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Case Report

Neuroregenerative Rehabilitation Therapy with long-term Lithium in a Male Amyotrophic Lateral Sclerosis Patient: A Case Report.

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Abstract: Various cellular therapies are being increasingly investigated for the treatment of Amyotrophic Lateral Sclerosis, a progressive neurodegenerative disease with selective loss of anterior horn cells. Lithium is known to enhance the potency of transplanted cells, while being well tolerated by ALS patients. Additionally, rehabilitation significantly improves outcomes in various neurodegenerative disorders. We present a 47-year-old male patient suffering from ALS for 2 years, whose treatment involved intrathecal transplantation of autologous Bone Marrow-Derived Mononuclear Cells and long-term Lithium, followed by multidisciplinary neurorehabilitation, and standard Riluzole treatment. ALSFRSr score improved from 39 to 41; FIM remained stable at 101; 6MWT distance improved from 396 m to 480 m and Berg Balance score remained stable at 56 over a span of 18 months. Symptomatic improvements were seen in speech, swallow, stamina, walking and muscle strength; fasciculations and cramps reduced drastically. The highlight of this case is the maintenance of the patient's condition in view of a degenerative prognosis. Cellular therapy along with long-term Lithium and holistic rehabilitation, in addition to standard Riluzole treatment—together termed as Neuroregenerative Rehabilitation Therapy—is a novel approach for halting disease progression and qualitatively improving living conditions, for ALS patients and caregivers alike.

Keywords: Amyotrophic Lateral Sclerosis (ALS), long-term Lithium, Neuroregenerative Rehabilitation Therapy (NRRT), Autologous Bone Marrow-Derived Mononuclear Cells (autologous BMMNCs), Amyotrophic Lateral Sclerosis Functional Rating Scale—Revised (ALSFRSr), Functional Independence Measure (FIM), 6 Minute Walk Test (6MWT), Berg Balance Scale (BBS).

Introduction

Amyotrophic Lateral Sclerosis (ALS) is an idiopathic, relentless neurodegenerative disorder with selective degeneration of anterior horn motor neurons[1]. Clinically, it is characterized by wasted, fasciculating musculature leading to progressive respiratory insufficiency. Prognosis varies depending on age of symptom onset and type of ALS[2]. An exact incidence is unknown[3], but has steadily increased globally over the past few decades[4]. Diagnosis is confirmed based on thorough neurological and electrophysiological investigation[5].

Standard care for ALS has barely evolved over the years; other than Riluzole administration[6], it involves palliative management at best. Only recently, Nuedexta[7] (symptomatic treatment of pseudobulbar affect) and Edaravone (solely effective in the early stages[8]) have been approved by the Food and Drug Administration of the United States (USFDA) for treatment of ALS in the USA. Given the multivariate pathophysiology of this disease, including the involvement of misfolded ubiquitinated aggregates[9], excessive free radicals[10], excitotoxicity[11], etc., ALS treatment demands a comprehensive approach, going beyond palliative care. Effective therapies for halting disease progression and improving quality of life are the need of the hour.

Various studies worldwide advocate the efficacy and safety of autologous bone marrow-derived mononuclear cells (autologous BMMNCs) as a therapeutic intervention for neurological disorders[12–14], including for ALS[15–17]. Lithium not only increases the survival and potency of these transplanted cells[18], but is also safe when administered to ALS patients[19,20]. Holistic rehabilitation bolsters the tendency of these cells to integrate into target tissue[21].

We present a case of a 47-year-old male with ALS, who underwent an intrathecal autologous BMMNCs transplantation in conjunction with long-term Lithium and standard Riluzole treatment, followed by customized, multidisciplinary rehabilitation to improve the musculoskeletal sequelae of transplantation—such as physical, occupational and speech therapy, and psychological counseling—together termed as

Neuroregenerative Rehabilitation Therapy (NRRT).

Case Presentation

A 47-year-old male, right hand dominant, with no family history of ALS or psychological disorders, felt sudden weakness in the right upper limb in August 2014. In a span of 6 months following this observation, weakness and muscle loss progressed to the left upper limb. In May 2015, based on a series of diagnostic tests such as electromyography (EMG), nerve conduction studies (NCS) and magnetic resonance imaging (MRI), he was diagnosed with ALS and prescribed 50 mg Riluzole once daily. Within a year, he stopped doing overhead activities; the UMN features of limbs manifested as neck muscle stiffness, and brisk superficial (plantar) as well as deep tendon (knee and ankle jerk) reflexes. The LMN features of limbs comprised of muscle wasting and weakness in thenar, hypothenar, pectoral, scapular, as also biceps, brachialis and brachioradialis. He had fasciculations in both upper as well as lower limbs, and decreased jaw jerk as well as supinator reflexes. He was categorized as Probable ALS according to the revised El Escorial criteria for ALS diagnosis[22] upon admission. His chief complaints at the time of transplantation included difficulty in gripping, pain in the left wrist, difficulty in getting up from the floor, dyspnoea after walking, occasional difficulty in drinking water due to impaired oromotor function, and pain and stiffness in the neck.

On assessment, his Amyotrophic Lateral Sclerosis Functional Rating Scale—Revised (ALSFRSr) score was 39/48; Functional Independence Measure (FIM) score was 101/126; and, 6 Minute Walk Test (6MWT) distance was 396 meters. Additionally, we tested his balance using the Berg Balance Scale (BBS). His balance was unaffected, as represented by his BBS score of 56/56. His average inspiratory volume was 2433.34 ml, with an average peak flow of 443.34 L/min and good inspiratory effort. Functionally, he required some assistance for all his activities of daily living. There was a slight slur in his speech as well. Temperamentally, he had become quite short tempered and was irritated easily.

His brain MRI showed normal parenchyma. However, an MRI of the whole spine showed mild bulges at C3–C4, C4–C5 and C5–C6, mildly indenting of the thecal sac with no nerve root compression, indicating spondylosis. Mild disc bulges were also observed at D10–D11 and D11–D12 levels. A vertebral body haemangioma was observed at L1, and an annulus tear was observed at the L4–L5 level. Further changes characteristic of spondylosis were disc desiccation and presence of osteophytes.

Motor NCS revealed a reduced Compound Muscle Action Potential (CMAP) amplitude in the right median nerve, and a mildly reduced CMAP amplitude in the right ulnar nerve. Bilateral common peroneal and tibial nerves showed normal conduction. Sensory NCS showed normal conduction in the right median and ulnar nerves, and bilaterally in the sural nerve; F-waves were normal.

Needle EMG revealed spontaneous fasciculations in the right vastus medialis and gastrocnemius, and left tibialis anterior. Large, wide polyphasic potential morphologies with mild to moderately reduced recruitment was seen in these muscles. Right deltoid, triceps, first dorsal interosseous and abductor pollicis brevis showed fibrillation potentials, positive sharp waves and fasciculations. Voluntary activity showed large polyphasic potential morphology with moderate to severely reduced recruitment. These NCS and EMG studies indicate a widespread active and chronic motor axon degeneration. His medical history was mostly uneventful, barring the fact that he had contracted chikungunya in early 2012.

Materials and Methods

Neuroregenerative Therapy

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 (IC-SCR). The procedure was then explained to the patient in detail, and a written informed consent was obtained. An experienced team of doctors and therapists thoroughly examined the patient. Pre-surgical routine blood tests, urinalysis, and chest X-ray were carried out for assessing anesthetic and surgical fitness.

Bone marrow aspiration

300 μg of Granulocyte-Colony Stimulating Factor (G-CSF) injections were administrated subcutaneously 48 hours and 24 hours prior to BMMNC transplantation, as it enhances the mobility of BMMNCs, stimulates $CD34^+$ cells, and increases their survival and multiplication rate[23]. The patient was given local anesthesia in the region of anterior superior iliac spine; 110 ml of bone marrow was aspirated using a bone marrow aspiration needle, collected in heparinized tubes, and transferred aseptically to the stem cell laboratory.

Separation of BMMNCs

Separation of BMMNCs was achieved by differential centrifugation under aseptic conditions as described previously[24]. Briefly, bone marrow was diluted in the ratio of 1:1 with normal saline. The diluted bone marrow was subjected to density gradient separation using Ficoll-Paque media, by centrifuging it at 440 g for 35 minutes in a swinging bucket rotor without brake at 20°C. BMMNCs were obtained as a buffy coat. The BMMNCs were washed thrice with normal saline, by centrifuging at 300 g for 15 minutes in a swinging bucket rotor without brake at 20°C, and finally resuspended in 1 ml of normal saline. Viable count of the isolated BMMNCs was done using Trypan blue vital dye, which is mixed in 1:1 proportion and loaded on to the haemocytometer, for the total cell count and viable count. 8.8×10^7 BMMNCs were obtained at a viability rate of 98%. This was further confirmed by TALI cell counter. $CD34^+$ analysis was done using Fluorescence Activated Cell Sorting (FACS) using CD34 PE antibody, and was found to be 6.36%.

Administration of BMMNCs

Isolated BMMNCs were administered intrathecally immediately post separation, in L4–L5 using a 25 G lumbar puncture needle, and intramuscularly bilaterally in biceps

brachii and brachioradialis. 1 gm methyl prednisolone in 500 ml Ringer's Lactate (RL) solution was simultaneously injected intravenously, to reduce local inflammatory response and improve stem cell survival[25]. The patient was then closely monitored for any immediate adverse events during his stay at the hospital.

Neurorehabilitation Therapy

The principal emphasis of physical rehabilitation is on strengthening muscles without fatigue, improving transitions, and improving endurance as well as respiratory capacity. The patient had difficulty performing certain activities of daily living (ADL), such as bathing, dressing, toilet hygiene, feeding and eating, and sitting in bed. Thus, he was administered occupational therapy to improve vital capacity, trunk mobility, posture, and sitting balance. Since the patient's primary complaint was reduction of upper limb function, strengthening activities for upper limbs along with functional and purposeful activities for improving gross and fine motor skills were prescribed to him. Speech therapy was performed to improve oromotor function, such as proprioceptive neuromuscular facilitation (PNF) exercises. Psychological and family counseling was also performed to help the patient and his family to cope with the difficult diagnosis of ALS.

Post discharge, he was put on a home exercise program for 6 months to enhance the effectiveness of autologous BMMNC transplantation. He was prescribed 50 mg Riluzole twice a day. 300 mg Lithium was also prescribed once a day, and serum Lithium levels were maintained at 0.5 to 0.8 mmol/L.

Based on improvements seen after the first transplant, a repeat intrathecal autologous BMMNC treatment was administered 8 months later, and a total of 2.08×10^8 BMMNCs with a cell viability of 98% were injected. We did not perform an intramuscular transplantation of autologous BMMNCs at this time, because there were no significant improvements seen in the individual muscles via Manual Muscle Testing (MMT). At the time of this transplantation, the $CD34^+$ fraction was 6.48%. This was followed again by a comprehensive neurorehabilitative routine, both as described above.

Results and Discussion

3 months following the 1st autologous BMMNC transplantation, the patient's ALS-FRSr Score improved by 2 points. Choking episodes reduced. Before the first transplant, he had slight dyspnoea after walking less than a kilometer; however, 3 months after the first transplant, he reported being easily able to walk 1-2 km without any shortness of breath. Abdominal cramps stopped completely. Good voluntary control was evident by a bilateral increase in the muscle strength of neck rotators, which was maintained 18 months later as well. He showed stability in his functional activities and reported an increase in his stamina and balance; he could perform exercises and activities for longer durations of time, especially lower limb exercises. This observation dovetailed with a corresponding increase in his 6MWT distance from 396 m to 501.6 m after three months. No episodes of falls were noted in this period. Static and dynamic sitting as well as standing balance showed improvement, and walking balance was maintained. His left and right reach increased; bed mobility also improved. However, left upper limb fasciculations had increased.

8 months post first transplantation, ALS-FRSr score was maintained and improved oromotor functions were evident. Choking stopped completely, and neck pain reduced. Speech intelligibility score improved to 1 from 2 at pre-assessment. But, fasciculations had increased in both lower limbs. At this point in time, given the improvements in his condition, the patient underwent a 2nd autologous BMMNC transplantation.

3 months after the 2nd transplantation, bilateral reduction in fasciculations in the lower limbs was observed. Minimal fasciculations that were present in the upper limb also disappeared completely. Oral Peripheral Mechanism Examination (OPME) revealed normal appearance and adequate function. His Maximum Phonation Duration (MPD) and Diadochokinetic (DDK) rate was good. Muscle strength analysis revealed increased bilateral strength in extensor digitorum longus. Backward, left, and right reach improved. However, muscle wastage was noticed bilaterally in arm, neck, and scapular muscles.

6 months after 2nd cell transplant, ALSFRSr and FIM scores were maintained. Fasciculations reduced even further. Forward, backward, left, and right reach score increased. 9 months after 2nd transplant, i.e. 18 months post first transplant, his condition remained stable. Fasciculations and cramping stopped completely. Improvements in the patient's outcome measures over a period of 18 months are listed in **Table 1**, and **Figure 1 charts these outcome measures depicting his stability over time**.

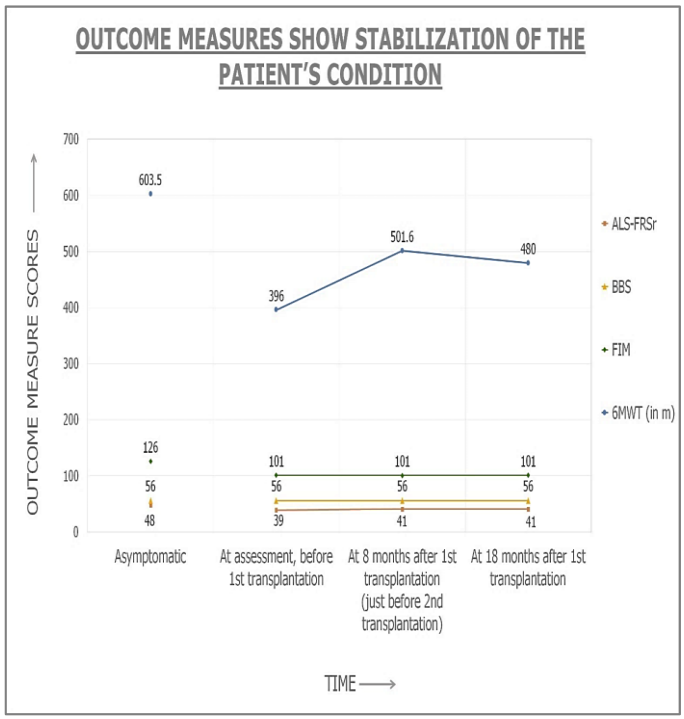

Figure 1: Various outcome measures over time.

Data points show score values measured at different intervals. Initial points indicate asymptomatic scores for each outcome, i.e. the highest possible score; these denote complete functionality. Amyotrophic Lateral Sclerosis Functional

Rating Scale—Revised (ALSFRSr) is scored out of a total of 48 points, Berg Balance Scale (BBS) is scored out of 56 points, and Functional Independence Measure (FIM) is scored out of 126 points. 6 Minute Walk Test (6MWT) distance in the asymptomatic state is the median distance obtained from values measured by Sanjak et al.[34] in healthy subjects aged 50 to 85 years, measured in meters (m). The patient also gave a history of walking over 600 m daily when he was asymptomatic. These outcome measures clearly demonstrate that the patient's condition has remained stable over time.

Outcome Measures	At Assessment, Before 1st Transplantation	At 8 Months After1st Transplantation (Just Before 2nd Transplantation)	At 18 Months After 1st Transplantation
ALSFRSr	39	41	41
BBS	56	56	56
FIM	101	101	101
6MWT (in m)	396	501.6	480

Table 1: Changes in outcome measures over a period of 18 months.

Amyotrophic Lateral Sclerosis Functional Rating Scale—Revised (ALSFRSr) is scored out of a total of 48 points, Berg Balance Scale (BBS) is scored out of 56 points, and Functional Independence Measure (FIM) is scored out of 126 points. 6 Minute Walk Test (6MWT) distance in asymptomatic healthy subjects aged 50 to 85 years is 603.5 m, which is the median distance obtained from values measured by Sanjak et al.[34], measured in meters (m).

Amyotrophic Lateral Sclerosis is a neurodegenerative disorder that selectively targets motor neurons of the spinal cord as well as the motor cortex, while sparing sensory neurons, as it progresses. The most evident hindrance to treatment is poor prognosis of this disease. Multiple factors have been implicated in promoting pathophysiology, like protein misfolding[9], glutamate excitotoxicity[26], global neuroinflammation[27], excessive nitric oxide[28], genetic mutations[29–31] , etc. This multivariate pathogenicity is the primary challenge faced by researchers globally. Multidisciplinary palliative care is the only available option in the management of this debilitating disease. Pharmacologically, Riluzole, the glutamate transmission inhibitor, is the best available treatment. However, it has a very modest effect on disease progression, and does not significantly change the quality of life or the survival duration of patients[6]. Edaravone, a free radical scavenger[32], and Nuedexta, a combination drug, have recently been approved by the USFDA for treatment of ALS[7,8]. However, these drugs do not halt the progression of the disease. A review of clinical trials for Edaravone by Takei *et al.*[33] concludes that Edaravone is effective only in the early stages of the disease. Nuedexta is prescribed for symptomatic treatment of Pseudobulbar Affect (PBA), or emotional incontinence, in ALS[7]; not for halting disease progression.

Various cellular therapies are being investigated for the treatment of ALS. In a controlled pilot study encompassing 35 patients followed over 4 months, Huang *et al.* show that although there was no significant difference in the rate of progression as measured by the ALSFRS total score during the first two months ($p>0.05$), there was significantly slower functional deterioration in the treated group than in the control group during the last two months ($p<0.05$). This study had transplanted fetal olfactory ensheathing cells (OECs) into the bilateral corona radiata involving the pyramidal tracts of the frontal lobes[34]. Long-term monitoring of 19 ALS patients enrolled in two phase-I clinical trials of autologous bone marrow derived Mesenchymal Stem Cell (MSC) transplantation by Mazzini *et al.* show that MSCs are a safe treatment modality[35]. In a phase I trial of intraspinal injections in twelve patients with ALS, Glass *et al.*[36] show that fetal-derived neural stems cells (NSC) are also safe and well tolerated by patients. Blanquer *et al*. attest for the safety of autologous BMMNCs and demonstrate the neurotrophic activities of these cells in an open single arm phase I trial for treatment of ALS[37]. We chose to work with BMMNCs given their safety and ethical approval.

Neuroregenerative Rehabilitation Therapy along with long-term Lithium is an effective, novel, multi-pronged therapeutic approach for the treatment of ALS. We have, in the past, published a study which showed that the survival duration of ALS patients, who underwent intrathecal transplantation of autologous BMMNCs, followed by 6 weeks of Lithium post intervention, was higher by 30.38 months[15] than the control group, who did not receive treatment. Subgroup analysis showed that the patients who received Lithium showed a clinically significant higher mean survival of 106.73 (±15.69) months as compared to the ones that did not receive Lithium [66.83 (±7.52) months] ($p = 0.121$). We observed that in this case, the patient—who had been on long-term Lithium following his transplantation—has remained stable, along with maintenance of functional activity, concurring with the study above; a major achievement in the face of a deteriorating diagnosis.

A study conducted by Prabhakar *et al.* treated 10 ALS patients with autologous BMMNCs intrathecally, and monitored their disease progression for a period of one year[38]. They show that the median time taken to achieve 4-point deterioration on the ALSFRSr scale was 16.7 months. In the case of this patient, not only did the ALSFRSr score increase by 2 points in a span of 6 months post intervention, but his condition also stabilized.

A study conducted by Sanjak *et al.*[39] shows that in healthy subjects aged 50 to 85 years, the mean walking distance reported during 6MWT ranged from 576 m to 631 m (median distance = 603.5 m; see Asymptomatic 6MWT data point in **Figure 1**). They also demonstrate that ambulatory ALS patients without assistive devices, like this patient, walked

significantly greater distance (418.7 ± 125 m) than ambulatory ALS patients with assistive devices, i.e. patients who had progressed in the disease (218.9 ± 108 m), thus correlating the 6MWT with disease progression in ALS. Here, the patient's 6MWT distance increased from 396 m at assessment to 480 m over 18 months. Another study by De Groot *et al.*[40] demonstrates that FIM correlates with the ALSFRS values in the different stages of ALS; in this case, the patient's FIM score remained constant at 101 over the course of 18 months.

This is a remarkable improvement, given the degenerating prognosis of ALS. The 2-point increase in ALSFRSr scale from 39/48 to 41/48, the stable FIM score (unchanged at 101/126), the increase in the 6MWT from 396 m to 480 m and the maintenance of the Berg Balance Scale at 56/56, for a stretch of 18 months, implies that the disease progression has been mitigated, in contrast to the stark natural deteriorating prognosis of ALS. Qualitatively, the patient also noted improvements in his temperament. The maintenance of the patient's condition over such an extended period of time may be attributed to the benefits of autologous BMMNC administration along with long term Lithium, rehabilitation, and standard pharmacological treatment.

The directed administration of adult autologous cells intrathecally may enhance the arsenal of neuroprotective cells that are capable of differentiation and subsequent integration into target tissue[17]. Being autologous, these cells are a safe treatment modality; and, because these are adult stem cells, they are not prone to developing tumorigenic attributes. Multiple clinical trials, in a variety of neurological ailments, have demonstrated the safety and efficacy of adult autologous BMMNCs as a therapy[12–14,41]. None of the studies have shown any major or irreversible adverse events post transplantation.

BMMNCs have been known to confer neuroprotection through various paracrine and somatic mechanisms. These cells secrete and regulate a plethora of neurotrophic factors, like ciliary neurotrophic factor (CNTF) and brain-derived neurotrophic factor (BDNF)[42], glial cell-derived neurotrophic factor (GDNF)[43], β-nerve growth factor (β-NGF)[44], vascular endothelial growth factor (VEGF)[45], tumor necrosis factor (TNF)-α and interleukins (IL-1α, IL-β, IL-6, IL-10)[46], granulocyte-colony stimulating factor (G-CSF)[47], granulocyte macrophage-colony stimulating factor (GM-CSF)[44], basic fibroblast growth factor (bFGF)[45], platelet-derived growth factor-BB (PDGF-BB)[44] and angiopoietin 1 (ANG-1)[48]. Sasaki and colleagues show that BMMNCs can differentiate into a myelinating phenotype *in vivo* and repair demyelinated CNS[49]. Transplanted adult bone-marrow derived cells have also been shown to migrate into the brain and differentiate into both glial and neuronal cell types[50,51]. BMMNCs may thus improve local microenvironment–by immunomodulation as well as integration into target tissue–and may attenuate damage caused by the disease, while restoring tissue function to an extent.

Furthermore, Lithium was prescribed to our patient, as it has long been known to improve the survival and potency of BMMNCs, as well as their integration into target tissue[18]. There have been mixed reports from clinical trials regarding the effect of Lithium by itself on ALS progression, reviewed in great detail by Gamez *et al*[52]. However, these trials varied greatly in their inclusion criteria, sample size, randomization, type of control population, primary and secondary endpoints, blinding, discontinuation criteria, analysis of results, etc. The trials with the most meaningful and robust study design and outcomes were the ones conducted by Al-Chalabi *et al.*[19] and Verstraete *et al.*[20]

The phase-3 multicenter, randomized, double-blind, placebo-controlled trial (LiCALS) by Al-Chalabi *et al.*[19] with the primary endpoint of an 18 month survival rate showed that Lithium, when administered in the therapeutic range of 0.4 - 0.8 mmol/L, is well tolerated by ALS patients who were on Riluzole; even though it may not be effective by itself for treating ALS. These results were replicated and confirmed by Verstraete *et al.* in a phase-IIb randomized, double-blind, placebo-controlled, sequential trial[20]. Importantly, however, following these trials, Yáñez *et al.* showed that Riluzole antagonizes Lithium-induced neuroprotection[53], suggesting that the potential neuroprotective activity of Lithium in the above clinical trials may have been masked by Riluzole.

We postulate that long-term Lithium administration, along with intrathecal transplantation of autologous BMMNCs, may be the key to the steady maintenance of the patient's condition. Previously, we have published a case report of a 40-year-old female diagnosed with ALS, who showed functional and neurological improvements on ALSFRSr and FIM scales over a period of 17 months post intrathecal transplantation of autologous BMMNCs, 6 weeks of Lithium and intensive neurorehabilitiation[54]. In this case, the patient showed better outcomes; these extended benefits may be attributed to long-term Lithium administration.

It is a well-established fact that Lithium increases the survival, potency and target tissue integration of BMMNCs[18], in addition to conferring neuroprotection *in vitro*[55] and *in vivo*[56] in the context of ALS. Hashimoto *et al.*[55] show that treatment of rodent cortical neurons *in vitro* with Lithium increased cellular BDNF in 3 days. BDNF plays a critical, multifaceted role in the nervous system[57]. In 5 days, the authors observed increased phosphorylation of Tyrosine receptor kinase B (TrkB—a BDNF growth factor receptor), suggesting that long-term Lithium administration enhances BDNF expression/secretion, leading to the activation of TrkB receptor. In an *in vivo* study, transgenic ALS mice treated with Lithium showed improved survival compared with wild-type mice treated with saline[56]. In a pilot study examining the effect of Lithium treatment in patients with ALS, a significant increase was seen in the Lithium plus Riluzole cohort compared with the Riluzole only cohort[56]. This clinical study reported a difference in survival at 15 months; 100% survival was observed in the Lithium plus Riluzole cohort, compared with 70% in the Riluzole only cohort. Taken together, these results suggest that long term Lithium may have played a pronounced, consequential role in the outcome of this patient.

The benefits of autologous BMMNC transplant and Lithium prescription may have been enhanced by the structured, personalized neurorehabilitative program that was customized

for our patient. Studies suggest that exercise leads to enhanced cell signaling, mobilizing stem cells into circulation, with some evidence of myocardial regeneration in patients[21]. The aim of rehabilitation was to maximize functionality, increase strength and flexibility, improve balance and coordination, and prevent fasciculations. In addition to the above, our patient was prescribed a standard Riluzole treatment at a dose of 100 mg/day as standard therapy to reduce the neurotoxic effects of excessive extracellular glutamate in the neuronal microenvironment.

Limitations

This report summarizes the totality of treatments administered to the patient. Although beneficial effects have been reported, the individual contributions of various treatment modalities could not be assessed independently. These findings must be confirmed via larger clinical trials for widespread acceptance and standardization. Another limitation is that a genetic test was not performed in this patient.

Conclusion

This case report demonstrates stabilization of a male ALS patient's condition via Neuroregenerative Rehabilitation Therapy along with long-term Lithium and Riluzole. Autologous BMMNC transplantation augmented by long term Lithium is a safe, effective therapy for ALS. This combinatorial treatment when administered in conjunction with a structured, personalized neurorehabilitative program and standard Riluzole prescription, is a novel, holistic therapeutic modality for the treatment of ALS and may have positive effects on survival duration as well as the quality of life of patients and caregivers faced with this devastating disease. The challenge for the future is to design controlled clinical studies—with large sample sizes—that standardize this therapeutic regime in attenuating disease progression in ALS.

Conflict of interest statement

The authors declare that there is no conflict of interest regarding the publication of this article.

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