Autologous Bone Marrow Mononuclear Cell Transplantation for Multiple System Atrophy Type C- a Case Report

Author's Details:
(1)(2)Alok Sharma [(2)]Hemangi Sane [(2)(3)]Sarita Kalburgi [(2)]Pooja Kulkarni [(3)]Sanket Inamdar [(3)]Khushboo Bhagwanani [(1)]Nandini Gokulchandran [(4)]Prerna Badhe
[(1)]Department of regenerative medicine and medical Services, NeuroGen Brain and Spine Institute, India
[(2)]Department of Research & Development, NeuroGen Brain and Spine Institute, India
[(3)]Department of NeuroRehabilitation, NeuroGen Brain and Spine Institute, India
[(4)]Department of regenerative laboratory services, NeuroGen Brain and Spine Institute, India
Corresponding author: Sarita Kalburgi NeuroGen Brain and Spine Institute, StemAsia Hospital & Research Centre, Sector 40, Plot No 19, Palm Beach Road, Seawood (W), New Mumbai - 400706.

Abstract:
Multiple system atrophy (MSA) is a neurodegenerative disorder clinically characterized by various combinations of cerebellar, autonomic or pyramidal signs and symptoms and pathologically by cell loss, gliosis in brain and spinal cord structures. Treatments available for MSA are largely palliative. Novel approaches to alter the disease progression are required. Cell therapy has shown promising findings in preclinical studies. Herein we present a case report of 50 years old male patient diagnosed as a case of Multiple System Atrophy type C. His symptoms started at the age of 46 years and the condition was deteriorating inspite of regular treatment. Patient underwent intrathecal autologous bone marrow mononuclear cell transplantation and neurorehabilitation. Six months after transplantation, significant improvements in speech, fine motor activities, balance and ambulation were noted. There were improvements in the cerebellar signs and symptoms and outcome measures of Modified International Co-operative Ataxia Rating scale (34 to 31) and the Brief Ataxia Rating Scale (7 to 6). In view of his improvements second cell transplantation was done after 9 months. The improvements were maintained with no further deterioration for the next 21 months post transplantation. This highlights the potential of combination treatment of cell therapy and neurorehabilitation to alter the disease progression in MSA.

Key words*: Autologous bone marrow mononuclear cells (BMMNC); stem cells; cell therapy; multiple system atrophy-C (MSA-C); MICARS; BARS.*

Introduction:

Multiple system atrophy (MSA) is a rapidly progressing neurodegenerative condition which affects multiple body systems in adults, and can be life threatening. (1). Abnormal aggregation of alpha-synuclein in oligodendrocytes is the primary pathological feature of MSA and it causes the cellular death in various brain areas. Most often, there is loss of cells in the striatonigral and olivopontine structures of brain. (2) According to the predominant motor presentation, MSA patients may be labeled as parkinsonian or cerebellar variant (MSA-P, MSA-C). Cerebellar features in MSA affects trunk and lower extremity first which causes gait and balance problems (3). Their survival is about 9 to 10 years after symptom onset with nocturnal sudden death being a major cause of death (4). So far few symptomatic, non specific therapies such as treating depression, cognitive impairment, drooling along with the medical rehabilitation and neuroprotective strategies which includes use of lithium, NSAIDS, rifampicin are available. But these strategies do not address the underlying neurological deficit in MSA, creating a strong need for new therapeutic approaches (5).

Neuroregenerative strategies, appear to be an alternative therapeutic approach for management of MSA. Various preclinical (6) and clinical studies have shown that Autologous Bone Marrow Mononuclear cell (BMMNC) can be used safely as a treatment option in various neurological disorders. (7, 8)

We hereby present a case report of 50 year old male diagnosed with MSA, who underwent intrathecal autologous bone marrow mononuclear cell transplantation. On follow up functional as well as clinical improvements were noted.

Case presentation:

A 50 year old man was diagnosed with Multiple System Atrophy - C (MSA-C) on the basis of clinical features. His symptoms started at the age of 46 years, with weakness in both lower limbs and difficulty in walking. Symptoms progressed gradually with increased incoordination, imbalance while walking on uneven surface, dysarthria, intention tremors and urinary urgency. He was prescribed Syndopa plus and was on continuous rehabilitation. In spite of taking regular therapy, his symptoms progressed further with increase in dysarthria, bradykinesia, difficulty in stair climbing, fine motor activities and writing. On neurological evaluation, he was hyperreflexic and normotonic. He had good sitting balance but poor walking balance. On standing his posture was stooped. Cerebellar signs like dysdiadochokinesia, truncal ataxia, intension tremors, asthenia and Rhomberg's sign were positive. He had difficulty in single limb standing and tandem standing. On objective evaluation he scored 116 on Functional Independence Measure (Wee FIM) scale, 34 on Modified International Cooperative Ataxia Rating Scale (MICARS), and 7 on Brief Ataxia Rating scale (BARS). On admission the Positron Emission Tomography and computed tomography (PET-CT) scan of the brain showed severe hypometabolism in right cerebellum and moderate hypometabolism in left cerebellum. Magnetic Resonance Imaging (MRI) of brain was suggestive of moderate cerebellar atrophy with mild volume loss of pons and T2 hyperintensity of median raphe of transverse pontine fibers consistent with MSA-C.

Material and methods:

The patient selection was in compliance with the World Medical Associations Helsinki declaration criteria. [9] The protocol of autologous BMMNC intrathecal administration has been reviewed and approved by the Institutional Committee for Stem Cell Research and Therapy (IC-SCRT).The patient was informed about the procedure and a duly filled informed consent was obtained. Pre-procedure biochemical and hematological blood tests, MRI and PET-CT scan of brain, chest X-ray, electroencephalography (EEG), and electrocardiography (ECG) were performed to rule out any active infection and to assess fitness for anesthesia [10]. 300 mcg of Granulocyte colony-stimulating factor (G-CSF) injections were administered 72 hours and 24 hours prior to BMMNC transplantation. This was given to stimulate CD34+ cells and increase their survival and multiplication. 100 ml bone marrow was aspirated from the iliac bone. The BMMNCs were then separated using density gradient centrifugation method. These cells were checked for viability and CD34+ markers. The viability of the cells was found to be 98%. Approximately $1.71x10^8$ cells were administered immediately post separation, in L4-L5 using a lumbar puncture needle. These cells consisted of 77.78 CD34+ cells/µl. 1 gm methyl prednisolone in 500 ml Ringer's Lactate (RL) was simultaneously injected intravenously to increase the survival and multiplication of cells.

Therapeutic exercises were given to improve trunk muscle strength, gross motor performance, postural correction, handwriting, coordination, balance and gait. The patient was also given deep breathing and oromotor exercises. To augment the effectiveness of the cell therapy exercise home program was given. In view of the improvements a second cell transplantation procedure was done after 9 months. The procedure was same as the first transplantation, which involved intrathecal administration of autologous BMMNCs followed by neurorehabilitation. For the second procedure the viability of cells was 94%. Approximately $1.2 x10^8$ cells were administered intrathecally which consisted of 64 CD34+ cells/ µl.

Results:

After the BMMNC transplantation, patient had no side effects and was evaluated regularly at three, six, nine months.

On follow up (FU) after 3 months of intervention, tongue curling and flexibility had improved. As the slurring of speech was reduced, he could speak more clearly and fluently. His maximum phonation duration increased

from 4 seconds to 10 seconds. There was improvement in handwriting (Figure 1). His standing posture, tandem standing, tandem walking and stair climbing was better due to improved standing dynamic balance. There was reduction in bradykinesia, truncal ataxia and postural tremors.

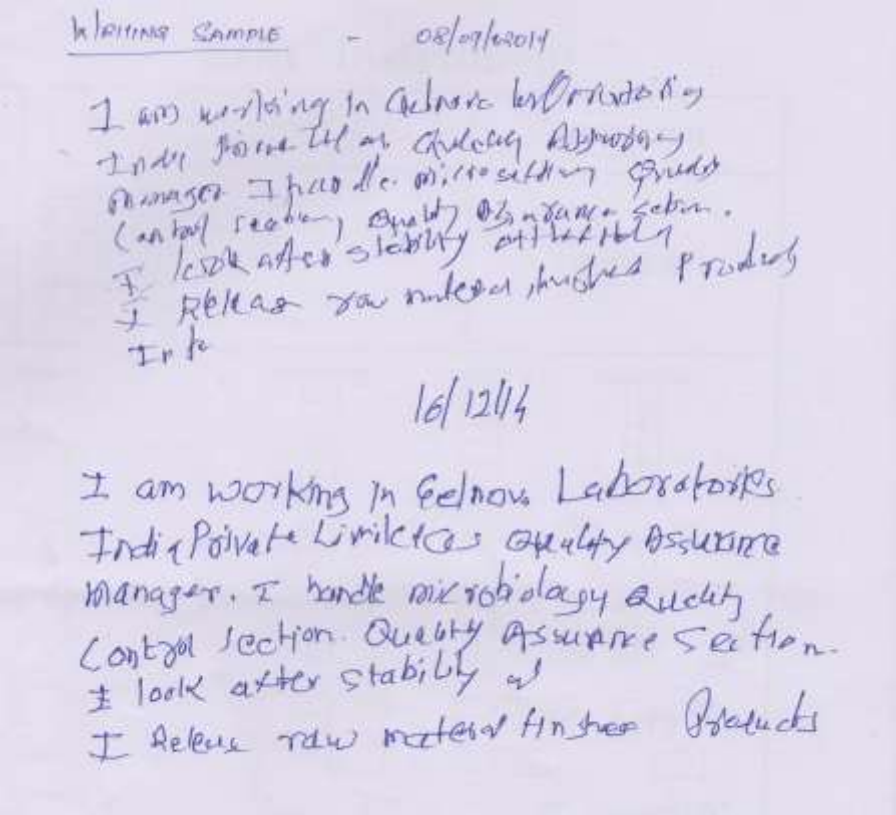

Figure1: Handwriting Sample on admission and on first FU at 3 months.

On follow up after 6 months of cellular transplantation, speech clarity had further improved with reduced slurring of speech. His maximum phonation duration increased from 10 seconds to 21 seconds. There was improvement in quality of fine motor tasks like buttoning, holding small objects, eating and handwriting (figure 2). His truncal ataxia and postural tremors were reduced, which led to improved steadiness while performing activities. As the dynamic balance improved he could pick up the objects from the ground. Stamina was improved and he could walk for 30 minutes every day without support. Stair climbing was easier as compared to before. As mentioned in table 1 his MICARS score improved from 34 to 31 and BARS score improved from 7 to 6, whereas FIM score remained same i. e. 116.

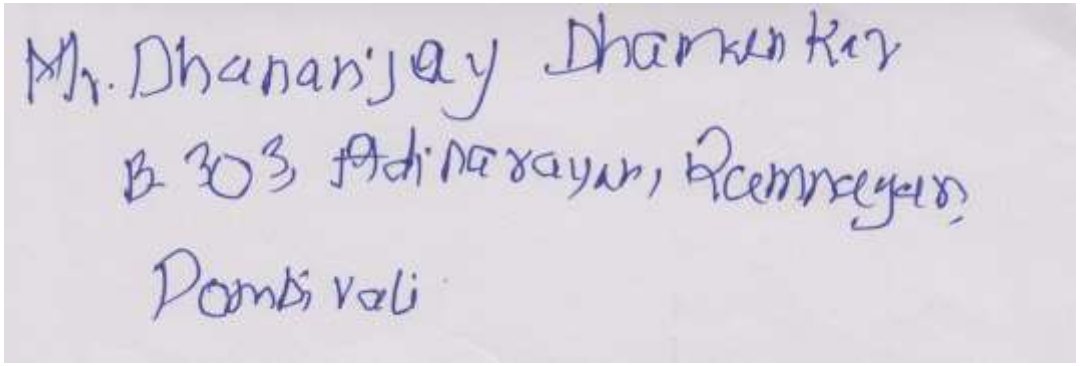

Figure2: Handwriting Sample on second FU at 6 months

In view of significant improvements, the patient was given the cell therapy for second time after 9 months. There was improvement in quality of fine motor activities. He was able to hold the objects more easily compared to before.

On telephonic follow up after 21 months of first cellular transplantation the patient reported maintenance in his condition and no further deterioration.

Table 1: Objective improvements

Scales	On Admission	3 month FU	6 month FU	9 months FU
FIM	116	116	116	116
MICARS	34	31	31	31
BARS	7	6	6	6

Discussion

Multiple system atrophy is progressive neurological disorder which results in problems with movement, balance and autonomic functions of the body. [11] Pathologically MSA is characterized by cell loss, gliosis and glial cytoplasmic inclusions due to aggregation of a-synuclein with loss of surrounding neurons in the brain. [12] The disease progression can be linked with increased accumulation and aggregation of a-synuclein. [13] Currently available medical and rehabilitation therapies are unable to halt or reverse disease progression.

The patient was deteriorating despite standard treatment and therefore autologous BMMNC transplantation in combination with neurorehabilitation was performed. The adult bone marrow stem cells are safe and have no major side effects [14]. The intrathecal route of cell transplantation was preferred because it is a targeted approach and the chemical properties of cerebrospinal fluid support the cell growth [15]. These MNC are composed of variety of cells like hematopoietic stem cells, tissue specific progenitor cells, stromal cells and specialized blood cells in different stages of development. These transplanted MNC play important role in production of neurotrophic factors, differentiation, transdifferentiation of cells and formation of new blood vessels and thereby improving hemodynamics of brain.[16]

In Multiple System Atrophy (MSA) there is striato-nigral degeneration and olivo-pontocerebellar atrophy. Several molecular and cellular changes such as oxidative stress, mitochondrial dysfunction and apoptotic processes might be involved in neuronal degeneration [17-19]. Microglial activation leading to neuroinflammation has been reported as pathogenic mechanism in MSA [20]. With the paracrine effect the transplanted MNC posses ability to modify the internal repair process of axon and myelin sheath. They also show properties of immunomodulation, regulation of apoptotic process and reduction of inflammation.[21-24] We hypothesize that these effects might be responsible for modulation of disease pathology. So the altered cellular environment may lead to improved brain function, clinically exhibited as reduced intensity of the cerebellar signs and functional improvement seen in this patient. Cell transplantation followed by rehabilitation has been found to be more effective than either of the therapies alone (25). One of our previous case report have also demonstrated safety and efficiency of BMMNC in the treatment of spinocerebellar ataxia (7). In this patient favorable changes in MICARS and BARS (table 1) were noticed, which can be correlated clinically with improvements in speech, fine motor activities, posture, balance and ambulation. FIM score remained same but qualitative improvements were reported by the patient. No deterioration on clinical symptoms and objective scales for 21 months denotes halting of the disease progression.

The limitation of this case report is absence of objective evidence using advanced neuroimaging techniques, which should be incorporated in future research. Though a single case report stabilization of condition post cellular therapy and neurorehabilitation highlights the potential of this novel approach. Since the patient was on standard neurorehabilitation before cell therapy the improvements noted cannot be attributed to neurorehabilitation alone. The patient can serve as a self control in this scenario.

Conclusion

The present case report suggests that intrathecal autologous bone marrow derived mononuclear cell transplantation along with neurorehabilitation can be used as novel therapeutic approach for the treatment of MSA-C. Cell therapy may alter the disease progression of MSA-C by addressing the core neural tissue damage. However further randomized controlled trials with neuroimaging are needed to support the findings.

References:

1. D J Burn, E Jaros, Multiple system atrophy: cellular and molecular pathology, J Clin Pathol: Mol Pathol 2001;54:419–426.
2. Wenning GK, Jellinger KA. The role of alpha-synuclein in the pathogenesis of multiple system atrophy. Acta Neuropathol, 2005; 109:129-40.
3. Olivier Flabeau, Wassilios G. Meissner and Franc¸ois Tison, Multiple system atrophy: current and future approaches to management Ther Adv Neurol Disord (2010) 3(4) 249_263
4. Schrag, A., Wenning, G.K., Quinn, N. and Ben-Shlomo, Y. Survival in multiple system atrophy. Mov Disord, 2008; 23: 294_296.
5. Wenning G.K., Stefanova N. Recent developments in multiple system atrophy. J. Neurol, 2009; 256:1791–1808.
6. Stemberger S., Jamnig A., Stefanova N., Lepperdinger G., Reindl M., Wenning G.K. Mesenchymal stem cells in a transgenic mouse model of multiple system atrophy: immunomodulation and neuroprotection. Plos ONE, 2011; 6.
7. Alok Sharma, Hemangi Sane et al. Cellular transplantation may modulate disease progression in spinocerebellar ataxia- A case report. Indian Journal of Medical Research and Pharmaceutical Sciences, 2014; 1(3).
8. Alok Sharma, Hemangi Sane et al. Autologous Bone Marrow Mononuclear Cells Intrathecal Transplantation in chronic stroke. Hidawi Publishing Corporation, Stroke research and treatment; 2014.
9. R. V. Carlson, K. M. Boyd, and D. J. Webb, "The revision of the declaration of Helsinki: past, present and future," British Journal of Clinical Pharmacology, 2004; 57(6): 695–713.
10. Hwan Yoon, Shik Shim et al. Complete Spinal Cord Injury Treatment Using Autologous Bone Marrow Transplantation and Bone Marrow Stimulation with Granulocyte Macrophage-Colony Stimulating Factor: Phase I/II Clinical Trial. Tissue Engineering, 2005; 11 (5-6):913-922.
11. Felix Geser and Gregor K. Wenning. chapt 20, Multiple System atrophy, Current Clinical Neurology: Atypical Parkinsonian Disorders; 335-360.
12. Wakabayashi K, Takahashi H. Cellular pathology in multiple system atrophy. Neuropathology 2006;26:338–345.

13. Windisch M, Wolf HJ, Hutter-Paier B, Wronski R. Is alpha-synuclein pathology a target for treatment of neurodegenerative disorders? Curr Alzheimer Res 2007;4:556–561.

14. Sharma A, Gokulchandran N. Stem cell therapy in neurological disorders. 1 st edition, India 2010.

15. D. I. Jung, J. Ha, B. T. Kang et al., "A comparison of autologous and allogenic bone marrow-derived mesenchymal stem cell transplantation in canine spinal cord injury," Journal of the Neurological Sciences, 2009; 285 (1-2): 67–77.

16. A Sharma, P Badhe, Administration of Autologous Bone Marrow Stem Cells Intrathecally in Multiple Sclerosis Patients is Safe and Improves their Quality-of-life. Indian Journal of Clinical Practice, 2011, Vol. 21 No. 11;622-25

17. Stefanova N, Bucke P, Duerr S, Wenning GK (2009) Multiple system atrophy: an update. Lancet Neurol 8: 1172–1178.

18. Giasson BI, Duda JE, Murray IV, Chen Q, Souza JM, et al. (2000) Oxidative damage linked to neurodegeneration by selective alpha-synuclein nitration in synucleinopathy lesions. Science 290: 985–989.

19. Jellinger KA (2003) Neuropathological spectrum of synucleinopathies. Mov Disord 18: Suppl 6S2–12

20. Hirsch EC, Hunot S (2009) Neuroinflammation in Parkinson's disease: a target for neuroprotection? Lancet Neurol 8: 382–397.

21. N. Payne, C. Siatskas, A. Barnard, and C. C. A. Bernard, "prospect of stem cells as multi-faceted purveyors of immune modulation, repair and regeneration in multiple sclerosis,"Current Stem Cell Research and Therapy, 2011; 6 (1): 5.

22. P. M. Chen, M. L. Yen, K. J. Liu, H. K. Sytwu, and B. L Yen, "Immuno-modulatory properties of human adult and fetal multipotent mesenchymal stem cells," Journal of Biomedical Sciences, 2011; 18 (49).

23. M. X. Xiang, A. N. He, J. A. Wang, and C. Gui, "Protective paracrine effect of mesenchymal stem cells on cardiomyocytes," Journal of Zhejiang University B, 2009; 10 (8): 619–624.

24. P. R. Crisostomo, M. Wang, T. A. Markel et al., "Stem cell mechanisms and paracrine effects: potential in cardiac surgery," Shock, vol. 28, no. 4, pp. 375–383, 2007.

25. 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(11):2824-31