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Stem Cell Therapy in Pediatric Neurological Disorders

Farnaz Torabian[1], Arvin Aghayi nejad[1], Arash Akhavan Rezayat[1], Mehran Beiraghi Toosi[2], Hamid Reza Rahimi[3], *Ali Reza Ataei Nakhaie[2]

[1]Member of Science and Technology Stem Cell assembly of Mashhad, Mashhad University of Medical Sciences, Mashhad, Iran.
[2]Department of Pediatric Neurology, Ghaem Hospital, Mashhad, Mashhad University of Medical Sciences, Mashhad, Iran.
[3]Student Research Committee, Department of Modern Sciences and Technologies, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

Abstract

Pediatric neurological disorders including muscular dystrophy, cerebral palsy, and spinal cord injury are defined as a heterogenous group of diseases, of which some are known to be genetic. The two significant features represented for stem cells, leading to distinguish them from other cell types are addressed as below: they can renew themselves besides the ability to differentiate into cells with special function as their potency. Researches about the role of stem cells in repair of damaged tissues in different organs like myocardium, lung, wound healing, and others are developing. In addition, the use of stem cells in the treatment and improving symptoms of neurological diseases such as autism are known. Many epigenetic immunological studies on effects of stem cells have been performed. The action of stem cells in tissue repair is a need for further studies. The role of these cells in the secretion of hormones and growth factors in the niche, induction of cell division and differentiation in local cells and differentiation of stem cells in damaged tissue is the samples of effects of tissue repair by stem cells.

Cognitive disorders, epilepsy, speech and language disorders, primary sensory dysfunction, and behavioral challenges are symptoms of non-neuromotor dysfunction in half of pediatrics with Cerebral Palsy (CP). Occupational therapy, oral medications, and orthopedic surgery for supportive and rehabilitative approaches are part of Conventional remedy for cerebral palsy. This paper summarizes the clinical world wide experience about stem cell based therapeutic procedures for pediatric neurological disorders.

***Key Words*:** Cerebral palsy, Spinal cord injury, Stem cells.

**** Corresponding Author:***

Ali Reza Attaei Nakhaie, MD, Department of Pediatric Neurology, Ghaem Hospital, Mashhad, Mashhad University of Medical Sciences, Mashhad, Iran.
E-mail: Ataei NA1@mums.ac.ir

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Introduction

Neurological disorders accompanied by nervous and musculoskeletal dysfunction, resulting in movement impairment and muscle tone abnormalities(1). Clinical symptoms in such patients include motor weakness, muscle tone changes, delayed milestones, headaches, seizure, and coordination loss. The growing concern about neurological disorder treatment is due to disability of brain and spinal cord neurons to regenerate instinctively(2).

These defects in infants effect on their lifestyle through their life. So early treatment is important for reduce development of neural defects. Treatments like moderate hypothermia that is done in newborn with hypoxic-ischemic but about one-third newborn die or not impairment. So research for new treatment methods with more efficacy is necessary(3).

Researches about the role of stem cells in repair of damaged tissues in different organs like myocardium, lung, wound healing and others are developing (4-9). Also the use of stem cells in the treatment and improving symptoms of neurological diseases such as autism are known. Many epigenetic and immunological studies on effects of stem cells has been performed(10).

The action of stem cells in tissue repair is a need for further studies. The role of these cells in the secretion of hormones and growth factors in the niche, induction of cell division and differentiation in local cells and differentiation of stem cells in damaged tissue is the samples of effects of tissue repair by stem cells(11). Moderate and severe neural defect is almost not repaired by human body, so the use of stem cells with high differentiation potency like umbilical cord blood cells and Mesenchymal stem cells (MSCs) can be effective in these injuries(12).

The aim of this review is survey the effectiveness of stem cells transplantation in pediatric neurological disorders.

Stem cells

Stem cells are able to renew themselves and have the ability to differentiate into distinctive mature cell types, leading to new tissue formation, repair, and regeneration (13-16).

Mononucleocytes (MNCs) originated from bone marrow consist of various cell types including hematopoietic stem cells, tissue-specific progenitor cells, stromal cells, and specialized blood cells within different developmental stages. Data of researches show that stem cells can migrate from site of injection into the injured position (17).

Moreover, increase in angiogenesis, producing signaling factors including Vascular endothelial growth factor (VEGF) and Fibroblast growth factor (FGF) by stem cells result in neovascularization (18). Other relevant mechanisms are tissue remodeling, apoptosis prevention, inflammation decline, and satellite cells activation (15). Hematopoietic, endothelial and angiogenic cells are found in Bone marrow (BM), which is a source for many stem cells(19, 20). Stem cells can able to differentiate in brain(21, 22)

Application of stem cells in neurological disorders

Recently, in vivo and in vitro studies have claimed that Bone marrow stromal cells (BMSCs) could be induced into neuron-like cells and glial cells (23-25). Intravenous transplantation of BMSCs in newborn rats affected by hypoxic-ischemic encephalopathy, have been performed in some studies, and indicated that stem cells could be passed through blood-brain barrier(26). Neurotrophic factors including Brain-derived neurotrophic factor (BDNF) and Nerve growth factor (NGF) secreted by BMSCs, based on their nutritional effect mechanism, could repair the neuron injuries (27).

Data of a clinical trial on 71 children suffering from incurable neurological

disorders who underwent via intrathecal and intramuscular procedure autologous bone marrow-derived mononuclear cells transplantation demonstrated safe treatment without any critical adverse effect, besides considerable promotions found in life quality(15).

Repairing injured organs and tissues in animal models, replacing injured or dead neuronal cells with stem cell that is a new procedure, has proven effective (28). In an experimental model study , CD34 + BM cells were administered intravenously after stroke, leading to neovascularization and neuronal regeneration(29). Moreover, $CD34^+$ and/or $CD13^+$ cells were grafted intracerebrally, enabling neurological function improvement in animal studies(30). Administration by means of carotid artery or intracerebrally injection of Bone marrow mesenchymal stromal cells(BM-MSCs), in rats showed remarkable promotion in their function of ischemic brains(31, 32) .

In case of muscular dystrophy, trials on transplantation of myoblast cells, mesenchymal stem cells and umbilical cord stromal cells demonstrated safety and efficacy(33, 34). Studies have demonstrated development of bone-marrow-derived cells into neural tissue(35). Published researches have depicted bone marrow stromal cells differentiation in to neurons (23, 36, 37). Animal studies have claimed effectiveness and efficaciousness of stem cell transplantation as good as researches that assessed patients suffering from stroke and demyelination (38-40).

Chop and colleagues provided functional improvements in induced rodent bone-marrow cells transplanted ischemic rat brain(41). Previous studies represented that neurons and astrocytes have been derived from transplanted murine MSCs(37, 42).

The clinical study showed that rise in nervous tissue capacities have been derived from grafted low-differentiated (stem) cells (43-45). Motor and cognitive functions could be improved via umbilical cord blood stem cell transplantation(46).

Animal studies have asserted Central Nervous system (CNS) regeneration after stroke, traumatic brain injuries, and spinal cord injuries by means of stem cell transplantation (47-51). Data resulting from study in primate stroke model have depicted motor function improvement after Bone marrow mesenchymal stem cell (BM-MSC) therapy(52).

To repair injured brain tissues and ameliorate neurological disorders, stem cell therapeutic approaches have been used, and showed potential effects(51, 53). Notable effects resulting from BM-MSCs administration on cerebral repair such as cerebral palsy, Spinal cord injury, stroke, have been detected in animal studies as well as clinical trials(51).

Cerebral Palsy (CP)

CP is characterized as a neurological disorder among children (54). It is defined as a spectrum of disorders accompanied with movement and postural development. It causes restriction in activity. Perception, hearing, vision, speech and psychic disabilities are cardinal symptoms of cerebral palsy(55). Also, it results from injuries causing motor control disturbances happening in newborns, infants up to 1 year after birth, or within the pregnancy(56).

Hypoxia is explained as the cardinal reason for CP(57). CP as a non-progressive disability characterized by an incidence of 2 per 1000 among live birth(58). Two categories of CP treatment are notable: treatment of injured site of brain, that are responsible for muscle coordination, and controlling the muscle coordination dysfunction resulting from cerebral palsy. CP encompasses variety sites of developing brain involved with several types of injuries including: migration failure within brain development from origin to suitable functional sites, failure to myelin deposition

of oligodendrocytes, causing weak impulses, death of cells located in grey matter and, synapses with poorly function in brain cells(59).

Published Studies about cerebral palsy in children have represented safety of cell transplantation and neurological improvements (16, 55, 60).

The case report accomplished in India, showed evidence of feasibility, safety, and effectiveness intrathecal infusion of autologous Bone-marrow-derived mononuclear cells (BMMNCs) in cases with CP. It also claimed considerable improvements in motor, cognitive and sensory function (58).

Clinical research carried out by Zali et al. confirm a safe approach by means of subarachnoid administration of CD133-possitive enriched bone marrow progenitor cells in children with CP(61). In an open-label phase I trial, depicted safety of autologous bone marrow-derived Total nucleated cell (TNC) placed in subarachnoid space in pediatric CP patients, leading to neurological function improvement(62).

CP risk factors are as below: low birth weight, multiple pregnancy, prematurity(63). The most frequent single form of CP is periventricular leukomalacia(62). A clinical study carried out by Wang X et al. in pediatric CP patients provided the safety feasibility, and effectiveness of autologous Bone marrow mesenchymal stromal cells transplantation using the Gross Motor Function Measure(GMFM) with regard to motor function development(64). A research in China evaluating the safety of neural progenitor cell transplantation in 45 children suffering from severe CP have depicted effectiveness of NPC transplantation as a therapeutic method (65).

Traumatic brain injury (TBI)

Traumatic brain injury (TBI) is an insult to the brain that disrupts neurological activity(66).

Patients suffering from Traumatic Brain Injuries (TBI), frequently have motor, cognitive, behavioral, and social dysfunction, as chronic or acute forms classifications (67-69).

During the last decade, hospitalization rate for moderate Glasgow Coma Scale (GCS 9-12), and severe Glasgow Coma Scale (GCS <9) TBI among pediatric has not been altered. About one-third of cases with severe TBI are experiencing devastating consequences such as death or severe/moderate disabilities (67-69).

Pharmacological-based therapies have been lost to obtain positive effect(68, 70). Treatment in patients with TBI is classified in to two categories: acute treatment, encompassing Intracranial pressure (ICP) control and optimizing Cerebral perfusion pressure (CPP); and chronic treatment, with the concentration on motor, cognitive, and behavioral rehabilitation(68, 70). A phase I clinical trial research in Texas, has evaluated the safety of autologous bone marrow-derived mononuclear cells (BMMNCs) therapy with intravenous infusion for children suffering from severe TBI, and determined its feasibility and safety(71).

Spinal cord injury

Spinal cord injury (SCI) is defined as a disruption in spinal cord continuity, causes an irreversible loss of neuronal connections, impairment in spinal cord function, considerable disorder, and notable impact on life quality. People throughout the world suffering from SCI exceed 130,000 cases, annually (72). In the past 20 years, studies claimed that cell-based therapy including MSC, and BM cells, have a potential safety in patients suffering from SCI (40, 73-87).

Studies suggested autologous bone marrow –derived stem cell delivery in patients suffering from sub- acute and chronic spinal cord injuries have demonstrated amelioration in electrophysiological alterations as well as American spinal injury

association(ASIA) scale changes (15, 74, 76, 79).

Findings from a case report, provided data on certain level of promotion in life quality and neurological improvements among children with chronic complete spinal cord injury after multiple Blood mononuclear cells(BMNC) implantation procedure(88).

Long term complications such as pneumonia, atelectasis, deep vein thrombosis, pulmonary embolism, fractures, neuronal calculi, spasticity, and neuropathic pain occur in patients with SCI (89-91).

The underlying reason for rehospitalization and the most common cause resulting in morbidity and mortality are complications of SCI(89).

Conclusion

Stem cell-based therapy may be an effective strategy to regenerate and repair pediatric neurological disorders. Current therapeutic intervention methods for children with neurological disabilities are limited, although various researches on animal models have carried out, resulting in effectiveness of cell therapy. Besides, case reports evaluating cell-based therapy have been performed, showing safety and effectiveness of this procedure also in pediatrics with CP intrathecal infusion of autologous bone-marrow-derived mononuclear cells (BMMNCs) was efficient and showed recovery of motor, cognitive, and sensory function. Because the performed researches about this issue do not seem to be enough, more investigations and experiments are suggested nonetheless this review showed pediatric clinical researches approaching challenges of neuronal repair development, and decreasing incidence among children are required.

Conflicts of interest: None.

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