Diplegic Dystonic Cerebral Palsy Treated With Cellular Therapy: A Case Report

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Abstract
Cellular therapy has gained acknowledgement as a novel modality for the treatment of Cerebral Palsy (CP) due to its neuro-regenerative and neuroprotective characteristics. CP affects movement and posture in childhood causing severe neuro-disability in children. The standard therapeutic approaches are seldom effective as they do not address the underlying neural damage. In this case of 4 years 10 months old boy with diplegic dystonic CP, we administered autologous bone marrow mononuclear cells intrathecally. The patient underwent two cellular therapies at an interval of seven months. The follow up assessment was conducted at 3,7 and 13 months after the first cellular therapy. Improvements in voluntary control, muscle tone (spasticity and dystonia), balance, weight bearing of the upper limbs, oromotor skills and cognition were noted over the follow up period of 13 months. Gross motor function measure (GMFM) improved from 30.59 to 69.87 %, and Wee-Functional Improvement Measure (Wee-FIM) improved from 45 to 84. No adverse events were reported post cellular therapy. This case study highlights the clinical benefits of cellular therapy with corroborative improvements in the outcome scales in a unique case of diplegic dystonic CP. We recommend that its effectiveness should be established in a more comprehensive randomised controlled study.
Keywords*: Bone marrow mononuclear cells, Cerebral Palsy, Diplegia, Dystonic, Autologous, Cellular therapy, Stem cells.*

Introduction

Cellular therapy has gained acknowledgement as a novel modality for the treatment of cerebral palsy (CP) due to its neuroregenerative and neuroprotective characteristics. Various preclinical and clinical studies have demonstrated benefits of cellular therapy in CP. CP affects movement and posture in childhood resulting from brain injury during the prenatal, perinatal, or postnatal period. It is the most common cause of severe neurodisability in children.[1] Slow motor development, abnormal muscle tone, and unusual posture are common initial clues to the diagnosis of cerebral palsy.[2] The standard approach involves medications, physical and behavioural therapy, hyperbaric oxygen therapy(hbot), use of assistive device, and medical management of associated conditions that aims at improving the functional abilities.[3,4] But in solitude these therapies are seldom effective as the underlying neural damage in CP is not addressed. This case describes the effect of intrathecal administration of autologous bone marrow mononuclear cells in diplegic dystonic CP along with neurorehabilitation.

Case representation

A 4 year 10 months old boy with diplegic dystonic CP was born at full term through vaginal delivery but with prolonged labour. He did not cry for 10 minutes after birth and developed seizures on the first day of birth. He was kept in NICU for 10 days. Gradually, the parents noticed that his motor milestones were delayed. A diagnosis of CP was made on the basis of clinical picture and MRI brain at the age of 2 years 10 months. Physiotherapy was started at the age of 3 years.

On neurological examination, there was hypertonia and hyperreflexia. Deep tendon reflexes at the cortical level were not well developed i.e. protective extension, and equilibrium reaction was affected. The voluntary control of the upper and lower extremities was fair. He sat with a 'W' posture. The shoulders were adducted

and were in internal rotation, and the knee had a mild flexion and outward curvature. He could assume quadruped, kneeling and standing positions but with a minimum balance. The speech was monosyllable. The fine motor activity of the upper extremity was found to be fair with the presence of gross grip. Diplegic gait with mass movement pattern was observed. Transitions could be performed with mass movement pattern due to fair dissociation skills. All sensations were intact. Cognition was normal with age appropriate comprehension and expression. Oromotor skills were affected by presence of drooling. He was not toilet trained and was dependent for all his activities of daily living (ADLs). Functional Independence Measure (Wee-FIM) score was 45; pediatric Berg balance score was 0/56, Gross Motor Function Classification System (GMFCS) was at level III with a Gross Motor Function measure (GMFM) score of 30.59.

Magnetic resonance imaging (MRI) brain revealed bilaterally symmetric T2 hyperintense signal abnormality in the posterior putamina and thalami. The imaging features were consistent with the sequel of perinatal hypoxic ischemic insult. Positron emission tomography-computed tomography (PET CT) brain showed mild hypometabolism in bilateral lenticular nuclei; moderate hypometabolism in the bilateral hippocampus , amygdala, and bilateral thalami; moderate to severe hypometabolism in the bilateral cerebellum.

Procedure

The selection of the patient was based on the World Medical Associations Helsinki declaration. [5] The protocol was reviewed, and ethics approval was obtained from Institutional Committee for Stem Cell Research and Therapy (IC-SCRT). The procedure of cellular therapy was explained in detail to his parents, and a duly filled informed consent was obtained from them prior to the therapy. Consent was also video recorded.

Before the intervention, the patient underwent a complete evaluation consisting of neurological, psychological and preoperative investigations to assess the anesthesia fitness. Granulocyte-Colony Stimulating Factor (G-CSF) (300 mcg) injections were administered subcutaneously, 72 hours and 24 hours prior to bone marrow aspiration. On the day of transplantation, 70 ml bone marrow was aspirated from the right anterior superior iliac spine under local anesthesia with sedation, using bone marrow aspiration needle and was collected in heparinized tubes. The BMMNCs were separated from the aspirate using density gradient method. The purified MNCs were tested for total cell count, viability and CD34+ cell content by Fluorescence Activated Cell sorting (FACS). The separated cells were then injected intrathecally at the level between L4 and L5. Simultaneous intravenous administration of 200 mg methyl prednisolone in 500 ml of Isolyte P solution was done to decrease immediate inflammation and to enhance the survival of the injected cells. Total numbers of cells injected were 2.4×10^8 with 98% viability. The CD34+ cell count was found to be 502 cells/uL.

Following the transplantation, he underwent multidisciplinary neurorehabilitation. Physiotherapy consisted of exercises to develop dissociations, to improve equilibrium reactions and weight bearing, gait training, trunk strengthening exercises and muscle elongating exercises. Occupational therapy aimed at improving the balance, bilateral coordination, upper extremity voluntary control and trunk control. Cognitive rehabilitation was provided by the psychologist to initiate and improve concept development, command following and tolerance level in the patient.

The patient was discharged after one week and was advised to continue the rehabilitation at home. The follow up assessment was conducted at 3,7 and 13 months after the first cellular therapy. In view of the improvements observed at 7 months, he underwent second cellular therapy. The transplantation procedure was replicated. Total numbers of cells injected were 9.8×10^7 with 98% viability. A total of 152 cells/uL of CD34+ cells were injected. The follow up assessment was conducted at six months after the second cellular therapy.

Results

Four months after the first cellular therapy, significant improvements were observed in the patient. The mass movement pattern improved with foot clearance and no scissoring while walking. Neck righting reflexes and

protective extensions improved from poor to fair. He could perform reach out exercises in quadraped, kneeling and standing positions. The voluntary control of the ankle and the foot improved. He could ambulate indoors with supervision. The shifts in kneeling and crawling positions improved. Improvements in the activity of daily living were seen in terms of upper and lower body dressing, eating independently with the right hand. Attention, concentration, and memory also improved. The GMFM score improved from 30.59 to 45.178 and Wee-FIM from 45 to 55.

Seven months post first cellular therapy, the W sitting posture decreased. Posture in sitting and standing position was more erect. He could pick up objects from the floor in standing position. Balance while walking improved and he could walk without support. Oromotor skills improved with reduced drooling. The weight bearing of the upper limbs increased with improved bilateral hand activities like throwing the ball and catching with both the hands. The hand grip improved as he could eat with a spoon and hold a glass of water to drink using both his hands. The dystonic movements in the lower limb reduced. The FIM score improved from 55 to 69.

Taking into consideration the improvements observed over the 7 months after the first cellular therapy, he underwent second cellular therapy. The subsequent follow up at six months (13 months after first intervention) showed further improvements in weights shifts and balanced while walking. He would no longer spread out arms while walking. The dystonia in the lower limbs further reduced. The grasp and in hand manipulations improved. All the other improvements were maintained. The Wee-FIM score improved from 69 to 84 and GMFM improved from 45.18 to 69.87.

Discussion

Cellular therapy can treat the underlying neural damage in CP due to its neuroregenerative and neuroprotective properties. In this case, autologous BMMNCs were chosen as they are easily accessible, adequate in numbers and associated with minimal risk of cell rejection and graft versus host disease (GvHD). [6] BMMNCs consist of a heterogeneous mixture of different types of cells including hematopoietic progenitor cells at different stages of maturation, as well as lymphoid cells (lymphocytes, plasmatic cells), monocytes, and macrophages. [7] This heterogenous population produces its functional effect through the balance between potential beneficial properties of all cell types. [8] Stem cells induce neuroprotection and neural repair by inflammatory suppression, the release of neurotrophic factors, angiogenesis and by the stimulation of endogenous neurogenesis. These mechanisms prevent the cell death and improve blood flow to the affected area in the brain and thereby helps in the establishment of neuronal circuits and synaptic connectivity. [9] These cells also stimulate the repair process by homing at the site of injury and restoring the lost cells and regenerating into neuronal cells, oligodendrocytes, etc. [10] These mechanisms of stem cells can be utilised to repair the underlying neural damage in CP.

The neurodeficits in CP are due to the injury of the fetal or infant's brain. [11] Risk factors for this case included hypoxic ischemic damage due to prolonged labour, delayed cry at birth, NICU stay, and seizure. The focal lesions in the gray matter and the brainstem nuclei in full-term newborns are the abnormalities of brain seen in CP. [12] The brain MRI of the patient revealed an abnormality in the putamen of the basal ganglia and thalamus caused by perinatal, hypoxic-ischemic brain injury. Hypoxia causes excessive production of pro-inflammatory cytokines, deprivation of growth factors, oxidative stress and extracellular matrix modifications. These trigger the excitotoxic cascade which eventually results in cell death. [13] All these mechanisms result in a primary defect in myelination, gliosis, and thalamic degeneration with secondary cortical and thalamic maldevelopment. [14]

Various studies have demonstrated that cellular therapy stimulates neurogenesis in the damaged brain, especially in children. Different types of cell, routes of administration have been studied to address the multifactorial pathophysiology of CP and to obtain the best possible clinical outcome. [15-22] Magnetically labelled mesenchymal stem cells were found to migrate to lesion sites and proliferate. [23] Human umbilical cord blood (hUCB) cells have also shown to reduce sensorimotor deficits after hypoxic ischemic brain injury in neonatal rats.[24] *Chen et al.* and *Luan et al.* reported the improvement in gross motor, fine motor, and cognition of the treatment group after the administration with neural stem like cells and neural progenitor cells respectively in CP subjects. [17,19] In our previous case studies on CP, we demonstrated

significant improvement in brain metabolism as shown by the PET-CT scan and correlating clinical improvements after cellular therapy. [25,26.] Following the cellular therapy, rigorous rehabilitation regime was given to the patient. It has been observed that exercise accelerates the recovery process by helping the mobilization of local stem cells, improving angiogenesis and release of cytokines and nerve growth factors after cellular therapy. [27]

The cumulative effect of two cellular therapies in the patient revealed cognitive and clinical improvement which were also noted on the outcome measures (GMFM, FIM). The correlating clinical improvements with functional benefits direct us to explore cellular therapy as a potential modality of treatment for CP. This study also suggests that a combination of cellular therapy and rehabilitation may lead to functional restoration which reduces disabilities in CP, thereby improving the quality of life of the patient.

Limitation:

This is a solitary case, and the results cannot be generalised. But looking at the multiple deficits observed prior to cellular therapy and the functional improvement post cellular therapy, the patient could serve as a self- control.

Conclusion:

This study implies that autologous bone marrow mononuclear cell transplantation in combination with rehabilitation is safe, feasible, and efficacious. It may help
to reduce the degree of impairment in diplegic dystonic CP and improve the quality of life. The symptomatic improvements and the correlating improvements in the objective scales are the supporting evidence. Larger studies are required in future.

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