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RESEARCH PAPER

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Multidisciplinary Approach of Cellular Therapy with Neurorehabilitation in a Case of Mixed Cerebral Palsy

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ABSTRACT

Cerebral palsy (CP) encompasses a group of non- progressive disorders of movement and posture causing activity limitation or disability. Presently, the treatment options are limited with primary focus being on rehabilitation of the patients. Cellular therapy is being considered as an alternative therapeutic strategy. Our patient is 11-year-old girl diagnosed as a case of mixed cerebral palsy with both spastic and dystonic components. She presented with complaints of poor sitting and walking balance, incoordination and faltering school grades. Autologous bone marrow derived mononuclear cells were administered intrathecally along with extensive neurorehabilitation.

On follow up at 1 week, 7 months and 12 months, patient showed significant signs of improvement in higher brain functions like attention, awareness and judgement. Muscle tone had shifted from hypertonic to normotonic. There was significant improvement in gait, posture, balance and movement as well as in her oromotor skills. Over 1 year, Gross motor function measure (GMFM) scale improved from 49.06% to 87.68%, Berg Balance Scale (BBS) improved from 50 to 54, Wee- Functional Independence Measure (Wee-FIM) scale increased from 78 to 100. No adverse events were noted after the procedure. Cellular transplantation along with neurorehabilitation has the potential to significantly improve the quality of lives of CP patients by enhancing their functional abilities through the properties of neuroprotection and neurorestoration. The symptomatic improvements and the correlating improvements in the objective scales are the supporting evidences. Larger controlled studies are required in future for mixed CP.

Keywords: Cellular transplantation, Dystonia, Spasticity, Cerebral Palsy, Stem cells, Neurorehabilitation.

INTRODUCTION

Cerebral palsy (CP) is a group of permanent motor and cognitive disorders caused due to injury to the developing brain which leads to impaired coordination, balance and posture. (Morris, 2007) The neurological insult can occur at any stage of gestation, during the process of birth and post-partum. (Suvanand et al, 1997) CP is characterised by abnormal muscle tone, reflexes, motor development and coordination, joint deformities and contractures. It is also compounded with problems in communication, cognition, behaviour, vision, learning difficulties, epilepsy. (Gowda et al, 2015) Current therapeutic treatment modalities are aimed at functional improvement but are unable to cure the disease pathology. (Verrotti et al, 2006; Keen et al, 2014) Cellular therapy showed to alter the underlying brain pathology in various neurological disorders. (Sharma et al, 2013; Sharma et al, 2015, Sharma et al, 2017) Hence we studied the effect of intrathecal administration of autologous bone marrow mononuclear cells (BMMNC's) in mixed CP.

MATERIALS AND METHODS

Case report

This patient was an 11-year-old girl diagnosed as spastic dystonic CP. She was born full term normal delivery with a birth weight of 2.4kg. At birth, the cry was delayed. She was diagnosed with neonatal jaundice and was kept in an incubator for 2 days. Symptoms started at the age of 6 months when parents noticed delay in her development milestones. There was history of seizures, the first episode at 9 years and the second at 11 years. Her chief complaints were imbalance and incoordination in movements. Patient was undergoing rehabilitation for the past 10 years but had reached a plateau phase.

On neurological examination, patient was hypertonic and hyperreflexic. She had poor fine motor control. She walked with equinovarus foot drop and internal rotation of hip with wide base of support. There was weakness of abdominals and hip extensors. She also suffered from dysarthria and poor oromotor skills. She was moderately dependent for activities of daily living. Her Functional Independence Measure (FIM) score was 78, Gross Motor Function Classification Scale (GMFCS) level was III, Gross Motor Function Measure (GMFM) was 49.06% and Berg Balance scale (BBS) score was 50/56. Magnetic Resonance Imaging (MRI) brain showed bilaterally symmetric T2 hyperintense signal abnormality involving the posterior putamen and thalami with the features consistent with hypoxic ischemic insult.

Electroencephalography (EEG) was suggestive of generalised epilepsy syndrome. Positron Emission Tomography-Computed Tomography (PET-CT) showed hypometabolism in bilateral cerebellar hemispheres, thalami and mesial temporal lobes.

Intervention

Selection of this patient for the treatment was based on the World Medical Association Revised Declaration of Helsinki. (World Medical Association, 2013) Ethical approval was obtained from the Institutional Committee for Stem Cell Research and Therapy (IC-SCRT). Informed consent for the procedure was obtained from the parents of the patient.

Preoperative fitness was assessed by serological and biochemical blood tests, chest X-ray, electrocardiogram, and 2-D echocardiography a week before cellular transplantation. 300 mcg of Granulocyte colony stimulating factor was injected subcutaneously 72 hours and 48 hours prior to the intervention to enhance mobilization of MNCs. 110 ml of bone marrow was aspirated from the right anterior superior iliac spine under sedation and collected in heparinized tubes. MNCs were separated by density gradient centrifugation. The viability of cells was checked using trypan blue and total number of cells injected were 9.6×10^7 with 96% viability. CD34+ cells were checked using fluorescence-activated cell sorting (FACS) and the count was 3.82%. Cells were injected intrathecally at the level between L4 and L5. Methyl prednisolone (600mg) in 500 ml of Isolyte P was administered intravenously to reduce the immediate inflammation. Cellular transplantation was supplemented with extensive rehabilitation which included physiotherapy, occupational therapy, speech therapy, aquatic therapy and psychological intervention. After 6 days, the patient was discharged and was given a detailed customized home program.

RESULTS

Immediately after the intervention, upper limb coordination improved. Patient could maintain balance at half kneeling position. Lower extremity spasticity reduced and movements were smooth with reduced toe walking. At 7 months follow up, she had better attention and concentration in her studies. Speech was laborious and unintelligible but was clearer than before. The weight bearing capacity of the upper and lower extremity improved. Drooling had decreased but tongue movement was still restricted. The reach outs in different positions were easier than before. Muscle tone in the upper and lower extremity had shifted from hypertonic to normotonic. BBS score increased from 50 to 54. Wee- FIM score increased from 78 to 89. GMFM score increased from 49.06% to 77.57%.

At 12 months follow up, higher cognitive functions such as attention, awareness, concentration, memory and judgement had improved further. Her speech, eye and hand coordination was better than before. Fine motor skills improved along with hand eye coordination. Improvements were noted in the voluntary control of the upper and lower limbs, sit to stand transitions and balance. Her circumductory gait improved with only presence of foot drop. Ability to focus in studies improved which reflected in her scholastic performance. Patient was now independent in all activities of daily living. Wee FIM improved from 89 to 100. GMFM score increased from 77.57% to 87.68%. GMFCS levels decreased from III to II.

DISCUSSION

CP has multifactorial representations in children. In this patient both the spastic and dystonic components were evident and the neuroimaging reports displayed clear signs of

hypoxic ischemic encephalopathy. Hypoxic ischemia in the perinatal period can lead to periventricular leukomalacia, myelination defects, gliosis, and thalamic degeneration (Folkerth, 2006; Pocock, 2007). Cellular therapy has been proved its efficacy in addressing the core neuropathology of brain in CP. (Sharma et al, 2015; Sharma et al 2012) Autologous BMMNCs has no risk of tumorigenicity and is not associated with any ethical issues. (Prasongchean et al, 2012) Intrathecal route of administration is minimally invasive and allows efficient delivery of cells to the site of injury. (Callera et al, 2007) BMMNCs induce neovascularisation and secrete neurotrophic factors such as vascular endothelial growth factor, nerve growth factor, brain derived nerve growth factor, and glial derived growth factor. (Tse et al, 2003) These molecules stimulate endogenous neural cells, promote the activation, differentiation and migration of oligodendrocyte precursor cells and suppress neuronal apoptosis. (Tran et al, 2015) The counteractive mechanisms such as angiogenesis and myelinogenesis, reverses the hypoxic pathologies, improves the neuronal connectivity and signal transduction. Cellular therapy was supplemented with extensive rehabilitation. Exercise has been shown to enhance cognitive function in CP patients by increasing processing speed, improving gait function and postural control (Maltais et al, 2016; Lee et al, 2008). It also helps in mobilisation and proliferation of injected cells. (Rehman et al, 2008) The combined effect of cellular therapy and neurorehabilitation resulted in improved motor functions, cognition, muscle tone, posture and gait supported by improved scores on objective scales. This is only a single case to establish the therapeutic effects of cell therapy. However, this patient can be considered as self-control as she had been on continuous rehabilitation for 10 years prior to cell therapy. This study implies that intrathecal administration of autologous BMMNCs along with neurorehabilitation is a safe and feasible treatment for patients with mixed CP. Larger controlled studies are warranted in future.

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