Possible Relations between Stem Cells and Parkinson Disease among Other Neurological Disorders

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Abstract

Background: Parkinson's disease (PD) is considered the most common type of parkinsonisms, a term reflecting a group of neurological disorders with PD like movement problems such as rigidity, slowness, and tremor. Less common parkinsonisms include other neurodegenerative diseases (eg, multiple system atrophy, progressive supranuclear palsy), drug-induced parkinsonism, and vascular parkinsonism. Stem cells are unspecialized cells in the human body that have a remarkable capability to regenerate continually. The key abilities of stem cells to constantly self-renew, proliferate and differentiate into specialized cells under adapted physiological environment allow them to restore tissue to its pre-injurious state. Stem cells types are either neural stem cells (NSCs), human embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) or mesenchymal stem cells (MSCs). NSCs are the origin of various types of neurons, astrocytes, and oligodendrocytes during embryonic development of the CNS and subsequently exist primarily in the subventricular zone and subgranular zone of the hippocampal dentate gyrus in the adult mammalian brain. Stem cell transplantation and activation of endogenous neurogenesis represents one of the most promising therapeutic approaches to CNS repair in neuroregenerative medicine. Treatment with CD34+ stem cells was reported to improve locomotor activity, dopamine and ATP levels, as well as mitochondrial DNA and nuclear DNA integrity. In accordance, intravenous umbilical cord MSCs (UC-MSCs) therapy was reported to restore dopaminergic function in humans. Furthermore, stem cell therapy improved dopaminergic degeneration and induced a marked increase of TH-immunopositive neurons. Similarly, stem cells can differentiate into dopaminergic neurons that reinnervate the denervated striatum, become functionally integrated and restoring striatal dopamine release. Also, transplantation of ESCs has provided proof of the principle that neuronal replacement can work in PD patients.

Keywords: Stem Cells, Parkinson Disease

Introduction

Neurological disorders are the leading source of disability worldwide, and the prevalence of PD is increasing more rapidly than other neurological disorders **(1)**.

An estimated 6.1 million individuals globally had PD diagnosis in 2016, 2.4 times higher than in 1990. This increasing prevalence was attributed to improved methods of diagnosis, greater awareness of the disease, aging populations, longer life expectancy, and increased environmental exposures**.** PD is uncommon among individuals younger than 50 years, peaking between ages 85 and 89 years and more common in men (1.4:1.0 male-to-female ratio) **(2)**.

The exact etiology of PD still remains elusive and the precise mechanisms that cause this disease remain to be identified**.** Most cases of PD are idiopathic, but there are known genetic and environmental contributions **(3)**.

PD is a slow progressive neurodegenerative disorder that predominately affects dopaminergic neurons in the substantia nigra pars compacta (SNpc) inducing imbalance of the nigrostriatal pathway that causes the main symptoms of PD to arise. However, pathology across the rest of the brain is thought to be responsible for some of the non-motor symptoms. Importantly, Lewy bodies (LB), one of the hallmarks of PD, were reported to be highly enriched in the brains of affected individuals**.** These are proteinaceous inclusions that are primarily formed of aggregated forms of α-syn, but also contain a variety of different proteins and membranous components **(4)**.

For clinically established PD, individuals also need to meet at least 2 of 4 supportive criteria: (1) rest tremor, (2) a dramatic improvement with dopaminergic therapy, (3) the presence of levodopa-induced dyskinesias, or (4) the presence of either olfactory loss or cardiac sympathetic denervation on iodine-123-meta-iodobenzyl-guanidine myocardial scintigraphy (an imaging test that assesses cardiac norepinephrine uptake), which depends on intact postganglionic sympathetic neuron function **(5).**

Dyskinesias are involuntary dance-like choreoathetoid movements that occur with dopaminergic therapy. Dyskinesias usually occur years after PD medications are initiated and have limited benefit for diagnosis at symptom onset**.** Additionally, dopamine transporter single-photon emission computed tomography (DaT SPECT) identifies the presynaptic dopamine neuronal dysfunction present in PD and other neurodegenerative parkinsonisms by demonstrating reduced uptake of a radioactive tracer that binds to dopamine transporters in the basal ganglia **(6).**

Moreover, DaT SPECT is highly accurate (98%-100% sensitivity and specificity) in detecting nigrostriatal cell loss in individuals with PD. If a patient has unequivocal PD, the scans are typically positive and add little to the diagnostic assessment. However, they cannot differentiate between PD and other parkinsonisms (eg, multiple system atrophy, progressive supranuclear palsy) that also involve dopamine transporter dysfunction. Also, magnetic resonance imaging (MRI) is not typically helpful for diagnosing PD. Specific MRI findings (eg, MRI parkinsonism index, which is abnormal in progressive supranuclear palsy) can help to differentiate PD from other parkinsonisms **(7)**.

PD is considered the most common type of parkinsonisms, a term reflecting a group of neurological disorders with PD like movement problems such as rigidity, slowness, and tremor. Less common parkinsonisms include other neurodegenerative diseases (eg, multiple system atrophy, progressive supranuclear palsy), drug-induced parkinsonism, and vascular parkinsonism **(6).**

Furthermore, initial subtyping focused on motor features, but recent categorizations use data-driven clustering approaches. These approaches suggest that subtypes are defined by motor and non-motor features**.** One approach to subtyping consists of 3 groups:

Mild motor predominant: younger age at onset, mild motor and non-motor symptoms, slow progression, good medication response.

Intermediate: intermediate age at onset and symptomatology, moderate-to-good response to medications**.**

Diffuse malignant: baseline motor symptoms accompanied by rapid eye movement sleep behavior disorder, mild cognitive impairment, orthostatic hypotension, worse levodopa response, more prominent dopaminergic dysfunction on DaT SPECT, more atrophy in specific MRI voxels, low amyloid-β and amyloid-β/t-tau ratio in the cerebrospinal fluid, and rapid progression **(8).**

Stem cells can exhibit a plastic phenotype and activity, when they interact with tissue microenvironment or in presence of local and systemic stimuli. It has been advocated as a novel yet promising treatment modality for a myriad of diseases, including cardiovascular, neurodegenerative and musculoskeletal **(9).**

Classification of stem cells

Stem cells may broadly be classified into totipotent (able to give rise to all embryonic and adult lineages), pluripotent (able to give rise to all cell types in an adult) and multipotent (able to give rise to multiple cells within a lineage) and each of these classes show enormous therapeutic function **(10)**

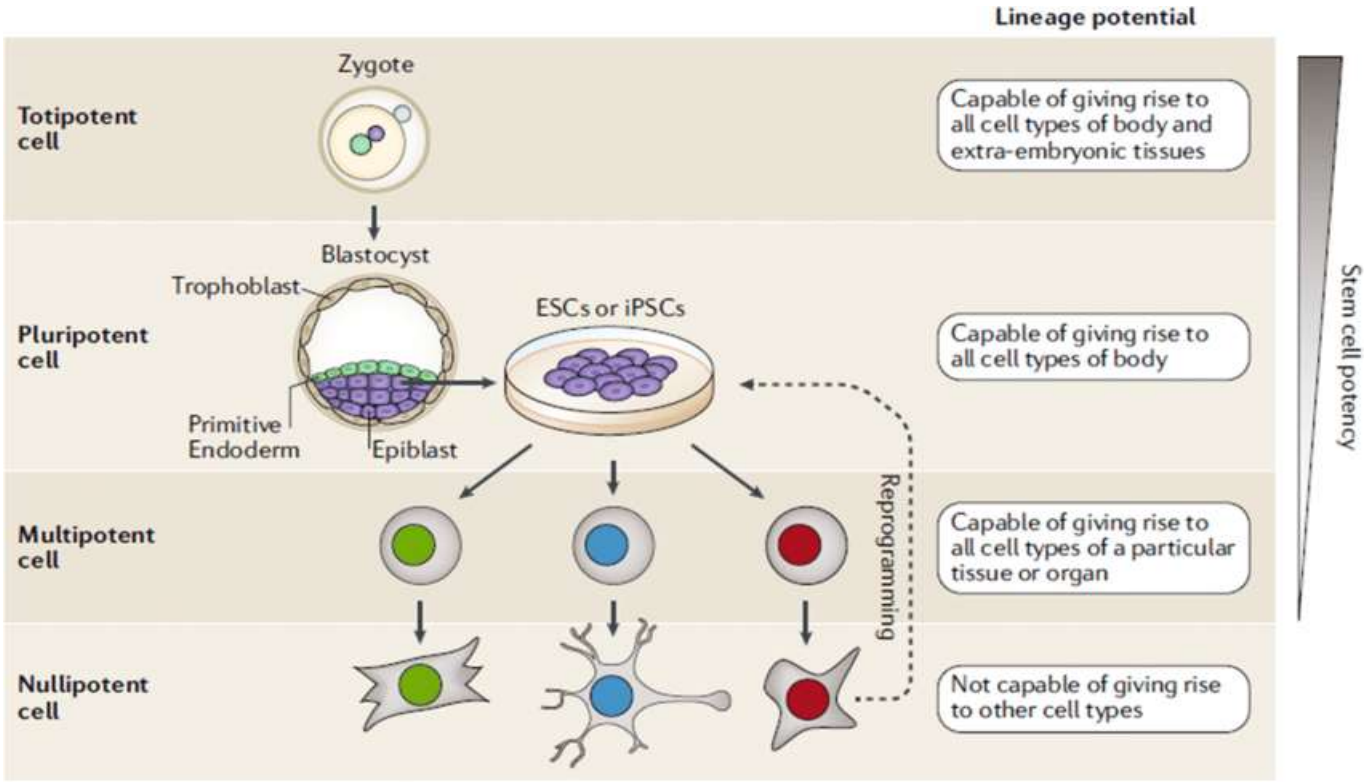

Figure (1): Schematic diagram illustrating the stem cell hierarchy **(11).**

Interestingly, totipotent stem cells can differentiate into 200 cell types of the body and also has the ability to reconstitute a stem cell-deprived organ. Similarly, pluripotent stem cells have been made to differentiate into neural tissues, insulin secreting cells, cardiomyocytes, hematopoietic cells, osteoblasts, endothelial cells and hepatocytes successfully **(12)**.

Also, multipotent stem cells promise self-renewal as well as demonstrate plasticity to transdifferentiate into muscle, skeletal, liver, kidney, muscle, skin, neural, and cardiac cell lineages. The subsequent grade of classification includes the stem cells that can only give rise to well specific cell lineages of a tissue or organ. Such cells are the adult multi potent/unipotent stem cells, also termed as progenitor cells **(13)**.

Types of stem cells

Stem cells types are either neural stem cells (NSCs), human embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) or MSCs. NSCs are the origin of various types of neurons, astrocytes, and oligodendrocytes during embryonic development of the CNS and subsequently exist primarily in the subventricular zone and subgranular zone of the hippocampal dentate gyrus in the adult mammalian brain **(14)**.

While, ESCs are undifferentiated pluripotent cells isolated from the inner cell mass of a blastocyst, are characterized by a group of surface markers including stage-specific embryonic antigen and alkaline phosphatase. ESCs have the potential to differentiate into cell types of all three germ layers. In addition, a number of transcription factors have been identified in human ESCs **(15).**

Similarly, iPSCs are able to form tissues of all three germ layers in vitro and in teratomas suggesting prospects for iPSCs in disease modeling and transplantation therapy. iPSCs are very similar to ESCs with regard to morphology, proliferation, expression of cell-surface markers, and gene expression profiles. Moreover, MSCs are a type of pluripotent stem cell extensively located in various tissues of the human body, especially connective tissues. MSCs were first discovered in human bone marrow, but can also be isolated from peripheral blood, adipose tissue, muscle, skin, placenta, and amniotic fluid. MSCs have the capability to differentiate into cell types of all three germ layers. This attracted a wide range of attention to utilize MSCs as replacement therapeutic source for various diseases **(16)**.

Beneficial effects of MSCs

Beneficial effects of MSCs were reported to be homing efficiency, differential potential, tissue engineering, production of trophic factors, and immunomodulation. MSCs were demonstrated to secrete various cytotropic factors that, in turn, exert neuroprotective effects. They also were reported to have neuroprotective effects via complex mechanisms, such as modulation of neuroinflammation, enhancement of cell survival signals, increased neurogenesis, and modulation of ubiquitinated proteins **.** Additionally, MSCs were shown to enhance angiogenesis, secrete numerous angiogenic factors, reduce inflammation, apoptotic protection and nerve fiber reorganization **(17)**.

Bone marrow mesenchymal stem cells (BM-MSCs) have been identified as a key candidate for cell therapy. However, their clinical application was reported to be restricted by the invasive procedures by which they are obtained, their decrease in proliferation and differentiation capacity with increasing age, and the difficulty of using them in the treatment of patients with hereditary diseases **(18)**.

Recently, placenta-derived stem cells (P-MSCs) of fetal origin have emerged as an alternative source of MSCs for use in regenerative medicine, because of their capacity for self-renewal, multipotent differentiation and their immunomodulatory properties. Also, the placenta contains large numbers of MSCs, and its use for research purposes is not affected by the ethical issues surrounding the use of ESCs **(19)**.

Human placenta and cord blood are rich in hematopoietic progenitor and hematopoietic stem cells (HSCs), which give rise to all the blood cell types including myeloid and lymphoid lineage cells. Like BM-MSCs, umbilical cord blood HSCs have been used to treat various genetic disorders including leukemia, certain cancers, and some inherited disorders **(19)**.

Furthermore, **Chia et al. (20)** reported that teratoma can arise from a term placenta so it may harbor some multipotent germ cells. Additionally, placenta contains a population of multipotent stem cells that express stem cells markers such as CD117, octamer-binding transcription factor 4 (OCT4), sex determining region Y-box 2 (SOX2), stage-specific embryonic antigen-3 (SSEA3), SSEA4, T cell receptor alpha locus-1-60 (TRA-1-60) and TRA-1-81. These cells possess mesodermal phenotype and demonstrate broad multilineage differentiation ability **(21).**

Likewise, P-MSCs express stromal markers, and are negative for the hematopoietic markers. Additionally, **Ghamari et al. (22)** reported that P-MSCs expressed pluripotency markers. P-MSCs were first described in 2004 as plastic-adherent cells that share a similar immunophenotype with that of BM-MSCs. Depending on the layer they originate from, their stem cell derivatives include amniotic MSCs (AMSCs), chorionic MSCs, chorionic villi MSCs and decidual MSCs. AMSCs , chorionic MSCs and

chorionic villi MSCs have a longer life span than the decidual MSCs population obtained from the maternal-derived decidua **(23)**.

Additionally, P-MSCs were reported to have the ability to migrate to tumors and inflammatory microenvironments, involvement in angiogenesis and wound healing as well as tissue repair activity through paracrine actions**.** The P-MSCs and UC-MSCs are excellent alternatives to BM-MSCs. The former was shown to share similar morphology, cell surface markers and some pluripotency-related markers with BM-MSCs **(20) .**

Moreover, lower immunogenicity was seen in UC-MSCs over BM-MSCs with lower levels of lymphocyte proliferation. Likewise, UC-MSCs were reported to have a higher overall immunomodulatory effect with increased expression of potent immunosuppressive factors such as CD200, Leukemia inhibitory factor (LIF), and Transforming growth factor beta (TGF-β). Furthermore, **Jin et al. (24)** showed that UC-MSCs have a higher cell proliferation rate and greater anti-inflammatory effects than BM-MSCs.

Also, P-MSCs were observed to consistently faster population doubling time and longer-term expandability under identical culture condition compared with BM-MSCs. and more homogeneous than BM-MSCs in culture. In addition, the advantages of P-MSCs over BM-MSCs and adipose tissue-derived stem cells were reported to include the ability to be obtained using a non-invasive method and in larger quantity. P-MSCs played a pivotal role as potent stimulator of perinatal lung morphogenesis in ex-vivo fetal lung culture model compared with BM-MSCs **(25)**.

Mechanism of action of MSCs

Upon transplantation, MSCs were reported to exert their immunomodulatory functions at damaged sites through a synergy of direct cell-cell contact between programmed cell death protein 1(PD-1) inhibitory molecule on T cells and its ligands PD-L1 on MSCs, inhibiting CD3+ T cell proliferation, inducing early apoptosis and suppressing effector T cell (e.g., IL-17 producing T cells, T helper 17 cells) responses **(26)**.

Similarly, TNF receptor superfamily member 6 (Fas)-Fas L interactions propagate the death signal and induce T cell apoptosis. In addition, expression of CD106(Vascular cell adhesion protein 1 (VCAM-1) on P-MSCs and CD54 (Intercellular Adhesion Molecule 1(ICAM-1) on UC-MSCs is crucial in mediating immunomodulatory functions on T cells improvement in tissue-to-airspace ratio and reduction in fibrosis in bleomycin-challenged aged mice. Also, P-MSCs improved vascular density, reduced TNF-α and IL-6 levels and collagen density, by exerting paracrine effects via increased vascular endothelial growth factor (VEGF) and decreased connective tissue growth factor (CTGF) **(20)**.

Moreover, MSCs were reported to express major histocompatibility complex class I (MHC I) molecules but not express MHC II molecules; therefore, MSCs exhibit limited immunogenicity and can be applied in allogeneic transplantation without causing severe immunorejection. They were reported to express also, a large number of adhesion molecules (e.g. CD44, integrins and some stromal cell markers (e.g. SH-2, SH-3 and SH-4) and some cytokine receptors (e.g. IL-1R, TNF-aR). In addition, MSCs were found to express CD90, CD73, and CD105 and not express CD45, CD34, CD14, CD31, Von Willebrand factor (vWF) or Human Leukocyte Antigen - DR isotype (HLA-DR). Cells fitting these criteria have been isolated from the amnion, and chorion membranes as well as from the amniotic fluid **(27).**

Moreover, MSCs cultivated in a standard medium were reported to express Brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and Glial cell line-derived neurotrophic factor (GDNF)**.** Therefore, the synthesis and release of neurotrophic factors (NTFs) relevant to PD by transplanted MSCs, or indirect stimulation of NTF-release from host tissue, might contribute in part to the functional recovery, survival, and stimulation of endogenous regeneration of neuronal cells after MSC transplantation.

These NTFs were suggested also to upregulate TH gene expression in pheochromocytoma cells and neural stem cells **(24)**

Furthermore, **Dezawa et al. (28)** reported that nerve system recovery after MSCs transplantation could be related to their secretion of NTF that restore the function of nervous system, promotion of local angiogenesis and vascular reconstruction and neuronal regeneration through promotion of autologous neuronal regeneration and differentiation of transplanted cells into neural cells.

Also, it was documented that MSCs have the ability to differentiate into glial cells that release diverse NTF to provide protection against neurotoxin after their grafting into Parkinsonian rat brains.

Additionally, BM-MSCs can be transdifferentiated efficiently into functional dopaminergic neurons capable of secreting DA and alleviating behavioral deficiencies. Moreover, the results of It was showed that grafting of BM-MSCs caused an increase in the immunostaining of TH in striatum associated with elevation in the number of TH + neurons in the SNPC.

Also, **Blondheim et al. (29)** stated that the transplantation of BM-MSCs into the animal model induced with 6-OHDA resulted in an increase in the level of TH in the striatal region thus improving motor behavior in a mouse model of PD. The observed increase in brain DA content and TH expression level as a result of treatment with BM-MSCs could be explained by the ability of MSCs to secrete a wide array of cytokines and growth factors, including BDNF which exert NTF and neuroprotective effects on DA neurons **(24)**. Moreover, it was reported that BDNF has a crucial role in the functional maturation of MSC-derived DA progenitors.

Furthermore, treatment with BM-MSCs induced significant up-regulation in nestin gene expression level which is a protein marker for neural stem cells. Moreover, the study of **Ye et al. (30)** indicated the presence of nestin positive cells in brain tissue of PD rat after transplantation of undifferentiated BM-MSCs, so the suggested mechanism could be that BM-MSCs might become nestin-positive stem cells that differentiate into astrocytes or other non-dopaminergic neurons and participate in the reconstruction of dopaminergic neurons circuits in addition to, enhancement of neurogenesis and inhibition of apoptosis through their secreted BDNF.

Therapeutic effect of stem cells in neurological disorders

Stem cell transplantation and activation of endogenous neurogenesis represents one of the most promising therapeutic approaches to CNS repair in neuroregenerative medicine**.** The existence of a population of neural-crest-derived stem cells in the bone marrow gives reliable explanation for their ability to generate neural cells**.** The therapeutic effects of MSCs are mainly dependent on their capacity to act as a trophic factor pool and NTFs secretion, leading to increased neuronal survival, endogenous cell proliferation, and nerve fiber regeneration **(19)**.

Moreover, MSCs exhibit immunosuppressive capacity and possess very limited immunogenicity. Using MSCs to regulate inflammation and the immune response was hypothesized to become routine in clinical treatment. Stem cells were reported to grow in the presence of different tissue types such as heart, lung and nerve tissue. The stem cells have been shown to differentiate into the same type of cells that were surrounding them **(31)**.

Furthermore, using rodent models, intravenous UC-MSCs have been reported to migrate and accumulate in injured areas of spinal cord, amyotrophic lateral sclerosis, heat and cerebral strokes, and to differentiate into neural cells, and thus improve functional recovery of these animals. Moreover, autologous BM-MSCs treatments of neurodegenerative diseases, including PD and AD, have manifested tremendous therapeutic efficacy in both disease models and clinical trials **(32)**.

Stem cells and Parkinson's disease

Treatment with CD34+ stem cells was reported to improve locomotor activity, dopamine and ATP levels, as well as mitochondrial DNA and nuclear DNA integrity. In accordance, I.V. UC-MSCs therapy was reported to restore dopaminergic function in humans **(33)**.

Furthermore, stem cell therapy improved dopaminergic degeneration and induced a marked increase of TH-immunopositive neurons. Similarly, stem cells can differentiate into dopaminergic neurons that reinnervate the denervated striatum and become functionally integrated, restoring striatal dopamine release. Also, transplantation of ESCs has provided proof of the principle that neuronal replacement can work in PD patients**.** Also, dopaminergic cells derived from various stem cell sources have been shown to survive in the host and induce behavioral improvement and motor recovery in mammalian models from rodent to monkey. In clinical trials patients were reported to manifest symptomatic improvements, such as a reduction in tremors, rigidity, and freezing attacks **(32)**. Also, Positron emission tomography showed increased dopamine release, while magnetic resonance spectroscopy revealed improvement in N-acetylaspartate/creatine ratio **(34)**.

Stem cells and Alzheimer disease

AD is a complex, fatal disease involving loss of brain cells that control thought, memory and language and irreversible decline of cognitive functions due to cell deterioration in a structure called nucleus basalis of Meynert. After grafting, stem cells have the capacity to migrate to lesioned regions of the brain and differentiate into the necessary type of cells to promote recovery **(35)**.

Moreover, transplanted stem cells can migrate into the nervous system and integrate into local neural circuits to enhance synaptogenesis and improve synaptic transmission**.** Improved neuropathological features can be detected after transplantation, including reduced deposition and upregulated amyloid β-protein clearance **(36)**.

Additionally, stem cell transplantation was reported to decrease neuroinflammation via suppression of proinflammatory mediators, such as IL-1, IL-6, and TNF-α, and to provide long term protective immunomodulatory effects. They are capable of secreting nerve growth factors and exerting neurotrophic influence, such that tested animals showed apparent or moderate cognitive and memory improvements **(37)**.

Stem Cells and Multiple Sclerosis (MS)

In an experiment treatment of 24 patients with relapsing-remitting MS in the course of 2-8 years, ESCS were used. After treatment, syndrome of early post-transplant improvement was observed in 70% of patients. Its main manifestations were decreased weakness, improved appetite and mood, decreased depression. In the first post-treatment months, positive dynamics was observed in nystagmus, convergence disturbances, spasticity, and coordination. Also, dysarthria, dysphagia, and ataxia, showed positive changes at much slower rate **(35)**.

Stem Cells and Amyotrophic Lateral Sclerosis (ALS)

ALS is an adult-onset disease which is characterized by the death of upper and lower motor neurons with subsequent muscular paralysis and atrophy. Stem cells were modified to release glial cell line-derived neurotrophic factor (GDNF) and improved motor function in transgenic rats **(38).**

Stem Cells and Cerebral Palsy

Cerebral palsy is a disorder caused by damage to the brain during pregnancy, delivery or shortly after birth. It is often accompanied by seizures, difficulty speaking, hearing loss, blindness, lack of co-ordination and/or mental retardation. Studies in animals indicated that benefit is possible by stem cell therapy with the hope of rapidly translating these experiments to human trials **(35)**.

Stem Cells and Stroke

In patients with severe cerebral infarcts, the intravenous infusion of autologous MSCs was suggested to be a feasible and safe therapy that may improve functional recovery **(35)**.

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