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CASE REPORT

APPLICATION OF AUTOLOGOUS BONE MARROW STEM CELLS IN GIANT AXONAL NEUROPATHY

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ABSTRACT

Giant axonal neuropathy is a rare disorder of autosomal recessive inheritance, morphologically characterized by accumulation of neurofilaments in enlargements of preterminal regions of central and peripheral axons. We present a 7-year-old girl with thick and tightly curled lackluster hair suffering from giant axonal neuropathy. The diagnosis was confirmed on the brain MRI which showed white matter abnormalities in the anterior and posterior periventricular regions as well as the cerebellar white matter. In view of the same, the patient was given intrathecal autologous bone marrow-derived stem cell therapy as part of the neuroregenerative rehabilitation therapy protocol. The patient showed functional improvements in her disability after receiving the therapy. A detailed case report is presented here with.

Key words: Bone marrow or stem cells, giant axonal neuropathy, peripheral nervous system diseases and axons/pathology

INTRODUCTION

Giant axonal neuropathy (GAN) is characterized by slowly progressive central-peripheral distal axonopathy.[1] It has an early onset, and appears in children between the ages of 3 and 5 years. GAN is a severe autosomal recessive disorder caused by the mutation of the GAN gene on chromosome 16q24.1.[2] The defective protein in GAN seems to play a central role in the maintenance of the intermediate filament (IF) integrity.[3] GAN results from mutations in the GAN gene, which codes for the protein gigaxonin. This alters the shape of the protein, changing how it interacts with other proteins when organizing the structure of the neuron.

We report a case of GAN administered with autologous bone marrow stem cells.

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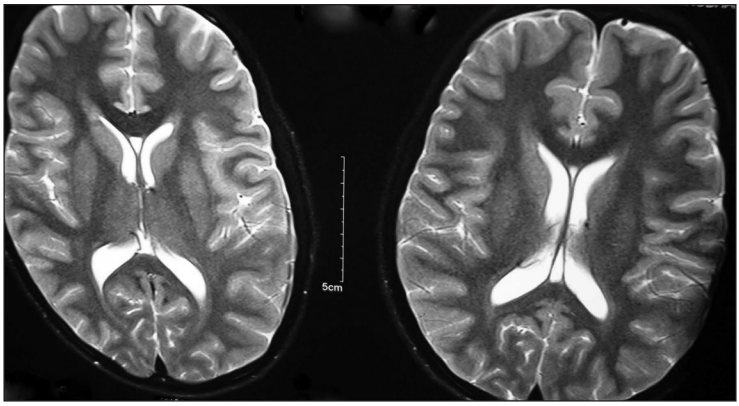

Figure 1: MRI of the brain demonstrated white matter abnormalities

Figure 2: MRI of the spine showing thinning of the myelin sheath

CASE REPORT

We present a 7-year-old girl with GAN with a history of delayed milestones. Gradually, she developed Equinus and flat foot deformity and showed characteristic thick and tightly curled lackluster hair. She presented with right foot drop and Genu Valgum while walking. She had a history of frequent falls while walking and running. On evaluation her skin biopsy showed an increase in IFs while the nerve biopsy showed several bloated axons of which some lacked the myelin sheath. MRI of the brain demonstrated white matter abnormalities in the form of altered signals on T2 sequences in the anterior and posterior periventricular regions as well as the cerebellar white matter [Figures 1 and 2].

MATERIALS AND METHODS

Patients selection and protocol design has been based on the inclusion criterion as per paragraph 32 of the World Medical Associations Helsinki declaration.[4] The protocol had been reviewed and approved by the Institutional committee for Stem cell Research and Therapy. The parents were informed about the procedure and a duly filled informed consent form was obtained from them. Blood Tests, MRI were performed 1 week before the transplantation. G-CSF (150 mcg) injections were administrated 48 h and 24 h subcutaneously, before bone marrow-derived stem cell (BMSC) 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. A viable count of the isolated MNCs was taken and was found to be

98%. The MNCS were checked for CD34+ by FACS analysis and its percentage was found to be 0.06%. Approximately 10×10^7 MNC were immediately injected post-separation, intrathecally in L4-L5 using a lumbar puncture needle and catheter. After cell transplantation, she underwent an intensive rehabilitation program. This therapy emphasizes the role of stem cells in taking advantage of the brain's capacity for repair and recovery. Rehabilitation interventions seek to promote recovery and independence through neurofacilitation.

DISCUSSION

GAN results from autosomal recessive mutations that affect cytoskeletal organization; specifically, IFs are found collapsed into massive bundles in a variety of different cell types.[5,6] Neurons affected by the altered protein accumulate excess neurofilaments (NFs) in the axon. These enlarged or "giant" axons cannot transmit signals properly, and eventually deteriorate, resulting in the range of neurological anomalies associated with the disorder. GAN is characterized by the presence of enlarged axons that present unusual thin myelin sheets according to their size. Such giant axons are filled with abnormally densely packed NFs that lack their normal parallel orientation along the axis of the axon.[7] Studies have shown abnormal accumulation of cytoplasmic IFs in various cell types. These IF bundles first appear distally in neurons that project into the periphery; as the disease progresses, central neurons that do not project into the periphery can also become affected.[1] GAN is associated with a characteristic "thick and tightly curled lackluster hair" abnormality, which is of interest because hair is also composed of epithelial IF.[8] Diagnosis of GAN is established by clinical findings including nerve conduction velocity (NCV), brain MRI, and peripheral nerve biopsy. Our case demonstrated the typical signs of GAN with thick and tightly curled lackluster hair.

Our goal is to promote the recovery of neural function which requires close integration of neuroregeneration and neurorehabilitation therapies. Since, many potential therapies have not been successful in treating the disorder, adult stem cell (autologous bone marrow-derived MNCs) transplantation was carried out. These cells in per se have no side effects and are very safe. Bone marrow contains multipotent cells that can be cultivated *in vitro*. These cells are called stem cells. They are easily isolated from patients themselves thereby bypassing the ethical problems associated with embryonic stem cells, and can easily be administered to the patients for auto-transplantation. Hence, they are a suitable candidate for use in cell-based therapy. The mechanism of recovery includes neuroprotection, creation of a favorable environment for regeneration, expression of growth factors or cytokines, vascular effects, or remyelination. These mechanisms are not mutually exclusive, and it is likely that more than one contribute to functional recovery. BMSC have a potential to differentiate into local cells in response to environmental signals and cues, they are known to home onto the site of injury and help in repair, they also promote angiogenesis, thereby acting as conduits for delivery of necessary trophic factors.

Recent advances in stem cell differentiation and transplantation techniques combined with

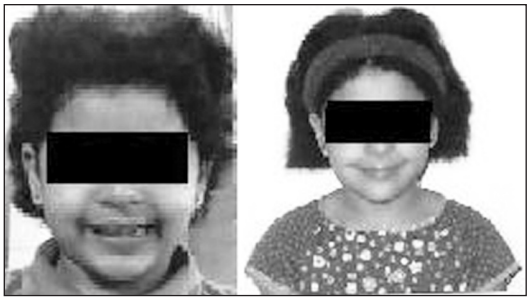

Figure 3: The patient showing thick and tightly curled lackluster hair before the therapy and showing improved hair texture post therapy

the need of GAN patients for new therapies prompted the exploration of stem cells.

This treatment showed significant improvements in the case. After the stem cell therapy, the patient had no side effects and was evaluated at regular time periods of one month and three months. On follow up, it was observed that her stability had improved, and her hand grip improved which helped in improving her handwriting as well. She could run on the ground without falling and her stamina had improved significantly. Drooping of shoulders decreased. Her hair appeared softer and straighter as compared to the earlier tightly curled hair [Figure 3].

The present data provide clear evidence that autologous hematopoietic stem cell transplantation along with neurorehabilitation can result in significant improvements in the case of GAN with no side effects, as this therapy is to treat the disability and not the disease.

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