



## REVIEW ARTICLE

### CELLULAR THERAPY IN MOTOR NEURON DISEASE: A CASE REPORT

<sup>1</sup>Alok Sharma, <sup>2</sup>Hemangi Sane, <sup>\*,2,3</sup>Amruta Paranjape, <sup>2</sup>Dhanashree Sawant, <sup>3</sup>Sanket Inamdar, <sup>1</sup>Nandini Gokulchandran and <sup>4</sup>Prerna Badhe

<sup>1</sup>Department of Medical Services, NeuroGen Brain and Spine Institute, Navi Mumbai, India

<sup>2</sup>Department of Research and Development, NeuroGen Brain and Spine Institute, Navi Mumbai, India

<sup>3</sup>Department of Neurorehabilitation, NeuroGen Brain and Spine Institute, Navi Mumbai, India

<sup>4</sup>Department of Regenerative Laboratory Services, NeuroGen Brain and Spine Institute, Navi Mumbai, India

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#### ABSTRACT

Motor Neuron Disease (MND) is a progressive neurodegenerative disorder. It selectively damages the motor neurons and is currently an incurable disease. Cellular therapy holds a promising future in the management of MND. We herewith present a case of a 63-year-old man who underwent intrathecal transplantation of autologous bone marrow mononuclear cells (BMMNCs) as a therapeutic treatment modality in a clinical case of MND. The transplantation was followed by multidisciplinary neurorehabilitation. Improvements were noted in the muscle strength, fine motor activities, fasciculation, cramps and walking. The outcome measures of Amyotrophic Lateral Sclerosis - Functional Rating Scale Revised (ALS-FRSR) score improved from 33 to 37; Bergs Balance Score improved from 43 to 50 and 6-minute walk test improved from 283.8 m to 303.6m. His Functional Independence Measure (FIM) remained unchanged at 113. These improvements may be attributed to cellular therapy along with standard treatment and neurorehabilitation. Cellular therapy, if administered in the early stages of disease may have beneficial effects in the treatment of MND. However, rigorous and heterogeneous methodologies are required for definitive findings.

#### INTRODUCTION

Motor Neuron Disease (MND) is a progressive neurodegenerative disorder with poor prognosis (Valetdinova *et al.*, 2015). The incidence of MND varies across the globe. A higher incidence of 2.08 per 100000 population and prevalence rate of 5.40 was noted in Europe. A lower incidence of 0.46 per 100000 population was seen in Asian countries such as Japan and China (Chio *et al.*, 2013). In USA, an incidence of 3.9 per 100000 was noted (Mehta *et al.*, 2014). MND is characterized by motor weakness, bulbar symptoms and respiratory insufficiency in the advanced stages of the disease (Kiernan *et al.*, 2014). The diagnosis of MND is based on thorough clinical neurological examination and electrophysiological investigation (Kiernan *et al.*, 2014). The etiology of MND remains unclear, however many theories have been proposed in the pathophysiology of MND. Structural changes in the mitochondria, accumulating proteins, release of free radicals, glutamate excitotoxicity, and series of neuroinflammatory reactions, apoptosis and genetic mutations contribute to the pathophysiology of MND (Kiernan *et al.*, 2014).

\*Corresponding author: <sup>1,2</sup>Amruta Paranjape,

<sup>1</sup>Department of Research and Development, NeuroGen Brain and Spine Institute, Navi Mumbai, India.

<sup>2</sup>Department of Neurorehabilitation, NeuroGen Brain and Spine Institute, Navi Mumbai, India.

Since MND is incurable, a multidisciplinary treatment is widely accepted in MND (Hardiman *et al.*, 2012). At present, Riluzole is the only drug that is found to be effective in MND. However, it does not halt or alter the course of the disease and its influence on the survival duration is also limited (Lee *et al.*, 2013). Currently, the management of MND involves physical therapy, occupational therapy, speech therapy, in the advanced stages of the disease artificial ventilation (Aleksander *et al.*, 2013), dysphagia management and percutaneous endoscopic gastrostomy (PEG) (Mazzini *et al.*, 1995) (Majumdar *et al.*, 2013). Cellular therapy is a novel approach that is being explored in the treatment of MND, as stem cells have a unique potential to self-regenerate and differentiate into multiple cell types. Various studies worldwide have investigated use of stem cells for other neurological disorders, thus suggesting its efficacy and safety. (Sharma *et al.*, 2012; Sharma *et al.*, 2013a; Sharma *et al.*, 2013b; Kim *et al.*, 2009). Pre-clinical studies have also proposed the use of stem cells in MND (Garbuzova-Davis *et al.*, 2003; Garbuzova-Davis, 2012). Autologous (BMMNCs) are being explored in MND in various human studies as well and have shown promising results (Deda H. *et al.*, 2009; Sharma A. *et al.*, 2011; Prabhakar S. *et al.*, 2012; Blanquer M. *et al.*, 2012; Sharma A. *et al.*, 2015). Studies suggest that lithium increases the survival and potency of the transplanted cells and may be effective if used in conjunction with cellular therapy (Richman *et al.*, 1981; Gallicchio

*et al.*, 1981). In this paper, we present a case report of a 63-year-old man with motor neuron disease, who underwent intrathecal transplantation of autologous BMMNCs as a therapeutic treatment modality. The transplantation was followed by a multidisciplinary rehabilitation such as physiotherapy, occupational therapy, speech therapy and psychological counseling.

### Case Report

A 63-year-old male complained of frequent falls while walking on uneven surfaces. After a series of diagnostic tests such as electromyography (EMG)/nerve conduction study (NCS) and magnetic resonance imaging (MRI), he was diagnosed as MND. He noticed weakness in the hands since 4-5 years and developed bulbar symptoms since 2-3 years. He took Riluzole for 3 months and has been taking Baclofen. He also underwent an appendectomy, transurethral resection of the prostate (TURP) surgery for urethral obstruction and uvula resection and mandibular repositioning for sleep apnea. His chief complaints at the time of transplantation were difficulty in walking, climbing stairs, fine motor activities, slow movements and cramps. He also complained of drooling and occasional episodes of choking while swallowing. Speech was clear; however slight disturbances were observed. On assessment, we found that he was normotonic and normoreflexic. He had good voluntary control in the upper and lower extremity. Heel toe pattern was affected and the patient show mild deviation while walking.

He walked with a wide base of support and reduced arm swing. Internal rotation of lower extremities and foot drop was present bilaterally. Bilateral hamstring and tendoachillestightness was also present. He had full range of motion in all the joints. He maintained good static and dynamic sitting balance; whereas his static and dynamic standing balance was affected. Fasciculations were present occasionally in the upper and lower extremity; cramps were present in both the thighs and legs. The patient had good strength (Above the functional level i.e. above Grade 3) in hip, knee, trunk, neck, proximal shoulder girdle, elbow, forearm, and wrist and hand muscles whereas below functional level strength (i.e. below grade 3) was noted in left tibialis posterior, left peroneii (longus, brevis and tertius). Plantar flexors, extensor hallucis longus and extensor digitorum longus exhibited functional level muscle strength i.e. Grade 3. He continuously used noninvasive positive pressure ventilation (NIPPV) at night for sleep apnea for 7 years. His ALS-FRSr score was 32 and FIM score was 113. Functionally, he was modified independent for all his activities of daily living. The distance covered by him in six-minute walk test was 283.8 meters. His EMG/ NCS findings were suggestive of chronic motor axonal degeneration involving bilateral cervical and lumbosacral segments. His MRI showed normal brain parenchyma; sacralization of L5 vertebral body-normal variant, focal posterocentral protrusions at C5-C6, C6-C7, C7-D1 and L4-L5 levels with mild soft tissue spinal canal stenosis at C5-C6 to C7-D1 levels.

### Intervention

The ethical basis for choosing BMMNCs for the treatment was according to the World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving

Human Subjects. The ethical approval for the intervention was obtained from Institutional Committee for Stem Cell Research and Therapy (IC-SCRT). The patient was explained about the procedure and a written informed consent was obtained from him. He was thoroughly examined by an experienced team of doctors. Pre-surgery routine blood tests, urinalysis and chest x-ray were carried out for anesthetic and surgical fitness. 300 mcg of Granulocyte colony-stimulating factor (G-CSF) injections were administered 72 hours and 24 hours prior to BMMNCs transplantation as it enhances the mobility of BMMNCs, stimulates CD34+ cells and increases their survival and multiplication rate (Hwan Yoon *et al.*, 2005). The patient was given local anesthesia in the region of anterior superior iliac spine and bone marrow of amount 100ml was aspirated from the iliac bone with the help of a bone marrow aspiration needle and collected in heparinized tubes.

Separation of mononuclear cells was achieved by the density gradient method under aseptic condition in a stem cell laboratory. The MNCs were then examined for CD34+ by FACS analysis and the viability of the cells was calculated. Cell viability was 96% and  $9.6 \times 10^7$  mononuclear cells (MNC's) were administered intrathecally at the level of L4-L5 using 25 G spinal needle. 1 gm methyl prednisolone in 500 ml Ringer Lactate (RL) solution was simultaneously injected intravenously to reduce the local inflammatory response and improve the stem cell survival. He was then closely monitored for any immediate adverse events during his stay at the hospital. The patient was prescribed upper and lower extremity strengthening exercises, trunk strengthening exercises, bed mobility exercises, balance exercises, gait training, exercises to improve gross and fine motor function as well as breathing exercises. He was put on a home exercise program for 6 months to enhance the effectiveness of stem cell transplantation. Post discharge, he was prescribed 50 mg Riluzole once a day. 300 mg lithium was also prescribed once a day for 6 weeks. Serum lithium levels were monitored and were maintained within a range of 0.5-0.8 mEq/L for six weeks; thereafter lithium was discontinued.

### RESULTS

6 months after the stem cell transplantation he observed improvement in different clinical areas. **Bulbar Symptoms:** His drooling stopped completely. The speech clarity was maintained, though occasional episodes of choking were observed.

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**Hand functions:** No significant changes were noted in his gross motor activities. His fine motor activities such as zipping-unzipping, buttoning-unbuttoning improved significantly. His handwriting remained unchanged.

**Ambulation and transfers:** Walking balance improved. His confidence while walking also increased. There were no episodes of falls noted in this period. Static and dynamic balance in standing showed improvement. Bed mobility also improved. Side sway while walking reduced significantly.

**Muscle strength:** His muscle strength increased in hip adductors, plantar flexors, tibialis posterior, upper abdominal, back extensors and palmar interossei.

**Voluntary Control:** Was maintained as before. Significant improvements were noted in the foot drop. Toe movements also showed improvement as he could not move his toes before cell transplantation.

**Stamina:** His stamina increased as he could work for longer periods than before.

**Other subjective improvements:** Fasciculations and cramps also reduced. He reported qualitative improvements in ambulation. He showed stability in his functional activities. Improvements in the outcome measures are shown in Table 1.

**Table 1. Changes in outcome measures over the period of 6 months**

Outcome measures	Pre 1 <sup>st</sup> SCT	At 6 months post 1 <sup>st</sup> SCT
ALSFRS-r	33	37
FIM	113	113
6 minute walk test	283.8m	303.6m
Bergs Balance	43	50

## DISCUSSION

Motor Neuron Disease (MND) is a progressive neurodegenerative disorder. MND is characterized by progressive axonal degeneration of motor neurons in the spinal cord and motor cortex; selectively sparing the sensory neurons in this process. The revised El Escorial Criteria is widely accepted as a diagnostic tool for MND. It classifies the patients as Definite, Probable, Probable lab, Possible and Suspected. Pathophysiology of MND remains obscure. Glutamate-induced excitotoxicity has been implicated in the pathogenesis of MND. Due to the glutamate-induced excitotoxicity, free radicals are generated which in turn causes neurodegeneration of the neurons. Non-neuronal glial cells and up regulation of astrocytic glutamate, superoxide dismutase triggers a series of neuroinflammatory reactions that allude to the pathophysiology of MND. Mitochondrial structural defects, disruption in the axonal transport system and sodium potassium ion pump also contribute to the pathogenesis. Recently, mutations in the genes have also been found to be involved in MND (Gordon, 2011; Gordon, 2013) The pathogenesis of MND is heterogeneous; involving multiple physiological systems. Due to the unavailability of a definite cure, the treatment in MND would be palliative. Currently, Riluzole is the mainstay of pharmacological management in MND. Riluzole, reduces the over excitation of the neurons, thus decreasing the glutamate induced toxicity. This drug so far has shown modest effect in improving the survival duration in MND (Lee *et al.*, 2013; Lu *et al.*, 2016).

Cellular therapy in MND is a novel therapeutic intervention. Stem cells provide neurotrophic support and enhance the neuroprotective microenvironment (Moura *et al.*, 2016). It may alter or halt the progression if administered in the early stages of the disease as stem cells have a potential to replace diseased cells. Clinical trials suggest the efficacy and safety of the bone marrow stem cells in various neurological conditions (Deda *et al.*, 2009; Sharma *et al.*, 2011; Prabhakar *et al.*, 2012; Blanquer *et al.*, 2012; Sharma. *et al.*, 2015).

A recent systematic review and meta-analysis by Moura *et al* analyzed 12 clinical and 9 preclinical trials conducted in MND. It was seen that survival duration in preclinical studies increased by a period of 9.79 days; whereas clinical trials did not report any serious adverse events. This suggests that cellular therapy may be safe and effective in the treatment of MND (Moura *et al.*, 2016). Our published article on the efficacy of cellular therapy in MND was also included in the above meta-analysis. Our study showed that the survival duration of MND patients who underwent intrathecal transplantation of autologous BMMNCs was higher by 30.38 months than the control group who did not receive transplantation (Sharma *et al.*, 2015). A case report of a 40 year old female of MND showed that progression of the disease had slowed down after she was given intrathecal transplantation of autologous BMMNCs. Functional and neurological improvements were seen on the outcome measures of ALS-FRSr and FIM scale over a period of 17 months post intervention (Sane *et al.*, 2016). The mechanism of action of BMMNCs is not only to protect the existing motor neurons but also to replace degenerated motor neurons. Autologous BMMNCs have neurogenic potential (Sharma *et al.*, 2010). Adult bone marrow stem cells can be directly isolated from the patient and it adheres to the ethical principles. None of the clinical studies have shown presence of tumors post transplantation or any other irreversible or major adverse events (Deda *et al.*, 2009; Sharma *et al.*, 2011; Prabhakar S. *et al.*, 2012; Blanquer M. *et al.*, 2012; Sharma *et al.*, 2015). Lithium was prescribed to our patient as it improves the survival and potency of the BMMNCs Gallichio *et al.*, 1981; Richman *et al.*, 1981) A combination of neuroregeneration and rehabilitation may have significant therapy outcomes in MND. Studies suggest that exercises mobilize the local stem cells resulting in angiogenesis (Macaluso *et al.*, 2012). The aim of rehabilitation was to restore movement patterns, increase strength and flexibility of the muscles, improve balance and coordination and prevent contractures. In our study, the patient observed that his foot drop had reduced and his muscle strength had improved too.

The ALS-FRSr score improved from 33/48 to 37/48. The components of salivation, turning in bed and adjusting sheets, orthopnea and respiratory insufficiency showed improvements with one point increase in each of the above components respectively. A study conducted by Prabhakar *et al* (2012) treated 10 MND patients with autologous BMMNCs intrathecally and followed up for one year. The results showed that median survival post intervention was 18 months and the time taken to achieve 4 point deterioration on the ALS-FRSr scale was 16.7 months. In our study, the score increased by 4 points in a span of 6 months post intervention. We also observed that this patient maintained his functional activity. The 4-point increase in ALS-FRSr scale and the unchanged FIM score implies that the disease progression has halted after cellular therapy in contrast to the natural course of MND which shows progression and deterioration of symptoms. Bergs Balance score improved from 43/56 to 50/56. The 6-minute walk test distance increased from 283.8 m to 303.6m. The improvements in the outcome measures may be attributed to the beneficial effects of cellular therapy followed by neurorehabilitation. It is postulated that exercises increase the number of adult stem cells and enhance the paracrine effects of

cellular therapy (Macaluso *et al.*, 2012). Cellular therapy may have the potential to alter the course of the disease. These cells home onto the injured site through various neurochemical pathways. Neurotrophic factors such as connective tissue growth factor, fibroblast growth factor 2 and 7 and interleukins bring about cell proliferation. Secretion of growth factors like vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), brain fibroblast growth factor (bFGF) leads to neoangiogenesis. Improving microcirculation helps to regain tissue function. Hence, BMMNCs may play a pivotal role in ceasing the disease progression through the above-mentioned mechanisms (Gnecchi *et al.*, 2008). Limitation of this study was the absence of a control group. The patient was used as a self-control wherein his improvements were measured against the natural progression of the disease. The effect of cellular therapy alone could not be assessed as it was used in conjunction with neurorehabilitation, Riluzole and lithium.

## Conclusion

This case report demonstrated that autologous BMMNC transplantation in the early stages of MND has decelerated the progression. Cellular therapy is a novel therapeutic modality and may have augmentative effects on survival duration and progression when combined with standard treatment of Riluzole, neurorehabilitation and lithium intake. However, the primitive nature of cellular therapy requires rigorous and heterogeneous methodologies to establish its efficacy and safety.

## Conflict of interest statement

The author declares that there is no conflict of interest regarding the publication of this article.

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