This article was originally published in a journal by OMICS Publishing Group, and the attached copy is provided by OMICS Publishing Group for the author's benefit and for the benefit of the author's institution, for commercial/research/educational use including without limitation use in instruction at your institution, sending it to specific colleagues that you know, and providing a copy to your institution's administrator.

All other uses, reproduction and distribution, including without limitation commercial reprints, selling or licensing copies or access, or posting on open internet sites, your personal or institution's website or repository, are requested to cite properly.
Autologous Bone Marrow Derived Mononuclear Cell Therapy for Vascular Dementia

Sharma A¹, Badhe P², Gokulchandran N¹, Kulkarni P³*, Sane H², Lohia M², Avhad V¹ and Shetty A³

¹Department of Medical Services and Clinical research, NeuroGen Brain and Spine Institute, Surana Sethia Hospital and Research Centre, Suman Nagar, Sion-Trombay Road, Chembur, Mumbai, Maharashtra, India
²Department of Research and Development, NeuroGen Brain and Spine Institute, Surana Sethia Hospital and Research Centre, Suman Nagar, Sion-Trombay Road, Chembur, Mumbai, Maharashtra, India
³Department of Neurorehabilitation, NeuroGen Brain and Spine Institute, Surana Sethia Hospital and Research Centre, Suman Nagar, Sion-Trombay Road, Chembur, Mumbai, Maharashtra, India

Abstract

Background: Vascular dementia affects a broad spectrum of patients with various manifestations of cognitive decline, which are attributed to cerebral or cardiovascular disease. Laboratory studies have shown that transplanted bone marrow stem cells improve neurological diseases of the central nervous system by generating neural cells or myelin-producing oligodendroglial cells and enhancing neural plasticity. But till now, there has been lack of objective data in the form of investigational findings providing evidence for clinical improvements.

Method: We present a case of a 61 year old woman diagnosed with vascular dementia, who was administered autologous bone marrow derived mononuclear cells, intrathecally.

Result: Even after follow up of 2 years she showed sustained significant clinical improvements recorded by MMSE and FIM along with corroborating changes in PET CT scan of brain showing significantly improved metabolic activity.

Conclusion: Thus, demonstrating objective evidence showing benefits of neuroregeneration rehabilitation therapy in vascular dementia.

Keywords: Vascular; Dementia; Autologous; Bone marrow; Mononuclear cells; PET CT

Introduction

Vascular dementia (VaD) includes progressive loss of cognitive functions, evidence of cerebrovascular disease on brain imaging, focal signs of cerebrovascular disease and temporal relationship between stroke and dementia [1]. It results in an intellectual deficit which has a further significant impact on daily living, independence and relationships.

Interventions for vascular dementia are possible at a number of levels: primary prevention, secondary prevention, symptomatic treatments and disease modifying or curative approaches. There are various pharmacologic and nonpharmacologic therapies which have been tried as a treatment options. Currently, the medicines available are cholinesterase inhibitors, N-methyl-D-aspartate (NMDA) antagonists, and anti-depressants. Primary and secondary prevention is attempted by modification of vascular risk factors such as hypertension, hyperlipidemia and lifestyle. The drugs, cholinesterase inhibitors and memantine bring about only small cognitive improvements without global clinical outcomes and are also associated with adverse effects. Selective serotonin reuptake inhibitors and dihydropyridine calcium channel blockers may improve cognition only for a short-period [2]. Hence, at present there is no definitive treatment for VaD. Recently, studies have been carried out to demonstrate the beneficial effects of bone marrow derived stem cells in dementia.

We describe a case of vascular dementia, which underwent autologous bone marrow derived mononuclear cell transplantation.

Materials and Methods

We present a right handed, 61 year old South Asian woman from India with a past medical history of hypertension and vascular dementia since 2002, showing history of incoordination and imbalance while walking and a wide based gait. There was a noticeable deceleration in all her movements. Her orientation in time, place and person was also affected with apraxias. She noticed difficulty in swallowing, along with dysarthria and was emotionally labile. Gradually, she developed loss of short-term memory and decline in higher functions. Functionally, she required assistance for activities of daily living and supervision while walking and climbing stair. On the Functional Independence Measure (FIM), she scored 75/126. On psychological assessment using mini mental state examination (MMSE), she scored 10/30.

She was on neuroprotective medications such as Rivotril, Syndopa and Pramipexol. She underwent rehabilitation including physiotherapy, occupational therapy for over 4 years, but her symptoms continued to deteriorate.

On investigation, her CT scan showed diffuse cerebellar and cerebral atrophy while her MRI scan showed generalized cerebral and cerebellar volume loss. Small ischemic foci were also noticed in the bilateral frontal white matter (Figure 1). Angiography showed mild diffuse narrowing in M2 segment of right middle cerebral artery.

*Corresponding author: Kulkarni P, Department of Research and Development, NeuroGen Brain and Spine Institute, Surana Sethia Hospital and Research Centre, Suman Nagar, Sion-Trombay Road, Chembur, Mumbai-400071, Maharashtra, India, Tel: 022-25281610/25283706; E-Mail: poojakul28@gmail.com

Received October 16, 2012; Accepted November 02, 2012; Published November 04, 2012


Copyright: © 2012 Sharma A, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
improved from 13/30 to 16/30 at 6 months follow up and finally to 20/30 at the end of 2 years. Her FIM score improved from 75 to 80 after 2 years.

In addition, the PET scan repeated after 2 years, showed moderate reduced uptake of FDG only in the Wernicke’s area, theinsula, the lateral temporal and lobulus quadrilatere areas of the right hemisphere in the brain (non-dominant side). While the rest of the brain showed normal FDG uptake (Figure 2B).

Discussion

VaD is considered as the second most common cause of dementia in the elderly after Alzheimer’s disease [4]. Between 1 to 4% of people over 65 years suffer from VaD [5].

It is assumed to be the outcome of lesions in the vascular distribution of the posterior or anterior circulation, which causes alterations in awareness, memory deficits, and abulia and may also produce disturbances in neuropsychological testing [6].

Inspite of being a common condition, there are no effective approved pharmacological treatments available. Large randomized studies have been carried out for the symptomatic treatment of probable and possible VaD which includes studies of the anticholinesterase donepezil in VaD [7], the NMDA receptor antagonist memantine and a study of the anticholinesterase galantamine [8,9]. Experimental studies have also been carried out to demonstrate the efficacy of stem cells for vascular dementia and other neurological disorders [10-12]. Studies have shown that the bone marrow-derived stem cells are mobilized from bone marrow and home into the injured brain [13].

Experiments in rats suggest that bone marrow derived mesenchymal stem cells (BMSCs) transplanted into the subventricular zone (SVZ) most likely function for a short term, by interacting with the host brain and stimulating recovery of impaired brain function [14]. BMSCs have been shown to secrete an array of neurotrophins, growth factors, and other supportive substances such as BDNF, NGF, VEGF and glia derived neurotrophic factor. This can help in improved survival of the neurons through facilitation of neuroprotective responses such as angiogenesis, axonal guidance and regeneration, which may further result in improved cognitive function of aging vascular dementia in rats [14]. CD34 antigen is present on immature hematopoietic precursor cells and all hematopoietic colony forming cells in bone marrow and blood, including unipotent and pluripotent progenitors. The number of CD34+ cells is greater in bone marrow than peripheral blood. Circulating bone marrow-derived immature cells like CD34+ cells have also been implicated in homeostasis of the cerebral microvasculature. Decreased levels of circulating CD34+ cells correlate with poor clinical outcomes in patients with cerebrovascular disease. Clinical trials with local transplantation of bone marrow-derived immature cells for such patients have been shown to improve impaired microcirculation [10].

The cumulative effect of two doses of autologous bone marrow derived mononuclear cells in this patient of progressive vascular dementia revealed cognitive improvement as noted on functional and neuropsychological assessment. Further, the changes on PET scan are an evidence of the clinical changes seen [15]. Hypometabolic areas such as the parietal lobes, frontal lobes, thalam, basal ganglia and temporal lobe are seen to have reached a near normal metabolic state. This normalization of metabolism leads to speculation regarding the role of the stem cells in achieving balance in the brain functioning, possibly through the above mechanisms.
Though this is just a solitary case and more evidence, in terms of numbers, needs to be gathered, it does point towards the feasibility and possible potential of the use of autologous mononuclear cell transplantation for stalling the progression of dementia.

References


