CASE REPORT

Administration of Autologous Bone Marrow Stem Cells Intrathecally in Multiple Sclerosis Patients is Safe and Improves their Quality-of-life

A Sharma*, P Badhe**, N Gokulchandran*, P Kulkarni**, VC Jacob†, M Lohia†, J George Joseph†, H Biju†, Guneet Chopra**

ABSTRACT

Multiple sclerosis (MS) is widely believed to be an autoimmune disorder characterized by multifocal lesions of the central nervous system (CNS) myelin and accumulating clinical signs due to axonal damage. Persistent loss of myelin can make axons more vulnerable to repeated injury, induce axons to make compensatory changes in their properties that can result in further delayed insults to the axon. Autologous hematopoetic stem cell transplantation (HSCT) has been used as a treatment for MS. Stem cells have the ability to greatly assist in regenerating the damaged glial cells. We present herein a case of a patient who underwent transplant twice to improve his disability.

Key words: Multiple sclerosis, autologous, bone marrow, stem cells

Converging lines of evidence suggest that multiple sclerosis (MS) is widely believed to be an autoimmune disorder characterized by multifocal lesions of the central nervous system (CNS) myelin and accumulating clinical signs due to axonal damage.[1] Myelin is damaged due to an immune attack consisting of several pathways and molecules, leading to impaired nerve function. When myelin is damaged, electrical impulses cannot travel quickly along nerve fiber pathways in the brain and spinal cord. Disruption of electrical conductivity results in fatigue and disturbances of vision, strength, coordination, balance, sensations and bladder and bowel function. Autoantibodies and autoreactive T cells activated against myelin antigens such as myelin basic protein (MBP), proteolipid protein (PLP) and myelin oligodendrocyte glycoprotein (MOG), have been detected in MS patients.[2] This disease constitutes one of the most prevalent CNS disorders, progressive and chronic destruction of the nervous system.[3]

MS is most frequently characterized by a relapsing and remitting clinical course in which the affected individuals develop one or more neurologic deficits, which then resolve partially or completely over subsequent days or weeks. These relapses reflect the development of new lesions within the CNS as visualized by magnetic resonance imaging (MRI). The persistent absence of myelin contributes to the ongoing loss of axons, the apparent basis for the progressive nature of MS in some cases. Persistent loss of myelin can make axons more vulnerable to repeated injury, induce axons to make compensatory changes in their properties (changes ion channel expression) that can result in further delayed insults to the axon and remove the supportive factors required for long-term axonal survival. Autologous hematopoietic stem cell transplantation (HSCT) has been used as a treatment for such autoimmune diseases.[4] Stem cells seem to have the ability to greatly assist in regenerating the glial cells, injured and destroyed in MS. We describe a man who presented with a limp in the leg and some loss of dexterity in upper limb. The MRI of the patient also confirmed the diagnosis of MS. He underwent the transplant twice in a period of 10 months to improve his disability.

Case Report

We present a 32-year-old male with MS for last six years who underwent neuroregenerative rehabilitation therapy (NRRT) at our center after he had exhausted all other treatment options. The aim of NRRT is to reduce impairment and improve functionality. He had a history of multiple episodes of optic neuritis in both

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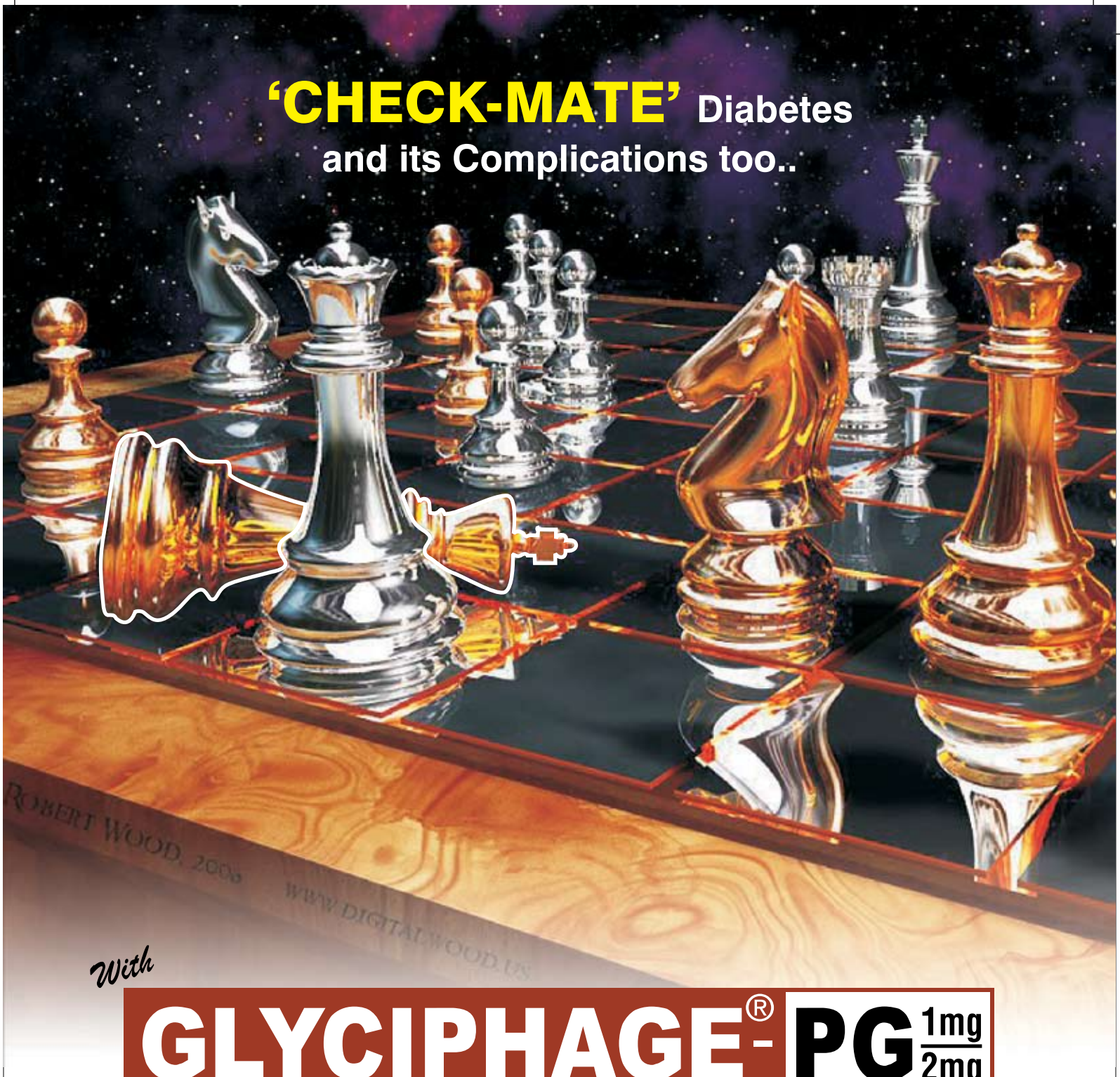

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eyes and weakness of limbs, which was treated. He had a limp in the left leg and some loss of dexterity in left upper limb. His pupils were reacting and vision was normal. The left hand showed mild weakness and power in left ankle and toes was impaired. Left upper limb showed a mild intention tremor and he had a circumductory gait in left lower limb. His speech and writing were affected. Prior to NRRT, the MRI of the patient showed fairly large amount of periventricular plaques with gross atrophy of the brain parenchyma including corpus callosum, two fresh plaques in the right anterior peritrigonal white matter and left paramedian position of pons (Fig. 1). Before NRRT, the patient was assessed neurologically and functionally using the Kurtzke Expanded Disability Status Scale (EDSS), Fatigue Severity Scale (FSS) and Functional Independence Measure Scale (FIMS). On FIM, he scored 126 and EDSS score on Kurtzke scale and FSS score was found to be 1.0 and 2, respectively prior to the stem cell therapy. In view of the clinical improvements seen after the first NRRT, he underwent NRRT for the second time after 10 months. During the second treatment, cells were injected in his left leg muscles (Tibialis anterior, peroneus longhouse and peroneus brevis) as well.

Material and Methods

Patient selection and protocol design was based on the inclusion criterion as per the World Medical Associations Helsinki declaration. The 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 a duly filled informed consent form was obtained from him. Blood tests, MRI were performed one week before the transplantation. The investigations were repeated prior to the second transplant as well. G-CSF injections were administrated 48 hours and 24 hours before bone marrow derived stem cell transplantation. Autologous bone marrow derived mononucleocytes (MNCs) were transplanted according to the NRRT protocol. Bone marrow (100 ml) was aspirated from the iliac bone. MNCs were obtained after density gradient separation. Viable count of the isolated MNCs was taken. The MNCS were checked for CD34+ by FACS analysis. Approximately 57×10^6 MNCs were immediately injected post separation, intrathecally in L_4-L_5 using a lumbar puncture needle and catheter. Methylprednisolone in doses of 30 mg/kg was administered intravenously over 30 minutes during the injection of the stem cells. Along with neuroregeneration, the patient also received neurorehabilitation, occupational therapy and speech therapy. This therapy emphasizes on taking advantage of the brain's capacity for repair and recovery. Rehabilitation interventions seek to promote recovery and independence through neurofacilitation.[5] During rehabilitation sessions, effective motor learning strategies with task oriented training, for real life environment were utilized and successful attainment of functional outcomes were achieved. 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.[5]

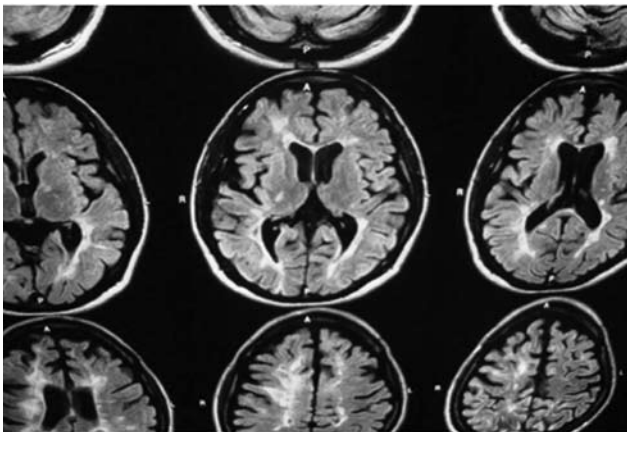

Figure 1. MRI before the stem cell therapy.

Result

After the first stem cell therapy, the patient had no side effects and was evaluated at regular time periods; at one month, three months and six months. On follow-up, his left foot muscles improved in strength, especially the extensor hallucis longus. The circumduction of the left foot while walking had reduced. After the second stem cell therapy, he could move his left foot better and actively. He could dorsiflex it now, which he could not do earlier due to the foot drop. His limping while walking had reduced comparatively' he could jog easily now. His motor activity and handwriting had improved. According to the patient his quality-of-life had improved post stem cell therapy; he had become more confident now as compared to earlier. The MRI was repeated 10 months post stem cell therapy and it did not show any new plaques (Fig. 2).

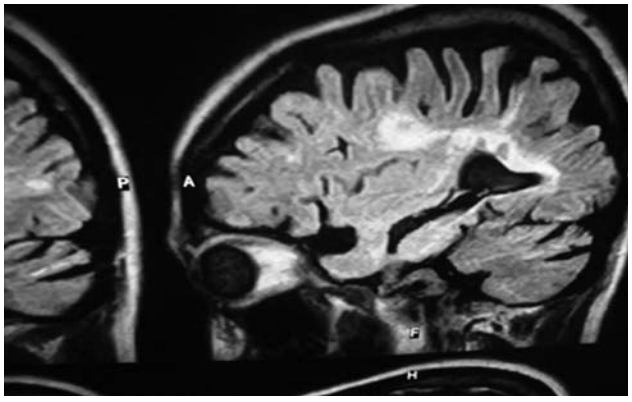

Figure 2. MRI post stem cell therapy.

Discussion

MS is one of the most common neurological disorders, which mainly affects young adults and causes gradual decrease of their QOL. The clinical course of the disease is very heterogeneous.[6] The cause of multiple sclerosis is unknown, but evidence suggests that the disease may result from an environmental agent that triggers the illness in a genetically susceptible individual. These lines of evidence have given rise to both environmental and genetic explanations for MS. Studies of the natural history of MS suggest that there are different patterns of disease activity. Some patients have rare attacks, some have frequent attacks, and others gradually but steadily worsen without experiencing attacks.

Conventional therapies did not provide satisfactory control of MS due to their inability to eradicate self-specific T-cell clones.[7,8] Hence, adult stem cell (autologous bone marrow derived MNCs) transplantation was carried out. The adult bone marrow stem cells *per se* have no side effects and are very safe. These MNCs obtained from bone marrow, comprise of a variety of cells like hematopoietic stem cells, tissue specific progenitor cells, stromal cells and specialized blood cells in different stages of development. We hypothesize that transplanted cells affect the brain of the recipient via a complex mechanism, but the leading role can be allocated to the production of neurotrophic factors, differentiation, transdifferentiation of stem cells and transmitters stimulating the formation of new blood vessels and improving cerebral hemodynamics.[9] Neurotrophic factors can stimulate functional activity of nerve cells and brain structures. The G-CSF and methylprednisolone administered before and during the transplantation respectively have been shown to stimulate CD34+ cells and also increase the survival and multiplication potential of the stem cells. The other possible therapeutic role of stem cells reported is the formation of new synaptic interactions with existing neurons and their participation in neural transmission. Intramuscular injection of MNCs during the second transplant resulted in significant improvements. The drag in the leg was reduced considerably. As the patient was quite independent in his daily activities he did not show any change on the EDSS score on Kurtzke scale, FSS score and FIM score. But, his QOL had improved comparatively after the treatment.

Conclusion

The present data provides clear evidence that autologous HSCT along with neurorehabilitation can result in significant improvements in the case of relapsing-remitting multiple sclerosis with no side effects. Further studies are required to substantiate this.

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