Open Access Journal

Indian Journal of Medical Research and Pharmaceutical Sciences

August 2014; 1(3) ISSN: 2349 – 5340

CELLULAR TRANSPLANTATION MAY MODULATE DISEASE PROGRESSION IN SPINO-CEREBELLAR ATAXIA – A CASE REPORT

Alok Sharma[1], Hemangi Sane[2], **Amruta Paranjape[3*],** Nandini gokulchandran[4], Hema Biju[5], Myola D'sa[6], Prerna Badhe[7]

[1] Department of medical services and clinical research, NeuroGen Brain and Spine Institute, Navi Mumbai, Maharashtra, India
[2] Department of research and development, NeuroGen Brain and Spine Institute, Navi Mumbai, Maharashtra, India
[3 *] Department of research and development, NeuroGen Brain and Spine Institute, Navi Mumbai, Maharashtra, India
[4] Department of medical services and clinical research, NeuroGen Brain and Spine Institute, Navi Mumbai, Maharashtra, India
[5] Department of neurorehabilitation, NeuroGen Brain and Spine Institute, Navi Mumbai, Maharashtra, India
[6] Department of neurorehabilitation, NeuroGen Brain and Spine Institute, Navi Mumbai, Maharashtra, India
[7] Department of medical services and clinical research, NeuroGen Brain and Spine Institute, Navi Mumbai, Maharashtra, India
Email: amruta.paranjape@live.co.uk, publications@neurogen.in

Keywords:
Spino-cerebellar ataxia, autologous bone marrow mononuclear cells, stem cells.

Abstract

Spino-Cerebellar Ataxia (SCA) encompasses a group of progressive disorders characterized by Neurodegeneration, specifically in the region of cerebellum, brainstem and spinal cord. The current therapies for SCA have limited potential for restoration of neuronal damage. Regenerative medicine may offer a more viable treatment option for the treatment of SCA as supported by some preclinical and clinical studies. We treated a 33 year old female with SCA with severe impairment of dynamic balance, coordination, speech, gross and fine motor control. Ambulation was dependent; requiring support from two people with an ataxic gait. Functionally she scored 86 on Functional independence measure and 62 on Ataxia rating scale. She underwent autologous BMMNCs intrathecal transplantation followed by standard rehabilitation. Six months after the transplantation there was a significant improvement in handwriting, fine motor activities, standing dynamic balance and intelligibility of speech. There was an improvement in the cerebellar signs and symptoms and outcome measures like Modified International co-operative Ataxia rating scale. SCAs lead to impaired cerebellar function secondary to the autoimmune degeneration of cerebellar neurons and impaired cerebellar perfusion. BMMNCs through various paracrine mechanisms promote neurotrophic growth factors secretion, angiogenesis and modulate immune responses. We postulate that the clinical benefits and altered progression of the disease observed in this patient may be attributed to improved cerebellar function due to enhanced perfusion and altered autoimmune responses. Singularly this case report presents the preliminary findings and suggests the need for further research to explore the potential of cellular therapy to control the progression of SCA.

Introduction

Spino-Cerebellar Ataxia (SCA) connotes a group of progressive degenerative disorders. It is a heterogenous group of inherited and sporadic disorders. Hereditary disorders have been studied to identify the chromosomal abnormalities and affected gene loci. Most of the subtypes are attributed to CAG Trinucleotide repeat expansions that encode for Polyglutamine repeats leading to formation of abnormal protein aggregates causing loss of neuronal function [1]. These are the changes at the cellular level. Structurally most prominent characteristics are cerebellum, brainstem and the spinal cord atrophy [2]. Electrophysiologically it shows neuropathic changes, slower nerve conduction velocities and abnormal motor and visual evoked potentials. The diagnosis is based on clinical features and confirmed using MRI [2].

The management of the SCA is predominantly symptomatic and the current therapies bring about limited neuronal repair [2,3]. The existing treatment strategies aim at symptomatic relief. The newer treatment strategies like gene silencing (using RNA interference and antisense oligonucleotide), Rapamycin (upregulate autophagy), Histone Deacetylase inhibitors, Congo red and Cystamine (mutant protein clearance) are being studied. These therapies have not yet been tested in humans and are still in pre clinical stages [4]. In recent years autologous bone marrow derived mononuclear cells (BMMNCs) have been Extensively studied and shown to be safe for the treatment of various diseases [5,6]. Preclinical animal studies have shown cellular transplantation may offer a more viable treatment option for SCA [7,8].

Case report

A 33 year old female with a diagnosis of SCA and strong family history of ataxia visited our center. She reported to have developed the symptoms at the age of 18 years of age. The initial difficulty experienced was difficulty of grasping objects due to intentional tremors. She also suffered from loss of balance while running and jumping. Symptoms progressed to difficulty in climbing up stairs and easy fatigability. Progression of the disease further lead to frequent falls while walking, difficulty in various fine and gross motor activities. As time progressed she developed slurring of speech and urinary incontinence. The symptoms were progressive despite standard treatment and hence she chose to undergo autologous BMMNCs transplantation.

On pre-intervention clinical examination muscle tone of both the lower extremities was increased to grade 2 on modified ashworth scale (MAS). Motor signs of inco-ordination were present. Speed and accuracy of performing gross and fine motor activities had significantly reduced. Signs of cerebellar impairment like intention tremors, dysdiadokinesis, nystagmus, truncal ataxia and pendular reflexes were noted. The sitting and standing static as well as dynamic balance was poor. Gait was ataxic and assistance of two people was required. Speech was slurred and speech intelligibility score was 3.

Functionally, she was independent in all self care activities with reduced speed of performing the activities. For transfers and ambulation she required assistance. Functional independence measure (FIM) score was 86 and Modified International co-operative Ataxia rating scale (MICARS) score was 62.

Magnetic resonance imaging (MRI) scan showed cerebellar atrophy. EMG study was suggestive of a lesion affecting the posterior column conduction at the higher cervical cord level. PET CT scan showed reduction of FDG uptake in both cerebellar hemispheres..

Methods and materials

She was treated with autologous BMMNCs cell transplantation and rigorous standard rehabilitation. This clinical decision was based on World Health Organization Revised Helsinki Declaration [9]. The protocol had been reviewed and approved by the Institutional Committee for Stem Cell Research and Therapy (ICSCRT) and was in accordance with Indian Council for Medical Research (ICMR) guidelines.

The patient was informed about the procedure and a duly filled informed consent was obtained from her and her family. Granulocyte colony-stimulating factor (G-CSF) (300 µg) injections were administered subcutaneously, 48 hours and 24 hours before the therapy to enhance mobilization [5,6]. On the day of transplantation bone marrow (100 ml) was aspirated from the iliac bone under local anesthesia. Density gradient separation was used to isolate the MNCs and 33 x 10^6 MNCs were injected intrathecally in the space between fourth and fifth lumbar vertebra. Fluorescence activated cell sorting analysis was used to calculate the cell viability. Cell viability was 98%. Methyl prednisolone, 750 mg in 500 ml ringer lactate solution was given intravenously simultaneously.

Following the transplantation, she underwent intensive neuro-rehabilitation, which included physiotherapy, occupational therapy and speech therapy as a part of the treatment program. Patient was observed post-transplantaiton for four days in the hospital to monitor any immediate adverse events.
Patient was followed up at 3 and 8 months after the therapy.

Results

During the first week after transplantation the frequency of tremors had reduced and ataxia while walking had reduced. At 3 months sitting balance had improved significantly and speech was clearer. After 8 months, motor co-ordination and fine motor activities showed improvement which was reflected as improved handwriting, ability to bead a thread faster. Frequency of intentional tremors had further reduced. Grasping of objects was better; components of reaching out, opening of hand and grasping the object had improved. Truncal ataxia and neck titubation had reduced significantly. Standing balance and postural control had improved. Speech was clearer than before. Speech intelligibility score had improved from 3 to 2. The FIM score was maintained at 86 and the MICARS score reduced from 62 to 58. The score was better in the components of drawing Archimedes spiral, Finger nose test, Quality of sitting position and Body sway with feet together. No immediate or long term adverse events were noted during the 8 months after cellular transplantation.

Discussion

Ataxia is a group of progressive neurological disorders, the rate of progression and prognosis varies greatly within this group. It is caused by mutation of the Trinucleotide CAG which results in repeat coding and abnormal translation into larger polyglutamine complexes in the mutant protein [1]. These mutant proteins form macro and micro inclusion bodies within the cells. The bodies are believed to be toxic, proteolytic and resistant to protein clearance. These abnormal proteins lead to altered interactions and binding with other proteins, hindering many of the cellular processes including autophagy, the salvage mechanism for the intracellular components. The Polyglutamine proteins are also believed to play an important role in the transcription of neuronal proteins and the mutation of these proteins leads to abnormal neuronal growth and degeneration. Functional abnormalities of the mitochondria and increased apoptosis are also proposed pathogenic mechanisms [3]. The pathogenesis of SCA is extremely complex and has still not been understood completely. Developing an effective management strategy therefore is a challenging for medicine.
Cellular therapies have opened new avenues for the treatment of SCA. Adult BMMNCs have been successfully transplanted in other neurological disorders with no major adverse effects [5,6,7]. Neurogenic potential of BMMNCs and functional potential of the regenerated neural cells is currently being tested in various clinical trials [10]. The pathology of SCA is believed to be due to autoimmunity towards the polyglutamine complexes formed by the mutant gene. MNCs have shown immunomodulatory effects [11,5,6]. Cellular transplantation has also demonstrated anti-inflammatory effects [11,5,6]. Cvetanovic et al, 2011 through preclinical experiments suggested that, reduction of Vascular Endothelial Growth Factor (VEGF) levels observed in SCA contribute to the SCA pathology. They also observed reduced density and shorter lengths of cerebellar blood vessels. VEGF is not only an angiogenetic but also a neurotrophic factor and reduced levels VEGF leads to stunted growth and limited repair of cerebellar neurons in SCAs [12]. BMMNC fractions on artificial growth media have been found to secret VEGF along with various other growth factors and cytokines [12]. These factors have been shown to give rise to various paracrine effects resulting in neoangiogenesis which in turn enhances tissue perfusion [13]. The various mechanisms along with paracrine effects of cellular transplantation may help alleviate the disease pathology.
Along with symptomatic relief the aim was to control the disease progression. We postulate that the disease progression can only be altered if the microcellular processes causing neural damage can be altered or modulated. Therefore we attempted to target these using the paracrine effects of cellular therapy. The effects of cellular therapy are thought to be augmented by rehabilitation [14]. The paracrine effects in combination with the rigorous rehabilitation therapies may have altered the microcellular environment simulating body's own repair mechanisms. We theorize that the altered cellular environment may have led to improved cerebellar function, clinically exhibited as reduced intensity of the cerebellar signs and functional improvement seen in this patient.
The limitation of this case report is absence of objective evidence using advanced neuroimaging techniques, which should be incorporated in future research. Singularly this case report presents preliminary findings. It suggests the need to further explore the potential of cellular therapy to control the progression of SCA.

Reference

1. Globas C, du Montcel ST, Baliko L, Boesch S, Depondt C, DiDonato S, Durr A, Filla A, Klockgether T, Mariotti C, Melegh B, Rakowicz M, Ribai P, Rola R, Schmitz-Hubsch T, Szymanski S, Timmann D, Van de Warrenburg BP, Bauer P, Schols L ,"Early symptoms in spinocerebellar ataxia type 1, 2, 3, and 6" in MOVEMENT DISORDERS 2008 NOV 15;23(15):2232-8.
2. Jung BC, Choi SI, Du AX, Cuzzocreo JL, Ying HS, Landman BA, Perlman SL, Baloh RW, Zee DS, Toga AW, Prince JL, Ying SH ,"MRI shows a region-specific pattern of atrophy in spinocerebellar ataxia type 2" in CEREBELLUM 2012 MAR;11(1):272-9.
3. Matilla-Dueñas A, Ashizawa T, Brice A, Magri S, McFarland KN, Pandolfo M, Pulst SM, Riess O, Rubinsztein DC, Schmidt J, Schmidt T, Scoles DR, Stevanin G, Taroni F, Underwood BR, Sánchez I ,"Consensus Paper: Pathological Mechanisms Underlying Neurodegeneration in Spinocerebellar Ataxias" in CEREBELLUM. 2013 DEC 5.
4. Chang YK, Chen MH, Chiang YH, Chen YF, Ma WH, Tseng CY, Soong BW, Ho JH, Lee OK, "Mesenchymal stem cell transplantation ameliorates motor function deterioration of spinocerebellar ataxia by rescuing cerebellar Purkinje cells" in JOURNAL OF BIOMEDICAL SCIENCES 2011 AUG 8;18:54
5. Sharma A, Gokulchandran N, Sane H, Nagrajan A, Paranjape A, Kulkarni P, Shetty A, Mishra P, Kali M, Biju H, Badhe P," Autologous bone marrow mononuclear cell therapy for autism: an open label proof of concept study" in STEM CELLS INTERNATIONAL 2013;2013:623875.
6. Sharma A, Sane H, Badhe P, Gokulchandran N, Kulkarni P, Lohiya M, Biju H, "A Clinical Study Shows Safety and Efficacy of Autologous Bone Marrow Mononuclear Cell Therapy to Improve Quality Of Life in Muscular Dystrophy" in CELL TRANSPLANTATION 2013 SEP 10.
7. Jones J, Jaramillo-Merchán J, Bueno C, Pastor D, Viso-León M, Martínez S, "Mesenchymal stem cells rescue Purkinje cells and improve motor functions in a mouse model of cerebellar ataxia" in NEUROLOGICAL DISORDERS 2010 NOV;40(2):415-23. EPUB 2010 JUL 15.
8. Chintawar S, Hourez R, Ravella A, Gall D, Orduz D, Rai M, Bishop DP, Geuna S, Schiffmann SN, Pandolfo M ," Grafting neural precursor cells promotes functional recovery in an SCA1 mouse model" JOURNAL OF NEUROSCIENCES 2009 OCT 21;29(42):13126-35.
9. Carlson RV, Boyd KM, Webb DJ ,"The revision of the Declaration of Helsinki: past, present and future" BRITISH JOURNAL OF CLINICAL PHARMACOLOGY. 2004;57(6):695-713
10. Sanchez-Ramos JR ,"Neural cells derived from adult bone marrow and umbilical cord blood" in JOURNAL OF NEUROSCIECES 2002 SEP 15;69(6):880-93.
11. Crisostomo PR, Wang M, Markel TA, Lahm T, Abarbanell AM, Herrmann JL, Meldrum DR. ,"Stem cell mechanisms and paracrine effects: potential in cardiac surgery" in *Shock*. 2007; 28(4):375-83.
12. Cvetanovic M, Patel JM, Marti HH, Kini AR, Opal P ,"Vascular endothelial growth factor ameliorates the ataxic phenotype in a mouse model of spinocerebellar ataxia type 1" in NATURE MEDICINE 2011 OCT 16;17(11):1445-7.
13. Yang B, Xi X, Aronowski J, Savitz SI , "Ischemic stroke may activate bone marrow mononuclear cells to enhance recovery after stroke." In STEM CELLS DEVELOPMENT 2012 DEC 10;21(18):3332-40.
14. Veen M, Jeppesen T, Hauerslev S, Køber L, Krag T, Vissing J, "Endurance training improves fitness and strength in patients with Becker muscular dystrophy." in BRAIN 2008 131(PT 11):2824-31.