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REVIEW ARTICLE

Therapeutic Effect of Mesenchymal Stem Cells in Neurological Diseases

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ABSTRACT

Background: Neurological diseases are becoming a more significant burden, and taking action on this developing issue is urgent. Developing solutions for these conditions using stem cell-based regenerative medicine is growing in appeal. Multipotent cells, or mesenchymal stromal cells, are used to treat various illnesses. The bone marrow (BM) and peripheral blood are the residence of mesenchymal stem cells (MSCs), also known as marrow stromal cells. By producing different integrins, growth factors, cytokines, and adhesion molecules, MSCs help hematopoiesis. Additionally, depending on the lineage of the MSCs, it will be possible to differentiate them. According to in vivo studies, injected MSCs have been identified in the host's adipose tissue, articular cartilage, lung, perivascular regions of the central nervous system. The preclinical and early clinical research on MSC therapy for neurological diseases like stroke, amyotrophic lateral sclerosis, multiple system atrophy, Parkinson's disease, and Alzheimer's disease is summarized in this article.

Conclusions: Much is still unclear, despite the rise in clinical trials of MSC-based treatments for neurological illnesses during the past ten years and experimental investigations utilizing animal models. Therefore, more study is required to assess and quantify the hazards associated with cell-based versus cell-free treatments, create new methods for obtaining larger numbers of healthy cells, and lessen the variability of outcomes caused by the inherent heterogeneity of MSCs.

Keywords: Therapeutic Effect, Mesenchymal Stem Cells, Neurological Diseases.

INTRODUCTION

A large category of conditions known as neurodegenerative diseases causes progressive neuronal loss that causes crippling neurological disorders. Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple system atrophy (MSA) are a few examples of neurological conditions that are ultimately fatal. Although there have been notable improvements in the symptomatic management of many diseases that enhance the quality of life and occasionally survival, the currently available drugs will likely only delay the onset of neuronal death by a few months. Since many years ago, the idea of employing cell therapy to treat neurodegenerative disorders has been discussed, particularly in the case of Parkinson's disease (PD), where numerous cell transplant studies have been carried out with varied degrees of success [1].

The bone marrow (BM) and peripheral blood are the residence of mesenchymal stem cells (MSCs), also known as marrow stromal cells. By producing different integrins, growth factors, cytokines, and adhesion molecules, MSCs help hematopoiesis. Additionally, depending on the lineage of the MSCs, it will be possible to differentiate them. According to in vivo studies, injected MSCs have been identified in the host's adipose tissue, articular cartilage, lung, perivascular regions of the central nervous system, endothelium, skeletal and cardiac muscles, BM, spleen, liver, and thymus [2].

MSCS in stroke:

Stroke symptoms include abrupt neurological impairments brought on by an interruption in cerebral blood flow. A stroke that is both ischemic and hemorrhagic occurs as a result of the pathophysiological mechanism. The most common type of neurological disorder is ischemic stroke. It is composed of a necrotic core and a penumbra around it pathologically. Symptoms include dementia, loss of consciousness and coma, and impairment in speech, feeling, and vision. Limbs and facial nerve paresis may appear depending on the stroke location [3].

The only pharmacological treatment for ischemic stroke that is currently approved involves giving patients tissue plasminogen activators intravenously to remove the blood clot that has blocked the blood artery. However, only a tiny proportion of patients (15%) may benefit from its use due to the minimal therapeutic window for performing this operation, up to 4.5 hours following the onset of stroke symptoms. Numerous articles published in the past few years have demonstrated the high efficacy of thrombectomy via the arterial route with a substantial expansion of the therapeutic window, in some cases reaching up to 24 hours (h). Consequently, this medication is still not widely available in most nations [4].

Stem cell-based therapy is an alternative therapeutic approach that has been suggested. MSCs appear to give the highest chances for stroke treatment among various stem cell types. MSCs are being studied as therapy in several animal models of subacute, acute, or chronic stroke due to their neurogenesis and neuroprotection abilities and their capacity to influence the immune system. Acute stroke causes neuronal loss in addition to an increased inflammatory response that destroys hypoxic tissue in the location of the injury and starts cytokine cascades, which cause damaged areas to increase. The transfer of neuroprotective factors and MSCs' capacity to modulate the immune system lessen inflammation. Additionally, it has been demonstrated that administering MSCs during the chronic stage of stroke activates regenerative pathways that can aid in the recovery of brain function [5].

MSCs may be injected directly into the brain, intravenously (IV), or intraarterially (IA). Brain edema and the lesion area decreased after the MSC injection. Increased remodeling and density of axons around the ischemic tissues were seen after MSC treatment in several animal stroke models, and these changes were connected with better functional recovery [6].

In addition to neurons, other cell types, particularly vascular cells, are also impacted by brain ischemia. It has been demonstrated that MSCs increase blood vessel density and release various growth factors that support angiogenesis. Additionally, engrafting MSCs guarded against ischemic reperfusion damage in the wounded cerebral microvasculature. Exogenous MSCs and injured endothelial cells may transfer their mitochondria, which could be one of the primary mechanisms causing the favorable effect [7].

Stabilizing the blood-brain barrier (BBB) may also be necessary for MSCs to fulfill their therapeutic potential in functional recovery following stroke. After MSC infusion in various stroke models, a BBB decreased permeability was seen in injured brain tissue. According to recent research, transplanted MSCs interact with neurons, astrocytes, and pericytes to maintain and restore the BBB [8].

Inflammatory and immunological responses triggered at each stage of the illness accompany stroke. Consequently, it has been hypothesized that neuroinflammation is a desirable stroke therapeutic target. MSCs have immunomodulatory qualities, which means they can reduce post-stroke inflammatory events. It was demonstrated that MSC implantation dramatically decreased the inflow of leukocytes, mainly T cytotoxic cells, and stimulation of astrocytes and microglia/macrophages in response to the brain injury [9].

Additionally, MSC infusion has been demonstrated to contribute to the inflammatory cascade by decreasing proinflammatory cytokine levels (IL-1α, IL-1β, IL-6, tumor necrosis factor (TNF-α), and increasing anti-inflammatory cytokine levels (IL-4,

IL-10, interferon (INF-β), while also growing chemokine levels [10].

MSCS in traumatic brain injury:

Traumatic brain injury (TBI) is the most severe condition that occurs often in children and young adults. It typically happens due to extrinsic mechanical forces acting on the head, which can impair neurological processes and even cause death. There are two phases to the harm brought on by TBI. The initial insult's immediate result, early stage, is BBB disruption, brain edema, and cranial bleeding. In the acute phase of the illness, oxidative stress and excitotoxicity cause rapid death of cells within a confined or spread brain area [11].

The following stage is the second injury, which lasts for weeks or months and is triggered by the prime injury 1-3 days after the initial traumatic experience. Continuous neurodegeneration is brought on by progressive secondary damage, contributing to excitatory amino acid release, ionic imbalance, calcium overload, and mitochondrial malfunction. Reduced neurogenesis, axonal damage, and cell death are consequences of TBI's mechanism. The inflammatory and immunological reactions that follow brain injury also increase neuronal damage. Pro-inflammatory cytokine secretion, provoked immune cells, and microglia activation are the hallmarks of post-traumatic neurological inflammation [12].

No single therapeutic strategy has proven successful in lowering TBI mortality or accelerating patients' recovery. Numerous pharmacological medications failed to improve the course of the condition. Due to the vast range of factors present during the disease's development, TBI monotarget therapy was ineffective. Consequently, a multitarget treatment approach is required. Cell transplantation is one potential choice. Numerous preclinical studies suggest that using MSC in several experimental models of TBI can address various disease pathology features [13].

TBI-induced motor and cognitive impairments in mice were reduced when MSCs were injected directly into the damaged brain or administered by IV or IA. The results of the experiments demonstrated that administering MSC therapy to TBI rats and mice stimulated the wounded brain to produce trophic factors that supported neuroprotection, neural repair, and neurogenesis [14].

It has been demonstrated that MSCs' therapeutic impact after transplantation in TBI animal models is enhanced by genetic alteration. When injected into the TBI mouse brain, genetically modified MSCs that upregulate fibroblast growth factor 21 (FGF-21) improved cell homing to the damage site and greater hippocampus neurogenesis [15].

The relationship between the secretion of bioactive substances and the potential therapeutic effect of MSCs is well established. According to recent research, exosomes released from MSCs appear to have a similar impact to their counterparts. Exosomes may be administered intravenously (IV), intramuscularly (IM), intrathecally (IT), or intravenously (IN). Experiments on living, breathing, TBI-exposed laboratory animals have been conducted with cell-free exosomes generated from human MSCs. MSC exosome intravenous infusion dramatically reduces motor impairments and enhances spatial memory in TBI rats by encouraging endogenous neurogenesis and angiogenesis [16].

Recent research has demonstrated that the secretome of IV-infused MSCs can reduce neuroinflammation by restricting the release of proinflammatory cytokines, controlling microglia polarization, and reducing neural cell death. In a different study, IC, MSC-derived exosome transplantation in TBI rats reduced microglia proinflammatory activation, reducing neuronal damage and promoting functional recovery following brain injury [17].

MSCs-derived exosomes have additionally been shown to lessen brain damage in a large animal model of TBI. Williams and colleagues showed exosomes generated from human BM-MSCs to restore BBB integrity, reduce brain edema, and reduce lesion sites in swine with severe TBI [18].

MSCS in Alzheimer's disease:

Alzheimer's disease (AD) is a long-term neurological condition that causes cognitive deficits and memory loss. The aggregation of amyloid β (Aβ) plaques and the intracellular development of neurofibrillary tangles that result in the death of cholinergic neurons are visible in the histological appearance of the brain in AD diseases. Additionally, it is well-established that neuroinflammation contributes significantly to AD. A chronic buildup of Aβ stimulates microglia, hastening cognitive decline and neuronal death. MSC-based therapy is a modality ready for AD among all therapeutic modalities. Animal models of AD, IV, IC, and intraventricular (INVE) infusions

of MSCs have all been the subject of experimental research [19].

Exogenous stem cells' therapeutic activity could ameliorate the pathological symptoms in animal models of Alzheimer's disease. Unfavorable reactions were infrequent after a bone marrow mesenchymal stem cell transplant. The effectiveness and safety of bone marrow mesenchymal stem cells were evidence of their benefits. The transplantation of mesenchymal stem cells from bone marrow has been optimized through suitable infrastructure and testing settings. Several research findings showed marked reduced cognitive decline and neuropathological symptoms in AD-like animal models [20].

Acetylcholine levels and the expression of choline acetylcholinesterase and acetyltransferase rose after MSCs were infused into the brain of AD rat models, providing evidence of improved hippocampus neuron function. Loss of synapses is also associated with cognitive impairment in AD. Recent research by Zappa Villar et al. suggests that MSCs may act as a protective mechanism against the loss of synaptic proteins by restoring levels of synaptic markers such as Synaptophysin (SYP), Synaptotagmin-1 (SYT1), and glutamic acid decarboxylase 65 in the hippocampus of the sporadic AD rat model. Furthermore, since it has been established that microglial processes are linked to neuronal synapses, continuous activation of AD-related microglia causes synaptic toxicity and speeds up neuronal death [21].

MSC infusion has been shown to alter the inflammatory response in animal models of AD. MSC recipients showed a remarkable reduction in the activation of microglial cells in the cortexes of mice and an inhibition in the expression of proinflammatory markers such as TNF-, IL-6, and Macrophage Chemotactic Protein (MCP)-1. It has been demonstrated that MSC transplantation changes active microglia from the proinflammatory M1 phenotype that produces cytokines to the M2 phenotype, which has an anti-inflammatory effect on AD and improves neuron survival [22].

In multiple animal models that were created through genetic modification, protein injection, or chemical administration, the beneficial benefits of BMMSC transplantation have been seen. There was no immunological reaction to the implantation of autologous BMMSC stem cells. Tremendous experiment results demonstrated the BMMSCs' therapeutic effects, which improved cognitive impairments and degenerative changes. Future clinical therapy of AD patients may very well involve the use of BMMSCs since (a) bone marrow aspiration is a simple method for obtaining stem cells, (b) peripheral vein delivery, and (c) autologous stem cells lack immunogenicity [20].

MSCS in Huntington's disease:

A mutation in the gene that produces the huntingtin protein, which builds up excessively in cells and has a cytotoxic impact, causes Huntington's disease (HD). Neurons in the brain that secrete -aminobutyric acid, such as those in the caudate nucleus and crust, are particularly susceptible to death during HD. The disease's symptoms typically start between the ages of 30 and 40 and are linked to diminished motor, behavioral, and cognitive abilities. There is currently no cure or viable therapy for HD. In animal models of HD, the curative capacity of MSCs was revealed [23].

Exogenous cells were injected intracerebrally in most MSC transplant investigations done thus far in HD. HD mice given BM-MSC had lessened motor impairments and enhanced spatial memory. Transplanted BM-MSCs induced trophic support with elevated BDNF levels in the striatum of HD mice, likely stimulating endogenous neural stem cell growth [24].

In HD model mice treated with MSCs (genetically engineered), there was a reduction in the number of apoptotic cells in the striatal area and decreased brain atrophy. Additionally, mice with HD issues lived longer than control mice after MSC transplantation, and less-misfolded huntingtin protein (m HTT) aggregates were found. According to recent research, spreading neurodegeneration in the brain may result from transferring m HTT aggregates from host neurons to donor cells [25].

The investigators have shown that intranasal administration of autologous BM-derived MSCs boosted the expression of phosphoproteins associated with the dopamine D1 receptor (DARPP-32) and tyrosine hydroxylase (TH) in the striatum, which is implicated in the dopamine signaling cascade. Additionally, the MSC treatment demonstrated immunomodulatory effects by changing the M2 anti-inflammatory subtype of microglia and reducing the pro-inflammatory gene production of TNF-, IL-6, and MCP-1, which is typically increased in HD mouse brains [26].

Due to the disease's complicated symptomatology, clinical treatment for HD has proven to be quite difficult. It has been shown that HD patients have reduced amounts of BDNF, which is necessary for

the survival and functionality of cortical neurons. In transgenic HD animal models, restoring BDNF levels enhances neuronal survival and lessens HD symptoms. BDNF may, therefore, be used to address the neuronal dysfunction seen in HD patients [27].

MSCS in Parkinson's disease:

Parkinson's disease (PD) develops as a result of the gradual degeneration of dopamine-producing neurons in the substantia nigra of the brain. Resting tremors, muscle rigidity, bradykinesia, postural issues, and a reduced capacity for fine motor control are some of the disease's primary symptoms. There is also cognitive function impairment, sleep difficulties, and odor issues. The disease's underlying causes are currently unknown. Most of the time, it arises spontaneously; however, about 5% of patients have mutations in the gene that codes for -synuclein, which is connected to the development of protein clumps called Lewy bodies in the bodies of neurons with a cytotoxic effect. MSCs were mostly administered intracerebrally in the PD model mice but were also given intravenously, intraarterially, and intranasally [3].

An MSC-based therapy for Parkinson's disease (PD) has two separate molecular effects: 1) trophic action mediated by cytokines and various neuroprotective, anti-apoptotic, and growth factors, and 2) differentiation of MSCs into several diverse cell types aiding cell replenishment. MSCs are also shown to generate anti-inflammatory cytokines, which support tissue healing. The ability of MSCs to develop into DA neuronal precursors has been shown in certain studies. However, it is still unclear if these differentiated cells can integrate into the host environment and create new synaptic connections with the host neurons [28].

MSCS in amyotrophic lateral sclerosis:

Unknown in its genesis, amyotrophic lateral sclerosis (ALS) typically manifests randomly and progresses fatally three to five years after the onset of symptoms. ALS, which is defined by the slow degeneration of upper and lower motor neurons in the brain and spinal cord, causes muscle weakness and respiratory failure [3].

MSC treatment has been demonstrated to reduce illness symptoms in ALS experimental animals. In ALS, problems after MSC transplantation, neuroprotection, stimulation of nerve tissue regeneration, and more extended longevity have been noted. Transplanted MSCs may function as bystander cells that secrete neurotrophic substances that are transported from the motor cortex to the spinal cord via cerebrospinal fluid (CSF) [29].

The neuroprotective effects of substances such as nerve growth factor (NGF) , brain-derived neurotrophic factor (BDNF), Insulin-like growth factor (IGF)-1, and vascular endothelial growth factor (VEGF) secreted by transplanted MSCs are most likely responsible for the beneficial benefits of MSC treatment in ALS. By simultaneously expressing glial cell-derived neurotrophic factor (GDNF), IGF-1, and hepatocyte growth factor (HGF), modified MSCs greatly enhanced the neurotrophic effect of donor cells and postponed the onset of symptoms in a mouse model of ALS [30].

MSC intrathecal infusion slowed the progression of ALS-related neurodegenerative alterations. Results from many research showed that MSC recipients had enhanced motor function in ALS models and that motor neuron degeneration was decreased by preserving the structure of altered perineuronal nests [31].

According to Kook et al., MSCs injected IM into an ALS mice model were found to have positive effects. Recurring injections of human umbilical cord blood MSCs into the gastrocnemius muscles of superoxide dismutase 1 (SOD1) G93A mice lowered the rate of degeneration of neuromuscular muscular atrophy, which enhanced motor function and increased their lifetimes [32].

Through the reduction of astrogliosis and microgliosis as well as the peripheral levels of proinflammatory cytokines, including TNF-, IL-1, and IL-6 in CSF, experimental studies demonstrated that MSCs transplanted in ALS also contain an anti-inflammatory potential [33].

Based on postmortem analysis of patients with ALS treated with MSCs, more motor neurons were preserved at the height of the spinal cord area where the cells were injected, compared to other spinal sites. The observed clinical improvement in ALS transplant recipients may be linked to the immunomodulatory effects of MSCs [34].

The FDA-approved pharmaceuticals for treating ALS showed only a minor improvement in disease-related survival rates and a marginal reduction in functional impairment. Based on the encouraging outcomes of preclinical trials, MSC therapy has recently been suggested as a potential treatment for ALS. Transplanted MSCs act as bystander cells, removing harmful compounds from the environment and secreting trophic factors that aid in the survival and neuroprotection of neural cells, as

seen in many motor neuron models. The lifespan of animals and motor symptoms are improved by MSC infusion into ALS rodents [3].

MSCS in multiple sclerosis:

MS is a CNS autoimmune disease that causes inflammation and demyelination. The body's production of autoreactive lymphocytes and antigen-presenting cells is linked to the pathophysiology of the illness. The inflammatory cytokines these cells produce encourage the immune system's lymphocytes, neutrophils, mast cells, and macrophages to gather in the CNS regions linked to astrogliosis and microgliosis. Multiple sclerosis (MS) manifests as multifocal degenerative alterations, including areas of demyelination and significant neuronal loss. These changes are caused by neuroinflammation-related neurodegeneration, which kills myelin sheaths and axon neurons during the chronic phase of MS. The location of the lesion has a significant impact on the clinical profile of an MS patient. However, paresis, sensory impairment, speech, balance, coordination, memory issues, and cognitive decline are frequently present [35].

Experimental allergic encephalomyelitis (EAE) is an animal model of the condition, and systemic treatment of MSCs causes the transplant recipient to develop tolerance for its antigens. MSC-transplanted animals showed greater remyelination and higher oligodendrogenesis in the spinal cord region than control animals, which inhibited the invasion of autoaggressive leukocytes in the brain. MSC injections into EAE mice reduced the level of CNS local inflammation [9].

In the brain cortex and spinal cord of EAE patients, the anti-inflammatory impact of MSCs promotes neuroprotection, inhibits axon loss, and lowers neuronal necrosis and apoptosis. Acute EAE patients' corpus callosum and spinal cord showed signs of newly created myelin sheaths around axons after receiving transplanted MSCs, which also encouraged oligodendrogenesis and prevented demyelination [36].

As a result, the disease has a considerably milder course with a reduced frequency of relapse, a more minor infiltration of immune cells, and less demyelination and axonal damage. A primate MS model has recently undergone MSC treatment. Infusion of MSCs intrathecally delayed neurodegeneration and demyelination in EAE monkeys [37].

Intracerebral MSC transplantation reduced neuroinflammation in a cuprizone (CPZ)-induced animal model of chronic MS by lowering astrocyte and microglia activity as well as changing proinflammatory subtypes of microglia (M1) into anti-inflammatory microglia (M2) in the host brain. Additionally, remyelination and axonal regeneration improved due to MSC treatment, as seen in investigations using immunohistochemistry. This finding is consistent with earlier research in which MSC infusion in a chronic demyelination mouse model of MS exhibited increased myelinated fibers in the corpus callosum and oligodendrocyte progenitor cell migration and homing [38].

CONCLUSIONS

Much is still unclear, despite the rise in clinical trials of MSC-based treatments for neurological illnesses during the past ten years and experimental investigations utilizing animal models. Therefore, more study is required to assess and quantify the hazards associated with cell-based versus cell-free treatments, create new methods for obtaining larger numbers of healthy cells, and lessen the variability of outcomes caused by the inherent heterogeneity of MSCs.

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