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Case Report 1

Autologous Stem Cell Therapy in Acute Motor Sensory Axonal Neuropathy

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Abstract

Guillain-Barré Syndrome is a heterogeneous group of immune-mediated peripheral neuropathies. The Acute Motor Sensory Axonal Neuropathy (AMSAN) variant is characterized by axonal degeneration with myelin sparing in both motor and sensory nerves. Despite low incidence, AMSAN variant is more severe and is associated with the longer recovery period. This report describes a case of AMSAN unresponsive to conventional therapy. Our treatment protocol comprised of autologous mesenchymal stem cell therapy and neuromuscular rehabilitation, which resulted in shorter duration of recovery along with improved functional outcomes.

Introduction

Guillain-Barré Syndrome (GBS) refers to a heterogeneous group of immune-mediated peripheral neuropathies. The syndromes consist of demyelinating and acute axonal degenerating forms of the disease. Earliest found data of the condition, based on a report by Landry in 1859, referred to GBS as 'ascending paralysis'[1]. The syndrome was named in 1916 after Guillain, Barré, and Strohl, reported cases of motor weakness, areflexia, increased cerebrospinal fluid protein levels in French soldiers [2] Epidemiological studies suggest an annual incidence of 1-3/100,000 individuals with bimodal age distribution, wherein the condition peaks in young adults and the elderly [3,4]. Studies have reported male predilection in GBS, the incidence being 1.5 times higher than that among females [5].

Table: Four forms of Guillain-Barré Syndrome

Acute inflammatory demyelinating polyneuropathy	**Acute motor axonal neuropathy**	**Acute motor and sensory axonal neuropathy**	**Miller Fisher Syndrome**
Most common form accounting for 85-90% cases of GBS	Axonal degeneration in motor nerves	Low incidence. Indicates axonal degeneration of both sensory and motor nerves	Clinical triad of ophthalmoplegia, ataxia, and areflexia
Known to be preceded	Triggered by C. jejuni, Hemophilus influenza		Preceded by C. jejuni infection

by Cytomegalovirus, Epstein-Barr virus, Mycoplasma pneumonia infection	infection	
Shows prominent lymphocytic infiltration of peripheral nerves and macrophage invasion of myelin sheath and Schwann cells	The paucity of lymphocyte infiltration, lengthening of nodes of Ranvier followed by macrophage recruitment in the nodal region. Myelin sparing noted.	Antiganglioside antibodies expressed in nodal regions of oculomotor nerve
Slowing of nerve conduction in motor nerves suggestive of demyelination	Pure motor/sensory/both axonal degeneration without demyelination, indicative of immune response directed against axonal membrane	Discrete changes in sensory conduction may be observed

Bacterial or viral infection commonly precedes the occurrence of GBS. Campylobacter jejuni infection has been implicated as a common gastrointestinal antecedent in acute motor or acute motor-sensory axonal neuropathy [6]. Upper respiratory tract infection has also been shown to occur prior to the onset of neurological symptoms of GBS. The interval between infection and onset of symptoms of GBS is between 1-3 weeks. The condition occurs suddenly, usually with no or minimal symptoms prior to the onset. Weakness and/or tingling sensation in legs are the initial complaints reported. Symptoms gradually increase in severity and lead to partial or total paralysis of muscle groups. GBS is especially life-threatening if respiratory muscles are involved. Symptoms progress over days to weeks following which recovery begins. The mortality rate in GBS is approximately 8% and around 20% individuals remaining disabled throughout life [7]. Recurrence may occur in 1-10% patients after an asymptomatic period of several months to years [8, 9].

Acute motor sensory axonal neuropathy (AMSAN) is considered to be a rare variant of GBS showing <10% incidence compared to acute motor axonal neuropathy form [10]. However, AMSAN variant follows a more severe clinical course and is characterized by acute onset of distal weakness, loss of deep tendon reflexes and sensory symptoms. Intravenous immunoglobulin and/or plasmapheresisis the treatment of choice for this variant of GBS; however, recovery is slower compared to other variants of GBS.

We present a case report of a patient suffering from acute motor sensory axonal neuropathy since one year treated with autologous mesenchymal stem cells.

Case report

A sixty years old female patient had complained of sudden weakness in her legs and had collapsed without any obvious signs before one year. She was completely unable to move her limbs and lay on the floor until her family came to her aid. The patient was taken to a hospital wherein she was diagnosed as a case of Guillain-Barré Syndrome following investigations. Conventional treatment was started immediately and the patient was hospitalized for a week. Following discharge from the hospital, she was advised to undergo regular physiotherapy to aid her regain some degree of muscle strength. However, no improvement was observed in the patient's condition, and she remained bed-ridden even 8-9 months after routine conventional as well as alternative treatment modalities and physiotherapy.

The patient is a case of Acute Motor Sensory Axonal Neuropathy (AMSAN). She underwent thorough clinical, hematological and radiographic evaluation at our hospital and was considered a suitable candidate for cell-based therapy. The assessment by the physiotherapist revealed:

- Areflexia in ankle and knee joints,
- Bilateral grade zero muscle power in lower limbs,
- Bilateral grade three muscle power in upper limbs,
- Inability to sit for more than a minute without support.

The patient was designated Score four (Bed or chair bound) based on Hughes functional grading scale for GBS. Informed consent was obtained from the patient after explaining details of cell-based therapy. The goal of treatment was to utilize the neuroprotective and other properties of mesenchymal stem cells to enable the patient regain muscle strength and reflexes and thereby overall quality of life.

Three sessions of autologous mesenchymal stem cell therapy was advised over a period of two months. Platelet Rich Plasma (PRP) therapy, which is an autologous platelet concentrate consisting of variety of growth factors, was also advised. Intensive rehabilitation protocol was followed in the form of physiotherapy exercises and neuromuscular stimulation.

Results

One week following cell-based therapy and rehabilitation program, mild improvement in muscle power grade was observed. The patient was able to sit for up to three minutes with support. Over the course of one month, further improvement in muscle power grade was observed in quadriceps (Grade 1-2) and Grade 4+ in upper limbs. She was now able to sit up by herself or with minimal support. By the end of the second month, ambulation was possible with aid of push knee brace and walker. The most significant improvements were with respect to excellent back control and maintenance of balance and equilibrium on standing. Post treatment Hughes functional grading scale improved by one point to Score three (Able to walk 5m with a walker or support).

Discussion

Guillain-Barré Syndrome is an acute peripheral neuropathy that progresses over weeks and results in limb weakness. AMSAN variant is associated with presence of macrophages in proximity to axons with relative sparing of myelin in both motor and sensory nerves [11]. Axonal variants of GBS are characterized by paucity of lymphocyte infiltration, lengthening of nodes of Ranvier followed by macrophage recruitment in the nodal region. Distortion of paranodal axons and separation of myelin from axolemma occurs. The ultimate result is reversible condensation of axoplasm [12]. In severe cases, Wallerian-like degeneration may occur resulting in longer recovery period when compared to the demyelinating variant of GBS [13].

In the present case, acute onset of GBS was following a viral infection. Studies have reported shorter recovery time in patients with GBS after intravenous immunoglobulin therapy when administered in early stages of GBS [14, 15]. Nonetheless, a persistent deficit in such patients has not shown improvement following either plasmapheresisor immunoglobulin therapy. Cell-based therapy along with intensive neuromuscular rehabilitation resulted in significant improvement in clinical outcomes in the present case, which was not achieved through conventional therapies.

Immune system dysregulation may be speculated to be responsible for initiation of attack on the nervous system. Therefore, immune-modulatory ability of mesenchymal stem cells may be beneficial in management of cases with GBS. Mesenchymal stem cells (MSC) owing to their properties of self-renewal, anti-inflammation and paracrine stimulation of healing mechanisms are showing tremendous potential in management of immune-mediated conditions. Nerve regeneration involves regrowth of injured axons as well as myelination, restoration of synaptic

connections and recovery of physiological functions. MSCs can promote neuroprotection and also stimulate local progenitor cells. Schwann cells play anmajor role in nerve repair in cases of degeneration, remyelination, and axonal growth in the peripheral nervous system [16,17]. Adipose tissue-derived MSCs are capable of inducing Schwann cells thereby facilitating axonal repair.

Growth factors such as PDGF, VEGF, TGF-beta, EGF, FGF, IGF-1 are present in platelet rich plasma. Studies have found that PDGF plays a significant role in multiplication and growth of neural progenitor cells. Additionally, growth factors present in platelet concentrate also promote angiogenesis [18,19]Recovery following cell-based therapy in axonal neuropathy variants of GBS may be explained by resolution ofphysiological conduction failure at the nodes of Ranvier inthe nerve fibres or by collateral sprouting of survivingaxons [20]. Improvement in the present case was seen as early one week following cell-based therapy. Clinically, cell based therapy results were observed in the form of reduced intensity of muscular stimulation required, which signified improved pain threshold and muscle response. A significant positive outcome of treatment in the form of assisted walking and back control was also observed.

Multi-differentiation potential, anti-inflammatory and immune-modulatory properties of MSCs play an important role in healing following GBS. Rehabilitation protocol ensured that specific muscle groups were targeted and strengthened. This gradually enabled the patient to walk and perform activities of daily living by herself comfortably.

Conclusion

The combination protocol employed in this case of Axonal Sensory Motor Neuropathy ensured better functional outcomes achieved in a short duration of time when compared to conventional therapies. Cell-based therapy is now emerging as an attractive and effective modality for treatment of various conditions. Documentation of results with larger study groups is the need of the hour in eradicating skepticism surrounding the application and effectiveness of cell-based therapy.

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