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IMPROVEMENTS IN A CASE OF SENSORY ATAXIA THROUGH CELL TRANSPLANTATION

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Abstract

Sensory ataxia is a type of ataxia that is caused by the loss of sensory input to control the movement of the body. It is both a sign and a symptom. There have been no curative modalities for treating sensory ataxia. Cellular therapy has gained significant attention as a therapeutic option for various neurological disorders. We present a case of an 18-year-old female diagnosed with sensory ataxia who was intrathecally administered with autologous bone marrow mononuclear cells (BMMNCs) along with neurorehabilitation. Twelve months after cellular therapy, signs such as ataxia, postural tremors, intention tremors and dysmetria improved. Functional Independence Measure score improved from 106 to 107. Berg Balance Scale improved from 18 to 34. Brief Ataxia Rating Scale improved from 7 to 5. Modified International Cooperative Ataxia Rating Scale improved 26 to 24. Comparison of the Positron Emission Tomography Computed-Tomography (PET CT) image before and 12 months after cellular therapy showed improved metabolism in bilateral sensory motor cortex, thalamus and cerebellum. These PET findings correlated with symptomatic improvements. The clinical improvements along with PET CT findings suggest that cellular therapy is a beneficial therapeutic modality for sensory ataxia. No major adverse effects were seen. Further clinical studies should be conducted to understand the efficacy of cellular therapy in sensory ataxia.

Keywords: Sensory ataxia; Cellular therapy; Autologous Bone Marrow Mononuclear Cells; Positron Emission Tomography Computed Tomography.

Introduction:

Ataxia refers to incoordination of movements caused due to damage to several different nervous system structures. It may result from cerebellar, vestibular or sensory (proprioceptive) dysfunction. Sensory ataxias involve disorders that affect the sensory fibers or their connections with the neuraxis causing loss of proprioception [1]. Clinically, Sensory ataxia is often misdiagnosed as cerebellar ataxia. Sensory ataxia is distinguishable from cerebellar ataxia as

it causes symptoms to worsen when movements are made with the eyes closed. [2] Demyelination and axonal damage may occur due to various reasons such as infection, auto-immune, metabolic, toxic, vascular diseases. [3] The progressive loss of myelin may lead to chronic demyelination, impairing the normal axonal conduction velocity and ultimately causing sensory ataxia. [4] There is yet no cure available for sensory ataxia. Pharmacotherapies are unsatisfactory as they lack desired effectiveness [5]. Rehabilitative therapies are widely available but have their own limitation of recovery [6]. Newer treatments to cure ataxia should therefore focus on addressing the core neuropathology of the disorder.

Cellular therapy has gained significant attention as a therapeutic option for various neurological disorders [7,8,9]. Stem cells are characterized by their ability to proliferate and differentiate into specialized cells [10]. Preclinical studies using different stem cells suggests that cellular therapy may be a beneficial therapeutic option for ataxia [11,12]. To study the effect of cellular transplantation in humans, we intrathecally administered autologous bone marrow mononuclear cells (BMMNCs) in an 18-year-old girl with sensory ataxia. She was followed up regularly and PET CT scan brain was used to monitor the metabolic changes occurring in the brain post intervention.

Case Representation:

We present a case of an 18-year-old female diagnosed with sensory ataxia since 3 years. She was born out of a consanguineous marriage and had achieved all the age appropriate milestones. She was diagnosed to have only one kidney. At the age of 10 years, she suffered from dengue and was on heavy antibiotics. Ever since then, imbalance while walking was experienced which increased the incidence of falls. With time, symptoms such as postural swaying, tremors, numbness in feet were also experienced. Symptoms had been slowly progressive. As she had a family history of peripheral neuropathy, she was taken to the neurophysician where Electromyography (EMG)/Nerve conduction study (NCS) were done. NCS showed absent sensory nerve action potential in all four limbs while motor nerve conduction study was normal. This was suggestive of severe sensory neuropathy and ganglionopathy. Somatosensory Evoked Potential (SSEP) studies showed absent posterior tibial and median latencies. Magnetic Resonance Imaging (MRI) was normal. All the other tests were found to be normal. At the age of 15 years, genetic testing showed no expansion evident for SCA 1, SCA 2, SCA 3, SCA 6 and SCA 7 trinucleotide repeat expansion. She was diagnosed to have sensory ataxia based on clinical presentation and EMG/NCS. Thereafter, she was on alternative medical treatment for 2 years but had no improvement. On pre-intervention clinical examination, all her reflexes were diminished. She was normotonic with distal hypotonia and was ambulatory with ataxic gait. She could not grasp any object due to tremors. Sitting balance was good. Standing and walking balance was fair. Voluntary control of the limbs and trunk was good. Motor signs of incoordination were present. Speech was affected as the fluency and pitch was decreased. Signs of impairment like ataxia, intention tremors, nystagmus, dysmetria, Rhomberg's sign, rebound phenomenon, postural tremors and pendular reflexes were noted. Upper limb fine motor activities and gross motor activities were affected. Concentration was poor.

Functionally, she was partially independent for all her activities of daily living (ADLs) but required assistance for bed mobility and transfer. Functional Independence Measure (FIM) score was 106 and Modified International Co-operative Ataxia Rating Scale (MICARS) score was 26. The Brief Rating Scale (BARS)was 7 and Berg Balance Scale (BBS)was 18.

PET CT scan showed mild hypo metabolism in the bilateral sensory motor cortex, thalamus and cerebellum. MRI brain with DTI was normal. Screening of the whole spine revealed no gross focal abnormality. EEG report was suggestive of generalized epilepsy syndrome.

Materials and method:

Patient was selected based on the World Medical Association Helsinki Declaration for Ethical Principles for medical research involving human subjects [13]. The Institutional Committee for Stem Cell Research and Therapy (IC-SCRT), reviewed and approved the protocol of the study. The intervention was explained to the patient and family in detail along with possible adverse events and written informed consent was obtained.

Granulocyte colony stimulating factor (GCSF) was administered 72 hours and 24 hours before the transplantation of BMMNCs. 110 ml of bone marrow was aspirated from the anterior superior iliac bone under local anesthesia, using bone marrow aspiration needle into a heparinized tube. Bone Marrow Mononuclear cells (BMMNCs)were separated using density gradient method. The cell viability was calculated using trypan blue dye which was confirmed by TALI (Invitrogen) using propidium iodide. CD34+ count was 7.18% using Fluorescence-activated cell sorting (FACS) analysis. 1.00×10^8 cells with 98% viability were injected intrathecally into the space between 4^{th} and 5^{th} lumbar vertebra via lumbar puncture using a spinal needle. Methyl prednisolone 1 gm in 500 ml Isolyte P was given intravenously simultaneously during the injection to reduce immediate inflammation post transplantation and help in survival of stem cells [14]. As a part of this protocol, the patient was given intensive neurorehabilitation therapy followed by cellular therapy which included physiotherapy, occupational therapy, speech therapy and psychological counselling. Physiotherapy was provided to improve muscle strength, balance, coordination and gait pattern and occupational therapy was done to improve the bed mobility, fine motor activities, gross motor activities involuntary movements and mobility. FIM, BBS, MICARS, BARS were the outcome measures used to measure changes at the functional level. Brain PET CT scan was performed before and 12 months after the intervention.

Results:

The patient was followed up regularly. 5 months after intervention, parents observed that ambulation and walking balance of the patient was improved. Frequency of falls had reduced. Ankle twisting had reduced. Posture while sitting and standing had improved as she could now sit and stand erectly with minimal stooped posture. Standing and sitting static as well as dynamic balance also improved. Tremors had reduced along with improvements in concentration.

12 months after intervention, upper limb fine motor activities and gross motor activities were improved as she was able to put pins in her dress and was able to hold small things. Ataxic gait had reduced and she could walk independently. Sitting and standing balance further improved due to which falls had completely stopped. Bed mobility improved as she could do rolling and sit to stand transitions with less efforts and at a faster speed. Her concentration was better than before. Improvements were seen in signs such as ataxia, postural tremors, intention tremors, dysmetria. FIM score improved from 106 to 107 and BARS from 7 to 5. BBS score had increased from 18 to 34. MICARS improved from 26 to 24. Comparison of the PET images before and 12 months after cellular therapy showed improved metabolism in bilateral sensory motor cortex, thalamus and cerebellum (Figure 1 and 2).

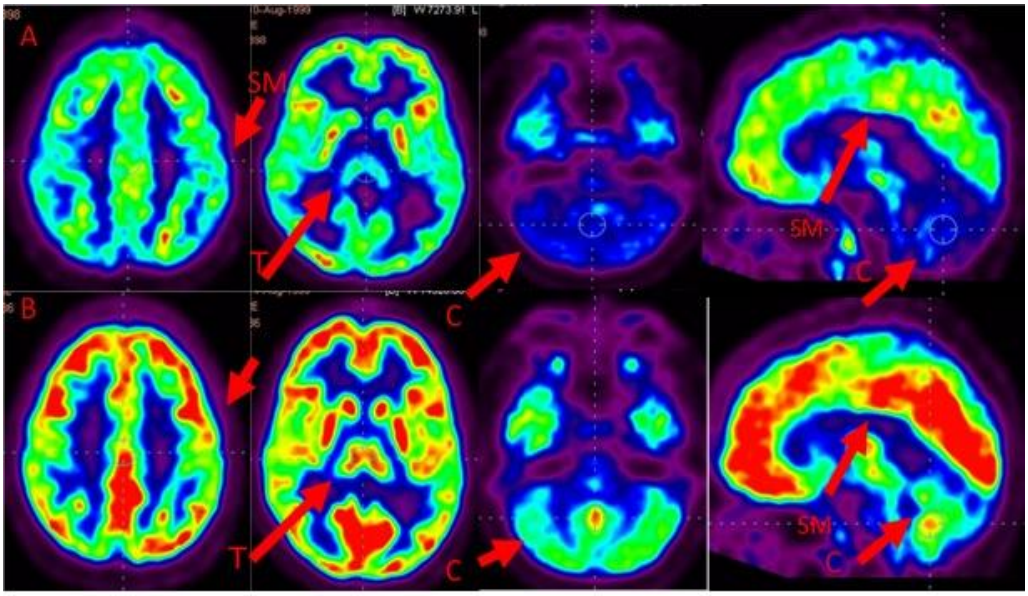

Figure 1: Representative Transaxial section of the sensory ataxia. (A) FDG PET/CT image before cellular therapy metabolism in bilateral sensory motor cortex (SM), thalamus (T) and cerebellum(C)
(B) FDG PET/CT image of six-months after cellular therapy showed improved metabolism in bilateral sensory motor cortex (SM), thalamus (T) and cerebellum (C).

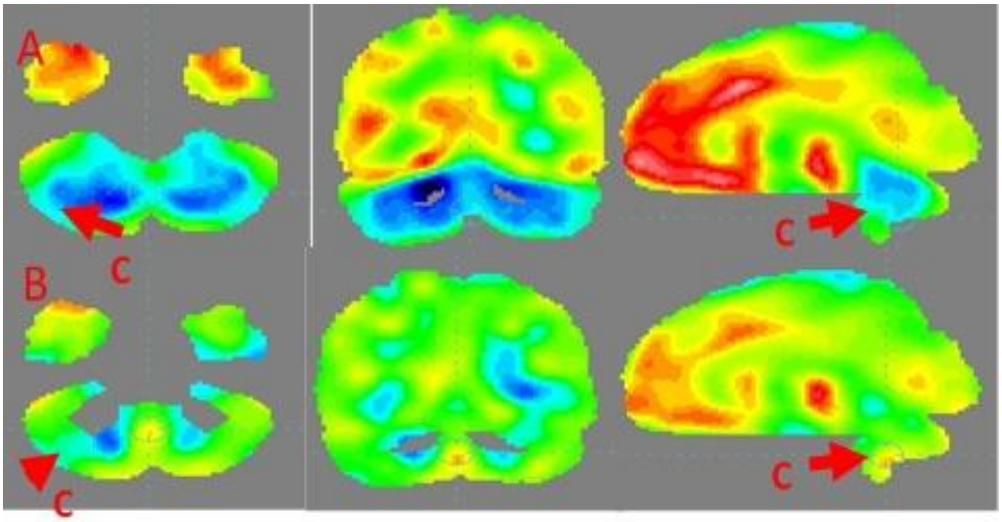

Figure 2: FDG-PET/CT image of a sensory ataxia patient showing reduction of hypometabolism in bilateral cerebellum (C). The images were normalized to the SCENIUM normal healthy brain volumetric template. (A) PET image before cellular therapy showed reduced metabolism in bilateral cerebellum (Blue – severe damage, yellow-green - normal) (B) PET image of six months after cellular therapy showed improved metabolism in bilateral cerebellum

Discussion:

Sensory ataxia is both a sign and a symptom. It is caused due to loss of sensory input to control the movement of body. Sensory ataxia may result due to various causes such as infection, auto-immune, metabolic, toxic, vascular and hereditary diseases. Until now, there have been no curative modalities for treating sensory ataxia [15]. Autologous bone marrow mononuclear cell transplantation (BMMNCs) has emerged as a therapeutic approach for various neurodegenerative diseases [8-9].

An infection triggers the basic cellular and humoral immune response in which the T Cells get activated against the antigen. These

activated T lymphocytes can cross the blood brain barrier and once within the peripheral nervous system these cells activate macrophages that enhance phagocytic activity, and the release of toxic mediators, including nitric oxide, reactive oxygen intermediates, matrix metalloproteinases, and proinflammatory cytokines. The immune-mediated attack by autoantibodies and/or T-cells to central nervous system myelin structure may result into demyelination and axonal damage. [16-19]The loss of myelin ultimately causes neuronal disruption, as the oligodendrocytes are crucial for both the metabolic support of the axons as well as the correct transmission of the nerve impulse.[20] Studies have demonstrated that bone marrow (BM) cells can differentiate into a myelinating phenotype in vivo and repair demyelinated CNS.[21] One study revealed that extensive remyelination had taken place after the transplantation of BM cells into the demyelinated rat spinal cord.[22] BMMNCs have a potential to differentiate into oligodendrocytes and astroglial cells which carry out the repair process by remyelinating axons.[23]

Bone marrow mononuclear cells contain hematopoietic stem cells, tissue-specific progenitor cells, mesenchymal stem cell (MSC) and specialized blood cells i.e. red blood cells, white blood cells in different stages of development [24]. Intravenous administration of mesenchymal stem cells in ataxic mice has shown that they can rescue the degenerating cells with the help of neurotropic factors such as NGF, BDNF and NT-3 by integrating into the central nervous system [25]. Another study in the rat model demonstrated that intravenous administration of human umbilical cord blood stem cells (HuUCBMCs) reduced neuronal loss and upregulated the expression of proteins critical for cell survival [26]. Clinical studies with BMMNCs showed efficacy in delaying the progression of cerebellar ataxia supported by improvements in various outcome measures such as the Berg Balance Scale (BBS), activity of daily living scale (ADL) and International Cooperative Ataxia Rating Scale (ICARS) scores [9].

The objective of our study was to evaluate the safety, feasibility, and efficacy of autologous BMMNCs in the treatment of patient with sensory ataxia. Autologous BMMNCs were used as they are easily obtainable and safe since they are derived from the same patient. They are able to escape alloantigen recognition because of their low immunogenicity and hence there is no need for immunosuppressive regimes. [27] There are no ethical issues and not likely to undergo malignant changes and genetic abnormalities [28]. The intrathecal route of administration was preferred as the cells are mobilized directly to site of injury through CSF. It is easy, relatively less invasive and has minimal risk. [8] G-CSF is administered before transplantation as it helps in the stimulation of the CD34+ cells and survival as well as multiplication of the stem cells [29]. Rehabilitation plays an important role in the recovery of the patient after cellular transplantation as it promotes neurogenesis, oligodendrogenesis and adaptive myelination. [30] Ilg and colleagues reported that physical training helps in better motor performance and reduction of ataxic symptoms. [31]

BMMNCs secrete various neurotropic and neuro-modulatory molecules like connective tissue growth factor, interleukins, vascular endothelial growth factor (VEGF), glial cell-derived neurotrophic factor (GDNF), insulin-like growth factor 1 (IGF-I) and basic fibroblast growth factor (bFGF) which may improve the survival and growth of the affected neural cells [32,33]. These factors act like catalysts for the stem cell-driven process by increasing angiogenesis, decreasing inflammation, preventing apoptosis and remodeling of extracellular matrix [34]. The neuroprotective and neuro-modulatory effects exerted by the BMMNCs repair the damaged neuronal tissue thereby improving synaptic connectivity. [35] These paracrine mechanisms could have attributed to symptomatic improvements such as ataxia, postural tremors, intention tremors, dysmetria seen in the patient,

12 months after cellular therapy. Improvements were also quantified using objective scales. FIM was used to assess a patient's level of disability which was improved from 106 to 107. In this case the change was not significant as she was already high functioning. BBS had improved from 18 to 34 which showed improvement in balance. BARS and MICARS were used for measuring clinical severity of disease. BARS have improved from 7 to 5. MICARS had improved 26 to 24.

Afferent fibers that mediate joint position sense and kinaesthesia enter dorsal horn of spinal cord. Many fibers go across the midline while others go ipsilaterally to enter the medulla, pons and midbrain. Many of these neurons enter at the thalamus. Others enter the reticular activating system or the cerebellum. Thalamocortical projections then ascend from thalamus to the primary somatosensory areas of the cerebral cortex. [36,37] Impairment in this circuitry will lead to symptoms of sensory ataxia. In this study, Brain PET CT scan showed decreased functioning in Thalamus, Cerebellum, and sensory motor areas. Brain PET CT scan was used to monitor the changes occurring after cellular therapy. It measures the change in metabolism thus demonstrating the effect of transplantation at a cellular level. [38] Comparison of the PET image following cellular therapy showed improved metabolism in bilateral sensory motor cortex, thalamus and cerebellum. Increased metabolism correlates with the improvements in the functions as shown in the Table 1.

Table 1: Areas of brain showing improved metabolism and their clinical correlation.

Areas of the brain showing increased metabolism	**Functions improved**
Sensory motor cortex	Fine and gross motor activities, Balance, Concentration
Cerebellum	Co-ordination of movements, Improved sitting and standing posture, improved gait, Tremors
Thalamus	Postural tremors, Co-ordination of activities, sensations

Limitation:

The limitation of this study is that it is a single case study and larger clinical studies are required to generalize the results for the larger population.

Conclusion:

Ataxia being a progressive disorder, stem cell in combination with neurorehabilitation has the potential to halt disease progression at least for 1 year. The clinical improvements along with PET CT findings suggest that this treatment strategy is safe, feasible and effective for patients suffering from sensory ataxia. Improvements in the PET CT scan points toward the ability of cellular therapy to enhance the brain function in affected areas. This could be attributed to neuroprotective and neuromodulatory. Further clinical trials should be conducted to understand the efficacy of the cell transplantation in sensory ataxia.

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