Autologous Bone Marrow Derived Stem Cells for Motor Neuron Disease with Anterior Horn Cell Involvement

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Abstract

Common causes of anterior horn cell disease are poliomyelitis, motor neuron disease and spinal muscular atrophy. The primary pathology is the progressive loss of anterior horn cells. We presents a 29 year old female suffering from the motor neuron disease with anterior horn cell involvement since the last five years. She had exhausted all treatment options so was given intrathecal autologous bone marrow derived stem cell therapy as part of the neuroregenerative rehabilitation therapy protocol at our centre. The patient showed functional as well as neurological improvements after receiving the therapy. A detailed case report is presented herewith.

Introduction

Motor neuron disease (MND) is a progressive neurodegnerative disorder affecting primarily lower motor neurons of the brainstem and spinal cord and upper motor neurons of the cerebral cortex.[1] It is third most common adult-onset neurodegenerative disease, with an incidence of 1-2 per 100,000.[4,15] The vast majority of MND cases are sporadic; the aetiology of which is unknown and the pathogenesis remains elusive[5,1]

In this paper, we present a case report concerning the potential use of autologous bone marrow stem cells given intrathecally as therapeutic agents in motor neuron disease.[5,9] The therapy was given to the patient as she had exhausted all other treatment options. She received the stem cell therapy to reduce the impairment and has shown significant improvements in her muscle strength of both upper as well as lower limbs.

The neurogenerative rehabilitation therapy at our centre integrates regenerative medicine using intrathecal administration of autologous bone marrow derived mononucleocytes. (BMMNCs) and rehabilitation therapies such as, physiotherapy, occupational therapy, psychological counselling, urorehabilitation and positive reinforcement techniques such as, creative visualisation.

Recent data have implicated the microenvironment of the MN, rather than the MN itself, as primary target of the

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pathophysiology.[5,9] Putative mechanism of toxicity targeting MNs include oxidative damage, glutamate excitotoxicity, accumulation of the intracellular protein aggregation, mitochondrial dysfunction, altered glial function, and dysfunctional axonal transport. The convergence of these events is likely to promote the onset and the progression of the disease. These mechanisms represent a potential therapeutic target and many clinical trials have been developed, even though, currently none of the candidate compounds have been demonstrated to be effective.[2,6,5] Despite our improved understanding of ALS pathogenesis from the use of transgenic animal models, there are still no effective treatments or preventive strategies in humans.[2,12,3]

Recent advances in stem cell differentiation and transplantation techniques combined with the need of MND patient for new therapies prompted the exploration of stem cell for MND.[13,14,3]

Case Report

We present a 29 yr old female of motor neuron disease with anterior horn cell involvement since 5 yrs. She presented with complaints of sudden onset of weakness in bilateral lower limbs post pregnancy which was progressive in nature followed by gradual involvement of upper limbs also. On clinical evaluation she was hypotonic and hyporeflexic, with a muscle power of grade 3^- in bilateral upper and lower limbs. She had no sensory involvement with intact bladder and bowel functioning. Her bilateral upper extremities started showing median and ulnar nerve affection thereby leading to partial clawing and pointing index deformities. The patient had weak knee extensors with the power of grade 1. She needed assistance for all her activities of daily living. She could walk with a walker with a wide base of support and high steppage gait. The right quadriceps muscle biopsy was suggestive of neurogenic atrophy and reinnervation consistent with an anterior horn cell disease (AHC). EMG studies were also suggestive of AHC disease.

Material and Methods

NRRT Protocol : The NRRT protocol has been designed and the patients are selected for the therapy based on the inclusion criterion as per the world medical associations Helsinki declaration. The NRRT protocol had been reviewed and approved by the Institutional committee for Stem cell Research and Therapy (IC-SCRT). The patient was informed about the procedure and duly filled informed consent forms were obtained from the patient prior to the therapy.

Neuroregenerative Therapy

Autologous bone marrow derived MNCs were transplanted according to the NRRT protocol. Bone marrow (100 ml) was aspirated from the iliac bone. Mononucleocytes (MNC) were obtained after density gradient separation. Viable count of the isolated MNCs was taken. The MNCS were checked for CD34+ by FACS analysis. MNC were then injected intrathecally in L4-L5 using a lumbar puncture needle and catheter.[10]

Neuro Rehabilitation Therapy

The principal emphasis of rehabilitation is on assisting in movement restoration, increasing muscle strength, endurance, co-ordination and balance, to reduce spasticity and increase joint range of motion and prevent contractures. Apart from their individual impact, research shows that exercise enhances the effect of stem cells by helping the mobilization of local stem cells, encouraging angiogenesis hence; the concept of NRRT endeavours to combine the impact of neuroregeneration and rehabilitation for a better therapy outcome. The patient was given active exercises for bilateral upper limbs and lower limbs. Trunk strengthening exercises to improve her hand function like grip, grasp, release exercises were emphasized. She was given bilateral push knee splints and high boots with posterior steel shanks and made to walk on parallel bars with assistance. She was also trained for daily activities like feeding, grooming

etc.

Results

Clinical improvements were seen immediate post stem cell therapy. She was able to flex her right index finger which was not possible before SCT, her grasp improved, which in turn improved her feeding. Strength of right wrist flexor and long finger flexor improved from 3^- to 3^+ along with strength of right index finger FDS (flexor digitorum superficialis) showed improved from 2^- to 3. After 2 months of therapy, she could now flex and extend her finger bilaterally which was not possible before. She had partial clawing and pointing index attitude which was now getting corrected. She felt that the girth in her right thenar muscles have increased as compared to before. She could eat on her own with a spoon. She could move to side lying position on her own which was not possible before.

Abdominal muscle strength improved from grade 2 to 3. Her knee muscles had improved in strength bilateral from grade 1- to 2 and she could feel her knees were much stronger while standing with bilateral push knee splints. Left knee extension was possible and right knee had become stronger than before. Her bilateral feet muscles had improved in strength. Bilateral dorsi flexors have started showing flicker on voluntary contraction along with bilateral plantar flexors which improved in left from grade 0 to 1+. Bilateral hip flexors have improved in strength. Right hip flexor from grade 1+ to 3 with left hip flexors from grade 1 to 2. With bilateral knee splints and high boots with posterior steel shank, she could walk much better and her foot drop also reduced. She could walk independently after putting splints with a walker.

The electrophysiological study (EMG) done after 2 months of the stem cell therapy correlates with the clinical improvements seen post therapy. It shows evidence of single motor unit potentials being recruited on attempted voluntary contraction in bilateral Tibialis Anterior, which were absent in the previous study done three months ago (before the stem cell therapy).

In view of the significant improvements after 4 months of NRRT, the patient was given the therapy for the second time. Improvements were noticed immediately after the therapy. She could get up from lying position on her own, which was not at all possible before. Her bilateral feet movements were much better than before. Also increase in knee musculature strength was observed, especially terminal knee extension done by vastus medialis muscle.

Discussion

MND is a devastating untreatable, fatal neuromuscular disease caused by reduced distribution of MNs leading to a loss of both upper and lower motor neurons.[6] The selective motor neuron degeneration observed in motor neuron disease pathogenesis is speculated to be partially due to the vulnerability of motor neurons.[15] These cells may be at a higher risk due to their high metabolic activity, low levels of reduced glutathione and high levels of unsaturated lipids on their large membrane surfaces along axons. These risk factors presumably contribute to an increased susceptibility to oxidative damage.[3,8] The release of trophic factors directly promote neuroprotection with decreased inflammation and restores lost and affected motor neurons. Autologous bone marrow stem cell transplantation is a potential therapeutic strategy for motor neuron disease. It results in replacement of affected motor neuron as well as the activation of molecular and cellular mechanisms that support endogenous neuronal regeneration and protection

against degeneration. Thus ultimately increasing the lifespan of the patients.[7] A number of potential benefits of stem cells in MND therapy have been demonstrated in experimental models.[5,15,16]

The patient reported in this case report showed features suggestive of pure motor system involvement affecting lower motor neurons. She had exhausted all treatment options before resorting to stem cell therapy. In view of the different approaches to stem cell therapy, it is mandatory to develop feasible and reliable methods of delivery. Proposed approaches include direct cell transplantation into the CNS parenchyma, replacement of dysfunctional astroglia, over activated microglia, intravenous, intraspinal, intraperitoneal or intrathecal delivery and combined strategies. Which aim at increased number of neuromuscular connections, decreased pro-inflammatory cytokines in brain and spinal cord, increased levels of MN bodies, decreased microglia and astroglia density and promote migration and differentiation of endogenous neuronal precursors.[3,5,9] At our centre the patient was given autologous bone marrow stem cells intrathecally and post therapy several improvements were noticed, as stated above. Many potential therapies for MND, ranging from drugs for anti-inflammation, anti-oxidation and anti-apoptosis, to providing trophic factors, have been unsuccessful in human clinical trials.[12,9] The only FDA-approved medicine for MND is Riluzole which acts as an anti-excitotoxicity agent and provides a marginal effect by prolonging lifespan for approximately two to three months.

Conclusion

Autologous intrathecal transplantation of bone marrow stem cells (BMSCs) fully circumvents the problem of immune rejection, as it does not cause the formation of teratomas and bears no ethical concerns. Preclinical studies have shown the effectiveness and positive safety profile of treatment with autologous bone marrow stem cells.[15,5,11] At our centre the patient was treated with autologous bone marrow stem cells as a last resort to decrease her disability. Immediately post therapy the patient showed motor improvements as mentioned above. This case report, thus represents a proof of principle that stem cell therapy via intrathecal delivery of autologous bone marrow derived stem cells is a feasible strategy for treating the disability in MND.[5]

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SCREENING FOR PROSTATE CANCER

The analysis of six randomised controlled trials, including the PLCO and ERSPC studies, found that screening increased the probability of being diagnosed with prostate cancer (relative risk 1.46, 95 % confidence interval 1.21 to 1.77) but had no significant effect on mortaily from prostate cancer (0.88, 0.71 to 1.09) or over-all mortality (0.99, 0.97 to 1.01).

In addition to the uncertain benefit on mortality, the human and economic costs associated with PSA based screening are substantial, mainly as a result of "overdiagnosis" and "over-treatment". To date, methods of reducing overdiagnosis and overtreatment of indolent tumours have included the use of 5α reductase inhibitors as an adjunct to PSA testing and "active surveillance" programmes for small "low risk" tumours.

Identification of cancer specific genes in cells sloughed into the urine after prostatic examination, which is now feasible with the commercially available PCA3 test, may reduce the number of benign biopsies in men whose increased PSA concentration is caused by benign prostatic hyperplasia, and identification of aggressive prostate cancer by its molecular signature should help clinicians decide which prostate cancers need aggressive treatment.

Young men at high risk of prostate cancer, such as those with a strong family history and higher baseline PSA concentrations, should be followed closely and could also be considered for "risk reduction" approaches with 5α reductase inhibitors or dietary and life-style modifications (or both).

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