientists have been working on the process of utilizing stem cells to replace or replenish the damaged cells.^[1-4] The recent advances in cultivation of human embryonic stem cells and the recognition of plasticity in the human nervous system have spawned new ideations into the possibility of using versatile stem or stem-like cells to treat neurological conditions.^[5] Though at present, very little experimental work has the potential to reach the phase 3 clinical trial level, there is substantial evidence to believe that stem cells can act as a support environment for survival or recovery of damaged neurons by reducing inflammation and helping remyelination. Stem cells have the ability to produce neurotrophic or immunosuppressive factors thus forming a favorable environment for brain tissue repair and long-term survival of transplanted cells in the central nervous system.^[6] In animal studies, benefits of stem cell-mediated gene transfer of therapeutic genes such as neurotrophic factors and enzymes have been demonstrated.^[7]

WHAT KIND OF STEM CELLS CAN BE USED?

Neurons and glial cells have successfully been generated from stem cells. There are fundamental and realistic

Access this article online	
Quick Response Code:	Website: www.jnaccjournal.org
	DOI: 10.4103/2348-0548.148379

Department of Pediatric Surgery, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India

Address for correspondence:

Dr. Shilpa Sharma, Department of Pediatric Surgery, All India Institute of Medical Sciences, Ansari Nagar, Room no 4001, PC Block, New Delhi - 110 029, India. E-mail: drshilpas@gmail.com

differences between grafts of primary neural cells and the transplantation of *in vitro* expanded neural stem cells (NSCs).^[8-10] A variety of stem cells have been explored as therapeutic options for treating many neurologic diseases.

These include

- Pluripotent stem cells like embryonic stem cells and induced pluripotent stem cells
- Multipotent adult stem cells like fetal brain tissue, fetal spinal cord derived tissue, NSCs or neural progenitor cells, and mesenchymal stem cells from various sources
- Autologous bone marrow derived mononuclear cells
- Adipose tissue-derived stem cells
- Umbilical cord stem cells.

A fully functional neuron cell derived from a stem cell should ideally be electrically excitable, have the ability to release the appropriate neurotransmitter and form neural structures like processes and synapses, before it can be justified in offering a complete therapeutic treatment for neurological diseases. Pluripotent cells possess the capacity to give rise to all three germ layers, while multipotent cells give rise to more restricted lineages. NSCs are capable of differentiating to cell types within a neural lineage and may be derived directly from fetal or adult neural tissue, or differentiation of embryonic stem cells via cell culture manipulation.^[11,12] Mesenchymal stem cells are derived from adult bone marrow and can transdifferentiate to a neural lineage.^[13]

Laboratory work has demonstrated that embryonic stem cells induced pluripotent stem cells and mesenchymal stem cells may help to generate neuron-like cells, but these cells are lacking in the functional aspects like proper fiber outgrowth and integration into the host neuronal networks. Induced pluripotent stem cells can be generated from autologous somatic tissue such as fibroblasts and reprogrammed into embryonic stem-like cells by the addition of transcription factors like Oct 3/4, Klf, Sox 2, and c-Myc.^[14] Reprogramming of fibroblasts has been accomplished successfully by using various combinations of factors delivered by vector, virus, protein, or RNA-mediated approaches.^[15]

NEUROLOGICAL DISEASES AMENABLE TO STEM CELL THERAPY

Neurological diseases that are of a degenerative nature characterized by the loss of neurons in the brain or spinal cord may be amenable to stem cell therapy. Alzheimer's and Huntington's disease result in widespread loss of neurons in the brain, while Parkinson's disease involves the specific and localized loss of dopaminergic neurons in the substantia nigra, amyotrophic lateral sclerosis

and spinal muscular atrophy involve the degeneration and loss of motor neurons in the brainstem and spinal cord. These are summarized in Table 1. The authors have experience of using stem cell therapy for patients of meningomyelocele, poliomyelitis, cerebral palsy, neurogenic bowel, neurogenic bladder, and amyotrophic lateral sclerosis.^[16] Stem cell mobilization has benefited our patients of cerebral palsy, spinal muscular atrophy, and Duchenne muscular dystrophy.

MECHANISM OF ACTION OF CELL-BASED THERAPIES

Neurodegenerative diseases caused by a loss of neurons and glia in the brain or spinal cord have the potential to be benefitted from stem cells. In the past, *in vitro* approaches like oncogene-induced immortalization and growth-factor stimulation of naturally occurring central and peripheral nervous system stem cells have been studied.^[8] The initial strategies were designed to replace dead cells in injured tissue, the potential of stem cells to migrate, secrete trophic factors, and immunomodulation allows their therapeutic use as a vehicle for gene therapy, as in Parkinson's disease, or as immunomodulators and neuroprotectors in diseases such as multiple sclerosis.^[17] It has been realized that we need to know much more about how to control stem cell proliferation and differentiation into specific phenotypes, induce their integration into existing neural and synaptic circuits, and optimize functional recovery in animal models closely resembling the human disease.^[18]

Today, the cell-based therapies are based on direct cell transfer or tissue grafts or providing environmental enrichment. In some diseases, the type of cells used may be more characterized for a particular function. The cell-based therapy for Parkinson's or Huntington's

Table 1: Neurological diseases amenable to stem cell therapy

Parkinson's disease
Alzheimer's disease
Huntington's disease
Multiple sclerosis
Amyotrophic lateral sclerosis
Stroke
Cerebral palsy
Head injury
Spinal cord injury
Spinal muscular atrophy
Neurological deficits in meningomyelocele
Neurological deficits in poliomyelitis
Duchenne muscular dystrophy

diseases is based on the ability of stem cells to replace lost dopaminergic mesencephalic or striatal neurons.^[6] On the other hand, amyotrophic lateral sclerosis is benefitted from cellular therapies that enrich the local spinal cord environment to support the remaining motor neurons. The newly transplanted neurons need to integrate, synapse, and recapitulate a neural network similar to the one lost in disease. Alternatively, stem cells may provide environmental enrichment to support host neurons by producing neurotrophic factors, scavenging toxic factors, or creating auxiliary neural networks around affected areas.^[19]

There are various strategies for environmental enrichment utilizing stem cells to provide *de novo* synthesis and delivery of neuroprotective growth factors at the site of disease. Growth factors such as glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), insulin-like growth factor-I (IGF-I), and vascular endothelial growth factor (VEGF) are protective in neurodegenerative disease models and provide *in situ* environmental enrichment at the main locus of disease.^[20-24] Other factors affecting the potential efficacy of cellular therapies include integration of grafted neurons, migration of engrafted cells, and the distances that axons need to extend to reach their targets. Bone marrow-derived cells developing neuronal and vascular phenotype and aiding in repair of injured brain have been reported.^[20]

Selecting the appropriate stem cell type and understanding the desired mechanism of support is the initial step in developing and translating cellular therapies to patients. Table 2 outlines the various neurological diseases where stem cells have been used.

ROUTES OF ADMINISTRATION OF CELL-BASED THERAPIES

It has been realized that an appropriate selection of the type of stem cells based on the kind of neurologic dysfunction is required to achieve optimal therapeutic efficacy.^[2] However, there is a paucity of suitable cell types for appropriate cell replacement therapies. The main aim while administering cell-based therapies is to ensure that the cells reach the desired site of action. The various routes that have been used for neurological disorders include:

- Intracerebral via cell transplants in the brain
- Intra-striatal, fetal neural transplants
- Intravenous route
- Intra-arterial via the cerebral artery
- Intrathecal
- Lumbar puncture direct lumbar and cervical intraspinal injections
- Intracisternal

- Stem cell mobilization approaches in which endogenous stem and progenitor cells are mobilized by cytokines such as granulocyte colony stimulatory factor (G-CSF) or chemokines such as stromal cell-derived factor-1 (SDF-1)
- Trophic and growth factor support, such as delivering BDNF or GDNF into the brain to support injured neurons.

The various approaches may be used in combinations to maximize the efficiency. Recent advances include research on use of three-dimensional substrate-adherent embryonic stem cell-derived neural aggregates to enhance the efficacy of treatment.^[64] The field of nanotechnology has been used to tag markers like superparamagnetic iron oxide nanoparticle with stem cells as a therapy for brain diseases and monitor the migration of stem cell in affected regions of the brain.^[65]

ETHICAL CONCERNS

During the beginning of the stem cell revolution, animal tissue was widely used to conduct experiments; and thus look for xenotransplants as a possible cure for some diseases.^[66] However, this field has not gained momentum particularly due to ethical issues and potential life-threatening complications.^[67-69]

Though clinical improvement has been observed in cases of Parkinson and Huntington disease patients transplanted with freshly isolated fetal brain tissue, but there are ethical issues in this kind of restorative treatment.^[6,70,71] The first concern is the use of human fetal tissue for treatment purpose and the very fact that this may be misused by planning pregnancy and termination only for the use of such tissue. Also the amounts of tissue obtained may not be adequate for full treatment, thus exposing the patient to tissues from multiple sources. The second concern is the need of use of immunosuppression and potential side effects like spread of viral infections and the risk of development of malignancy in future. Other issues include graft overgrowth and presence of non-neuronal cells within the graft. Side effects like dyskinesias have been reported following cell transplants.

There is no immunosuppression for cellular therapies derived from autologous sources. However, autologous cells may be less desirable when dealing with genetic diseases because the cells may possess the same genetic predisposition to disease.

The ethical concerns for use of human embryonic stem cells are equally significant as the use of the embryo for medicinal purpose is not approved ethically. Though autologous stem cells are less potent and may have a short duration of effect, they are free from ethical

Table 2: Various neurological diseases amenable to stem cell treatment with the plausible mechanism of action

Disease	Symptoms	Pathophysiology	Plausible mechanism of benefit with stem cell therapy
Alzheimer's disease ^[25-29]	Memory loss and cognitive decline	Widespread loss of neurons and synaptic contacts throughout the cortex, hippocampus, amygdala, and basal forebrain	Regulation of neurotransmitter activity Targeting the cholinergic system to provide environmental enrichment Enhance neurogenesis Replace lost neurons Enhancing BDNF levels Nerve growth factor production. Genetically engineered patient fibroblasts that produce NGF. Combination of above
Parkinson's disease ^[30-35]	Severe motor deficits, tremors, muscle rigidity, and unstable gait and posture	Progressive loss of dopaminergic neurons in the substantia nigra	Replacement of lost dopaminergic neurons Foetal ventral midbrain tissue transplant Embryonic stem cells Grafting both embryonic and mesenchymal stem cells-derived dopaminergic neurons Patient-specific dopaminergic neurons using induced pluripotent stem cells. Environmental enrichment may also support existing dopaminergic neurons and slow or prevent further degeneration. Growth factor therapy through direct delivery or viral-based systems Transplantation of mesenchymal and neural stem cells engineered to produce growth factors such as BDNF, VEGF, GDNF and IGF-I <i>in situ</i> Combination of cellular replacement and environmental enrichment
Huntington's disease ^[36-43]	Involuntary motor activity, dementia, personality changes, and cognitive impairment associated with the progressive loss of medium spiny neurons	Autosomal dominant polyglutamine disease caused by the accumulation of CAG repeats in the Huntingingene. Loss of these GABAergic neurons in the striatum is also accompanied by degeneration in the cortex, brain stem and hippocampus	Foetal tissue grafting using the whole ganglionic eminence as an optimal source of mesenchymal stem cells Transplantation of neural cells and striatal grafts into rodent models demonstrated that mesenchymal stem cells integrate and form circuitry in the host Striatal injections of neural stem cells demonstrate incorporation as well as migration to secondary sites associated with disease MSC in the brain promote endogenous neuronal growth, encourage synaptic connection from damaged neurons, decrease apoptosis, reduce levels of free radicals, and regulate inflammation Environmental enrichment with neural stem cells expressing GDNF protected neurons and promoted functional recovery
Amyotrophic lateral sclerosis ^[44-46]	Loss of coordination and muscle strength with transition to complete loss of muscle control Death typically results from respiratory failure within 2-5 years of diagnosis	Involving the degeneration and loss of motor neurons	Mesenchymal and neural stem cells Environmental enrichment via GDNF, VEGF and IGF-I Distal production of GDNF in muscle protects neuromuscular junctions and promotes motor neuron protection, likely by retrograde transport Environmental enrichment to motor neurons and neuromuscular junctions Foetal spinal cord-derived neural stem cells Cellular therapies provide both an integrating neural component and environmental enrichment to support and protect motor neurons from degeneration

Contd...

Table 2: Continued...

Disease	Symptoms	Pathophysiology	Plausible mechanism of benefit with stem cell therapy
Spinal muscular atrophy ^[47,48]	SMA type I early onset severe muscle weakness and fatality within 2 years	Selective loss of motor neurons (mutation or loss of SMN1 gene, alternative splicing variants encoded by SMN2 gene)	Grafting of embryonic stem cells-derived neural stem cells
Multiple sclerosis	Physical, mood disorders, and depression	Autoimmune chronic inflammatory disease of the central nervous system disease, results in the death of oligodendrocytes	Trials with haemopoietic stem cells, mesenchymal stem cells, neural stem cells, and oligodendrocyte precursor cells
Neurologic deficits in Meningomyelocele ^[16]	Lower limb neurologic deficit Neurogenic bladder Neurogenic bowel	A congenital defect in which the nerve roots are entrapped in a meningocele sac	Epidural injection of autologous bone marrow derived mononuclear cells may provide environmental enrichment and help the detethered nerve roots to regenerate
Stroke ^[49-55]	Sudden onset of neurological deficits	Usually a result of a vascular event	Foetal neural stem cells Embryonic stem cells Adult tissue sources Bone marrow-derived stem cells, Umbilical cord blood-derived haemopoietic stem cells Mesenchymal stem cells Multipotent adult progenitor cells
Spinal cord injury ^[56,57]	Neurological deficits following trauma	Trauma to spinal cord	Foetal neural stem cells Embryonic stem cells Adult tissue sources Bone marrow-derived stem cells Umbilical cord blood-derived stem cells Mesenchymal stem cells iPS cells
Head injury ^[58-61]	Neurological deficits following trauma	Trauma to brain and skull	Exogenous trophic factor administration Transplantation of neural progenitor cells Adult tissue sources Bone marrow-derived stem cells Umbilical cord blood-derived stem cells Mesenchymal stem cells iPS cells
Perinatal brain injury ^[62,63]	Neurological deficits following hypoxic trauma during and after birth	Perinatal hypoxic injury	Neural stem cells Embryonic stem cells Mesenchymal stem cells Umbilical cord stem cells iPS cells

GABA = Gamma-aminobutyric acid, GDNF = Glial-derived neurotrophic factor, BDNF = Brain-derived neurotrophic factor, IGF-I = Insulin-like growth factor-I, and VEGF = Vascular endothelial growth factor, SMA = Spinal muscular atrophy, NGF = Nerve growth factor, iPS = Induced pluripotent stem

concerns. Recently, the induced pluripotent stem cell shave gained importance due to their major potential advantages as patient-specific neuroblasts are suitable for transplantation, avoid immune reactions, and can be produced without the use of embryonic stem cells.^[72-76] The use of trophic factors has also gained momentum, but unless the benefits are shown to outweigh the risks and the scientific basis of mechanism of action is established, their use would continue to be in the trial

phases. Further research will definitely establish the utility in times to come.

FUTURE DIRECTIONS

Neurodegenerative diseases area burden in the society as they incapacitate the human brain and nervous system to a great extent. As the exact scientific pathophysiology of the various diseases still remains a mystery, we are

yet to find a permanent treatment. Though there are few medications for most of the diseases, the treatment mostly remains symptomatic and one has to bear with the side effects of lifelong medications.

The stem cell revolution has been looked upon as a breakthrough miraculous treatment as it may have the potential both to stop the further downhill course of the disease and also to reverse the symptomatology especially if given early in the onset of disease.

Cellular therapies and environmental enrichment offer great promise for the treatment of these diseases, and research progress to date supports the utilization of stem cells to offer cellular replacement and/or provide environmental enrichment to attenuate neurodegeneration.^[77-79] In diseases where specific subpopulations of cells or widespread neuronal loss are present, cellular replacement may reproduce or stabilize neuronal networks. In addition, they may provide neurotrophic support to remaining cells or prevent the production or accumulation of toxic factors that harm neurons. In many cases, cellular therapies provide beneficial effects through both mechanisms.

However, there are still many hurdles in reaching the goal of stem cell therapy for neurological diseases. These include:

- Lack of knowledge about the true mechanisms of these diseases
- It is still uncertain what kind of stem cells are an ideal source for cellular grafts for a particular disease
- The mechanism by which stem cells transplantation leads to an enhanced functional recovery and structural reorganization is not unraveled
- The molecular mechanisms underlying the critical steps in cell-based repair are still not known
- Angiogenesis and neurogenesis are coupled in the nervous system. Thus, both mechanisms might need a combination of therapies to be effective
- The optimal timing for intervention and patient selection has to be identified as the mechanism of action may not be the same in different stages of the disease
- The optimal delivery route and cell dose has to be evaluated by repeated studies
- The relevant clinical end points and monitoring for effectiveness have to be evaluated.

The way forward should include sound research on both the basic and preclinical settings for each neurological disease. There is a need to improve standardization and develop safe master cell lines derived from human embryonic stem cells, induced pluripotent stem cells, and NSCs. Cell therapy derived from these sources are expected to become available for cell replacement or production of trophic, anti-inflammatory, and restorative

factors for therapeutic use within a few years.^[80] Apart from cell replacement therapy, other strategies that need to be explored include enhancement of endogenous plasticity and recruitment of endogenous neurogenesis.^[81] The most immediate impact on patients will be achieved by making use of the trophic support capability of stem cell therapy.^[20]

The stimulation of endogenous adult stem cell-mediated repair mechanisms in the brain might offer new avenues for therapy. The stem cell therapy approach to neurological disease will have to be scalable, easily reproducible, and cost effective so that it is easily available to those in need. The future of stem cell therapy has still many unread chapters that need to be explored by scientists so that the maximum potential of this new emerging field of biology is utilized for the benefit of mankind.

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How to cite this article: Sharma S, Gupta DK. Stem-cell therapy for neurologic diseases. *J Neuroanaesthesiol Crit Care* 2015;2:15-22.

Source of Support: Nil, **Conflict of Interest:** None declared.

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