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Positron Emission Tomography-Computed Tomography Scan Captures the Effects of Cellular Therapy in a Case of Cerebral Palsy

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Abstract

Cerebral palsy is defined as motor impairment that limits activity, and is caused by non-progressive disruption during cerebral development in fetus or infant. The standard treatment is focused on rehabilitation and symptomatic management, which does not address the underlying brain damage. Recently cellular therapy has been seen as promising strategy to improve function of damaged areas of brain. Many mechanisms of action are postulated including cytokine release, angiogenesis, activation of satellite cells, decrease inflammation decrease neuronal apoptosis; and neuronal regeneration. We present a case of a two year old girl with spastic cerebral palsy, who was administered autologous bone marrow derived mononuclear cells intrathecally. Six months after the therapy she showed significant functional improvements along with correlating dramatic changes in Positron Emission Tomography-Computed Tomography scan. These changes provide objective evidence of functional restoration of affected areas of brain by cellular therapy.

Keywords: Cerebral palsy; Autologous; Bone marrow; Mononuclear cells; Positron emission tomography-computed tomography scan

Introduction

Cerebral Palsy (CP) is a term which describes a broad spectrum of non-progressive, motor disabilities resulting from damage to the brain at or around birth [1]. It affects at least 2 in 1000 children, leading to more than 1 million chronic patients under the age of 21 [2]. CP is characterized by muscle spasticity, involuntary movements, impaired mobility, seizures etc. The four major types are: spastic, ataxic, athetoid/dyskinetic and mixed. Currently, there is no cure available for cerebral palsy and mainstay treatment is symptomatic management and rehabilitation.

With the advent of cellular therapy, multiple new avenues for therapeutic strategies are viewed as available options.

Materials and Methods

Case report

A two year old girl with spastic cerebral palsy had birth history of premature delivery at six and half months, following which she was on ventilator for a day and then in the incubator for 25 days. She did not have any seizures. Gradually, the parents noticed delay in motor development and speech. Even at 2 yrs of age she had poor neck control, she could roll but could not sit without support and had bisyllabic speech only. Neurologically, she was hypertonic and hyperreflexic. Spasticity was present in all 4 limbs. Her sensations were normal but had no voluntary control in any of the limb muscles. Quadriparesis present. She had normal vision and hearing. The PET CT scan of brain showed mild degree of cerebral atrophy, with calcific foci in bilateral basal ganglia and multiple calcific foci adjacent to the gliotic areas, in the right frontal region. These gliotic areas were arranged linearly and extended upto the right supero-lateral aspect of the body of the right lateral ventricle. There was also an evidence of corpus callosal agenesis. There was reduced FDG (Fludeoxyglucose-18F) uptake in the left medial temporal lobe and the right basal ganglia. Elsewhere, the FDG uptake appears to be preserved or supra normal. No other focus of reduced FDG uptake observed. The MRI of Brain showed mild dilated bilateral occipital horns of lateral ventricles with irregular outlines. Small gliotic areas were noted in both high parietal regions, prominent on right side with dilated lateral ventricles and sulci (Figure 1).

She underwent intrathecal autologous bone marrow derived mononuclear cell transplantation as a neuroregenerative treatment option in concert with neurorehabilitation. The protocol design was based on the inclusion criterion as per the World Medical Associations Helsinki declaration. The protocol had been reviewed and approved by the Institutional Committee for Stem Cell Research and Therapy (ICSCRT). A duly filled informed consent was obtained from the parents prior to the therapy. G-CSF (150 mcg) injections were administrated subcutaneously, 48 hours and 24 hours prior to the bone marrow aspiration, to stimulate CD34+ cells and increase their survival and multiplication.. Bone marrow (100 ml) was aspirated from the iliac bone under sedation using a standard procedure. The mononuclear

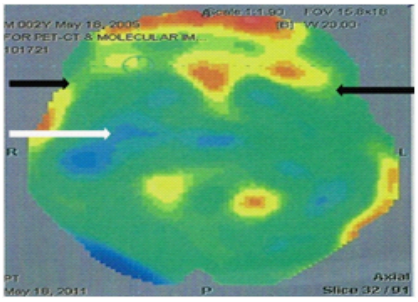

Figure 1: PET-CT scan before the stem cell therapy: Black arrow signifies reduced FDG uptake in the left mesial temporal as compared to the right side. The white arrow signifies reduced FDG uptake in the right basal ganglia seen as blue areas, as compared to the left side which are seen as green areas.

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cells (MNCs) were separated using density gradient separation and approximately 12×10^7 MNCs were immediately injected intrathecally in L4-L5 space using an epidural set and catheter. Following the transplantation, she underwent intensive neurorehabilitation which included physiotherapy, occupational therapy and speech therapy, as a part of the treatment program. We focused on neurological rehabilitation due to increasing evidence of its role in enhancing neuroplasticity. This approach aims to improve development and function by capitalizing on the innate capacity of the brain to change and adapt.

Results

After mononuclear cell transplantation, her follow up was done at regular intervals and no side-effects were observed. At 3 months her neck holding was better, sitting balance improved and she could sit without support. She showed progressive significant improvements in the span of six months. After six months, the spasticity of all limbs had reduced. She could balance herself while standing erect. Her head control improved and she was more co-operative than before. She could now speak sentences. On repeating the PET scan of brain, after a period of six months and comparing it with the earlier scan, it was noted that the morphological abnormality was more or less stable. The relative reduction of FDG uptake in the left medial temporal lobe and right basal ganglia had appeared to be resolved and they showed increased FDG uptake (Figure 2). Increase in FDG uptake was also recorded in the right medial temporal structures. The frontal, temporal, parietal and occipital lobes also showed increased uptake of FDG. (Figure 3)

Discussion

Cerebral palsy is one of the most severe childhood disabilities which are a consequence of lesion in the developing brain. This disorder does not necessarily reduce the lifespan of the patient but is an important social and economic problem [3]. This condition presents a considerable diagnostic and therapeutic challenge which differs according to the degree of involvement ranging from mild with minimal disability to severe, associated with several co-occurring conditions. The families have to face great difficulties in handling these children. Since there are very limited treatment options for cerebral palsy, research is focused on finding therapy aiming to manage or diminish the neurological problems associated with cerebral palsy.

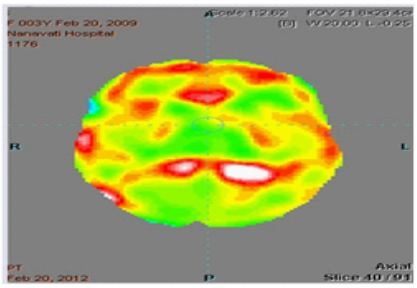

Figure 2: Relative hypometabolism of the left mesial temporal and right basal ganglia in the previous scan has resolved and these areas now show same metabolic activity as compared to the rest of the brain which is normal or supra normal post stem cell therapy.

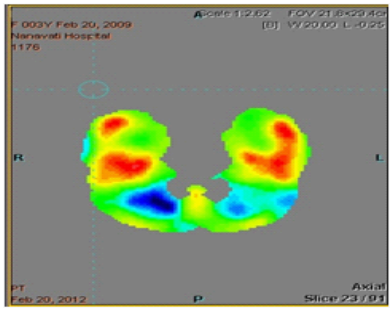

Figure 3: This focused slice of mesial temporal lobes show equal FDG uptake on both sides post stem cell therapy.

In our case, we have used autologous bone marrow derived mononuclear cells, as they are easily obtained and do not hold any risk of graft-versus-host-disease or tumors unlike allogenic and embryonic cell therapy. Furthermore, the mononuclear cell fraction have found to contain several types of bone marrow cells including hematopoietic stem cells, mesenchymal cells, tissue specific progenitor cells and stromal cells, which can produce large amounts of cytokines and trophic factors that promote angiogenesis, neuroprotection and neuroregeneration. The main objective of this therapy is to repopulate the damaged tissue with functional cells, with the final goal that these cells will integrate with the remaining functional native cells and contribute to the recuperation of the lost function. It has been found that after introducing hematopoietic cells in the subarachnoid space of the spinal cord, these cells may be transported through the cerebrospinal fluid and can be delivered more efficiently to the injured area, when compared to the intravenous route. These cells have a intrinsic tendency to home onto damaged tissue sites [4]. Recent studies have also shown that transplantation of different types of stem cells, including neural stem cells, Mesenchymal Stem Cells (MSCs), human umbilical cord blood cells, etc can have beneficial effects on ischemic brain injury [5,6]. Transplantation of MSCs in the injured brain has shown to improve endogenous repair processes by releasing growth and differentiation factors further enhancing the local trophic milieu [7]. In animal models, MSCs have demonstrated decrease in gray and white matter loss and also differentiate into neurons and oligodendrocytes. Furthermore, repairing the injured brain and improving neurological functions [8,9]. Studies showed that hBMSC transplantation in ischemic tissues improved the neurological functions and induced an increase in IL-10 expression, decrease in neuronal apoptosis and astroglial activity in the peri-ischemic area and increased the number of proliferating cells in the sub ventricular zone [10]

To find objective evidence regarding the effect of mononuclear cell transplantation, we repeated a PET CT scan and compared it to the previous one. PET imaging was done as it provides tomographic, quantitative, volumetric and functional information, allowing one to better localize and quantify the detected signal within the subject under study. The function of medial temporal lobes involves episodic/declarative memory. Hippocampi that are situated deep inside the medial temporal lobes are essential for memory function, especially the transference from short to long term memory and control of spatial memory and behavior. The temporal lobe is important for the processing of semantics in speech. The basal ganglia are associated with voluntary motor control and procedural learning relating to routine behaviors. In our case, improved function in these areas are recorded as resolution of reduced FDG uptake in the left medial temporal lobe and right basal ganglia and an increased FDG uptake in the right medial temporal structures, the frontal, temporal, parietal and occipital lobes. These findings correlate and explain the clinical improvements in the patient.

We hereby demonstrate objective evidence, in a cerebral palsy

case, in the form of increased FDG uptake, indicating improved brain function after bone marrow derived mononuclear cell intrathecal transplantation. This is amongst the very first verification data for effects of cellular therapy in cerebral palsy. These findings also correlated with the functional improvements observed by the parents, the therapists and physician.

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