



RESEARCH ARTICLE

HALTING OF FUNCTIONAL DECLINE IN A CASE OF DUCHENNE MUSCULAR DYSTROPHY AFTER CELLULAR THERAPY

¹Dr. Alok Sharma, ⁴Dr. Prerna Badhe, ²Dr. Hemangi Sane, ^{2,*}Suhasini Pai, ²Pooja Kulkarni, ³Dr. Khushboo Bhagwanani and ¹Dr. Nandini Gokulchandran

¹Department of Medical Services and Clinical research, NeuroGen Brain and Spine Institute, India

²Department of Research and Development, NeuroGen Brain and Spine Institute, India

³Department of Neurorehabilitation, NeuroGen Brain and Spine Institute, India

⁴Department of Regenerative Laboratory Services, NeuroGen Brain & Spine Institute, India

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ABSTRACT

Duchenne muscular dystrophy (DMD) is an X-linked genetic myopathy characterized by progressive skeletal muscle degeneration and weakness. Recent studies have shown that stem cell derived exosomes promote angiogenic and cardioprotective function of cellular therapy. With no known cure, cellular therapy has shown some promise in altering the disease process. We report a case of DMD treated with autologous bone marrow mononuclear cell (BMMNC) transplantation followed by long term multidisciplinary rehabilitation. At follow up assessment of 4 and 13 months after cellular therapy, qualitative improvements like increased stamina, decreased calf muscle tightness, reduced toe walking, improved gait and balance were witnessed. Functional Independence Measure improved from 93 to 96. The North Star ambulatory score and Berg balance score were maintained and no functional deterioration were evident over 13 months post cellular therapy. This case report highlights the improvements in function as well as halting of progression of the disease over a period of 13 months after cellular therapy. No adverse events were observed. The improvements provide an evidence of the restorative and disease modifying benefits of cellular therapy in DMD. More randomized clinical studies will be needed to effectively establish the therapeutic benefits of cellular therapy in DMD.

INTRODUCTION

Duchenne muscular dystrophy (DMD) is an X-linked genetic myopathy characterized by progressive skeletal muscle degeneration and weakness, leading to loss of motor functions in puberty, cardiac and respiratory involvement, and premature death. (Petrof, 2002) The frequency of occurrence of DMD is approximately 1:3500 male births due to spontaneous out frame mutations in the dystrophin gene (locus Xp 21.2). (Nallamilli *et al.*, 2014) The disease is caused by a deficiency of dystrophin or the synthesis of functionally ineffective dystrophin. (Braun *et al.*, 2014) Current treatment for DMD includes pharmacotherapy, rehabilitation, and surgical management that aim at preserving the child's ambulation and prolonging their functional independence. (Pane *et al.*, 2013) (Muntoni *et al.*, 2007) There is a need for a cure that could address the underlying muscular defect. Cellular therapy has shown potential to regenerate muscle fibers. (Price FD, *et al.*, 2007). To study the effect of cellular therapy in DMD, the patient was administered with autologous bone marrow

mononuclear cells (BMMNCs) followed by rehabilitation and monitored over a period of 13 months.

Case representation

A 10-year-old boy had a history of delayed walking which was achieved at the age of 3 years. Since the age of 7 years, he had difficulty in walking, getting up from sitting position and complained of frequent falls while walking. Muscle biopsy report was suggestive of generalized myopathic pattern involving proximal muscles more than the distal muscles. He was then diagnosed with DMD based on muscle biopsy, clinical picture and CPK serum levels [12181 IU/L]. As the weakness in the lower limbs increased, it led to toe walking. He faced major difficulty in staircase climbing, walking for prolonged distance, getting up from chair/ floor. He was dependent for all activities of daily living (ADL). On assessment before cellular therapy, there was pseudo hypertrophy in bilateral calf muscles. Neurologically, he was hypotonic and hypo reflexive. He sat with rounded shoulders and in standing, displayed lordotic posture and walked with an equinus gait and a wide base of support. Strength in the proximal muscle strength was less as compared to that in the distal muscles. The muscles would get fatigued very often.

*Corresponding author: Suhasini Pai,

Department of Research and Development, NeuroGen Brain and Spine Institute, India.

Muscular strength was measured by manual muscle testing, using a scale devised by our experienced physiotherapists based on the modified Medical Research Council's manual muscle testing scale (mMRC MMT). Since mMRC-MMT does not sub-classify grades 1 and 2 according to partial Range of Motion (ROM), in our scale (mMRC MMT – I) grades 1 and 2 were subdivided. (Table 1) This allowed us to measure the subtle changes in the strength as observed in patients with DMD (Appendix 1). The North Star ambulatory score was 12/34 and the Berg balance score was 34/56. His functional independence measure (FIM) score was 89. Brooke-Vignos scale score was 4. On investigations, serum CPK levels were elevated (12181 IU/l). His musculoskeletal magnetic resonance imaging (MRI – MSK) showed severe muscular atrophy and fatty replacement in both the extremities. Electromyography (EMG) showed generalized myopathic pattern involving proximal more than distal muscles. 2D Echo and Colour Doppler study and chest X-ray was normal.

MATERIALS AND METHODS

The patient was selected based on the World Medical Association's Helsinki declaration. (Carlson *et al.*, 2004) The protocol was reviewed and ethical approval was taken from Institutional Committee for Stem Cell Research and Therapy (IC-SCRT). The procedure of cellular therapy was explained in detail and a duly filled informed consent was obtained from the parents of the patient prior to the therapy. On the day of transplantation, 100 ml bone marrow was aspirated from the right anterior superior iliac spine under local anesthesia, using bone marrow aspiration needle and was collected in heparinized tubes. The BMMNCs were separated from the aspirate using density gradient method. The cell viability was calculated using Trypan Blue dye which was confirmed by TALI machine using propidium iodide. Fluorescence Activated Cell sorting (FACS) analysis showed CD34+ count to be 940 cells/uL. The cells were injected intrathecally at the level between L4 - L5 and intramuscularly at specific motor points in Glutei, Quadriceps, Abdominals and Back extensors. Simultaneous intravenous administration of 800 mg methyl prednisolone in 500 ml of Isolyte P solution was carried out to enhance the survival of the injected cells. Total number of cells injected was 1.92×10^8 with 96% viability. This was followed by multidisciplinary rehabilitation. Physiotherapy consisted of bed mobility exercises, training for various transfers, and suspension exercises for the muscles. Exercises aimed at strengthening the muscles were performed at moderate intensity within the fatigue range. Occupational therapy consisted of strengthening exercises of bilateral upper limb and trunk muscles and training for ADL. Counseling was provided by a psychologist to cope better with the disease. The patient was discharged at one week post transplantation and was advised to continue the rehabilitation at home. The follow up assessment was conducted after four and thirteen months after the cellular therapy.

RESULTS

At four months follow up, improvements in various aspects were noted. He took less time to perform overhead activities as compared to before. It has been observed that by the age of 12, decreased lower-limb muscle strength and joint contractures results in loss of ambulation. But in this case, improvement in

gait was observed with reduced toe walking and reduced calf muscle tightness. Muscle strength in the hip muscles also increased. (Table 1) The frequency of falls reduced from 4-5/day to 2-3/day. Getting up from squatting position had become easier. Pseudohypertrophy reduced in bilateral calf muscles. Fatigue level decreased and stamina improved. Functionally, bathing had improved as he could apply soap to upper body. No functional deterioration was noted in the last 4 months after cellular therapy. The North Star ambulatory score and Berg balance score were maintained. FIM increased from 89 to 93. Thirteen months after cellular therapy, stamina increased further and he could walk continuously for 20 minutes without fatigue. Overhead activities could be performed with ease and less assistance was required in lower body dressing. The frequency of falls reduced significantly with no complains of falls in last 4 months. FIM further increased from 93 to 96. There was no functional deterioration seen and all the other improvements were maintained in the patient over thirteen months, which is usually unheard of.

DISCUSSION

DMD is caused by a deficiency of dystrophin, a critical component of the dystrophin glycoprotein complex (DGC) that acts as a link between the cytoskeleton and the extracellular matrix in skeletal and cardiac muscles. (Durbeej *et al.*, 2002) This DGC inefficiency leads to fragility, contraction-induced damage, necrosis and inflammation in the dystrophic muscle. (Lapidos *et al.*, 2004) Recent advances in the management of DMD include exon skipping, gene therapy and cellular therapy that might alter and slow the disease progression. (Durbeej *et al.*, 2002) (Arechavala-Gomez V, *et al.*, 2012) (Sharma A, *et al.*, 2014). However, exon skipping and gene therapy pose several practical difficulties that have prevented them from being a clinically feasible and viable option for the treatment of DMD. (Konieczny P, *et al.*, 2013) Muscular dystrophy has been considered as a stem cell disorder caused by the imbalance between muscle damage, lack of endogenous stem cells to keep up with rapid degeneration and muscle repair. (Sacco A, *et al.*, 2010) Cellular therapy holds promise as a treatment for muscular dystrophy by providing cells that can support muscle regeneration through activation of endogenous stem cells and replenishment of the stem cell pool. Extensive preclinical studies have been done on various cell types for treating DMD which have demonstrated restoration of dystrophin expression in the affected muscles. (Gussoni E, *et al.*, 1999) (Benchaouir R, *et al.*, 2007) Human bone marrow mononuclear cell (BMMNCs) include hematopoietic progenitor cells at different stages of maturation, as well as lymphoid cells (lymphocytes, plasmatic cells), monocytes, and macrophages. (Challen GA, *et al.*, 2006) Many clinical studies have stressed on the combined use of the entire BMMNC fraction which are postulated to produce its functional effect depending on the balance among the different stem cell precursors. (Assmus *et al.*, 2002) (Mathieu *et al.*, 2009) Autologous BMMNCs is safe, and has shown functional improvements along with improvement in electrophysiological tests in patients with muscular dystrophy. (Sharma *et al.*, 2014) (Sharma *et al.*, 2013) (These cells are multipotent and capable of differentiating into several connective tissue types including myoblasts. (Tedesco *et al.*, 2010) They impose anti-inflammatory and paracrine effect on differentiation and tissue regeneration through cytokine pathways, anti-apoptotic

features and production of extracellular matrix molecules. (Bongso *et al.*, 2005) (Uccelli *et al.*, 2011) Recent studies have shown that stem cell derived exosomes promote myogenic, angiogenic and cardioprotective function of cellular therapy. (Sahoo *et al.*, 2011) (Lai *et al.*, 2011) They guide axonal development, mediate synaptic activity, initiate intercellular communication and thereby modulate the development and progression of disease (Alcayaga-Miranda *et al.*, 2016). Cellular therapy also contributes to repair of dystrophic muscle through the replenishment of the satellite cells which are a homogeneous population of committed muscle progenitors. (Meng *et al.*, 2011) Injections of stem cells directly into the motor points, where the innervating nerve enters the muscle, facilitates and increases the efficiency of engraftment of these cells in the affected muscles. (Torrente Y, *et al.*, 2007) The natural course of the disease shows reduction of muscle strength by 0.3 MMT units/year. (Collins *et al.*, 2005). Part of the cell fraction was given intrathecally that ensures nerve repair and tightening of neuromuscular junction (Blitzblau *et al.*, 2008) (Kilmer *et al.*, 1993). It is well known that DMD is a progressive disease which leads to decline in motor function including the ability to rise from the floor, climbing stairs, walking independently and sustaining normal ventilation without assistance (Petrof, 2002).

In a cohort study it was seen that patients treated with steroids were overall more stable compared with untreated patients (Mazzone E, *et al.*, 2010). Loss of ambulation is seen in DMD by the age of 10-14 years. (Chamberlain, *et al.*, 2006) In this case, improvements were observed in gait, overhead activities, stamina with reduced fatigue levels within a span of 4 months. The disease progression in this patient was static as no ambulatory loss or further decline was observed in any of the functional aspects in spite of not taking any steroid treatment. The improved and maintained muscle function as well as functional improvement consistently over the period of 13 months suggests some positive alteration of the disease progression after the intervention. Following the transplantation standard rehabilitation regime was given to the patient. Neuro-rehabilitation provided along with cellular transplantation has shown to promote recovery and independence through neurofacilitation. (Sharma A, *et al.*, 2014) Exercise accentuates the recovery after cellular therapy by helping the mobilization of local stem cells, improving angiogenesis and release of cytokines and nerve growth factors (Fabel *et al.*, 2009). One of the limitations of the study is the absence of a comparative MRI-MSK study which would have helped to determine the changes at the musculoskeletal level. The patient was followed up for only one year. In future, the progression of the disease for a longer period of time needs to be studied and the requirement of multiple doses of cellular therapy should be evaluated.

Conclusion

The knowledge regarding the underlying mechanism of action of cellular therapy in halting of progression of disease in DMD is still not clear. Still the present study successfully provides the evidence of safety and efficacy of administration of autologous BMMNC coupled with rehabilitation in DMD. The definite functional improvements and stability in the progression of disease seen in the patient shows great promise for cellular therapy as a therapeutic modality for DMD. More

robust and randomized controlled clinical studies will be needed to effectively establish the benefits of cellular therapy in DMD.

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Appendix 1: Comparison of the grades of the scales mMRC-MMT and mMRC-MMT (I)

m-MRC MMT grade	Description	mMRC-MMT (I) grade	Description
0	No Movement	0	No movement
1	A flicker of movement is seen or felt in the muscle	1	Flicker of contraction
		1+	Muscle moves the joint through up to 1/3 rd of the ROM when gravity is eliminated
		1++	Muscle moves the joint more than 1/3 rd less than 2/3 rd of the ROM when gravity is eliminated
2	Muscle moves the joint when gravity is eliminated	2-	Muscle moves the joint more than 2/3 rd to less than the full ROM
		2	Muscle moves the joint through complete ROM when gravity is eliminated
		2+	Muscle moves the joint up to 1/3 rd ROM against gravity
3-	Muscle moves the joint against gravity, but not through full mechanical range of motion	2++	Muscle moves the joint >1/3 rd , < 2/3 rd of ROM against gravity
3	Muscle cannot hold the joint against resistance but moved the joint fully against gravity	3-	Muscle moves the joint more than 2/3 rd to less than complete ROM
		3	Muscle moves the joint through complete ROM against gravity
		3+	Muscle moves the joint against combination of gravity and moderate resistance up to 1/3 rd of ROM
3+	Muscle moves the joint fully against gravity and is capable of transient resistance, but collapses abruptly	3++	Muscle moves the joint against combination of gravity and moderate resistance from 1/3 rd to 2/3 rd of ROM
4-	Same as grade 4, but muscle holds the joint only against minimal resistance	4-	Muscle moves the joint more than 2/3 rd to less than complete ROM against combination of gravity and moderate resistance
4	Muscle holds the joint against a combination of gravity and moderate resistance	4	Muscle moves the joint against combination of gravity and moderate resistance though complete ROM
4+	Same as grade 4 but muscle holds the joints against moderate to maximal resistance	4+	Muscle moves the joint against combination of gravity and moderate to maximal resistance up to 1/3 rd of ROM
5-	Barely detectable weakness	4++	Muscle moves the joint against combination of gravity and moderate to maximal resistance from 1/3 rd to 2/3 rd of ROM (Barely detectable weakness)
5	Normal strength	5	Muscle moves the joint against combination of gravity and moderate to maximal resistance though complete ROM (Normal Strength)

Table 1. Improvement in the muscle strength through manual muscle testing grading before and after the cell transplantation

MMT readings after 13 months of 1 st transplantation (RIGHT)	MMT readings after 4 months of 1 st transplantation (RIGHT)	MMT readings before 1 st transplantation (RIGHT)	Muscles	MMT readings before 1 st transplantation (LEFT SIDE)	MMT readings after 4 months of 1 st transplantation (LEFT SIDE)	MMT readings after 13 months of 1 st transplantation (LEFT SIDE)
3+	3++	3-	Hip			
2++	2++	2++	Flexors	3-	3++	3-
3++	3+	3-	Extensors	2++	2++	2++
			Abductors	3-	3+	3++
			Knee			
4	4	3++	Flexors	3++	4	4
3-	3-	3-	Extensors	3-	3-	3-
			Foot			
4	4	4	Plantar flexor	4	4	4
			Trunk			
			Abdominals(Upper)	2	2+	2+
			Abdominals(Lower)	3	2++	3+
			Shoulder			
3++	3++	3++	Flexors	3++	3++	3++
3++	3++	3++	Extensors	3++	3++	3++
3++	3++	3++	Abductors	3+	3++	3++
3++	3++	3+	Adductors	3++	3++	3+
3++	3++	3++	Ext. Rotators	3++	3++	3++
3++	3++	3++	Int Rotators	3++	3++	3++
			Elbow			
4	4	4	Biceps	4	4	4
4	4	4	Brachioadialis	4	4	4
			Forearm			
4	4	4	Supinator	4	4	4
4	4	4	Pronator	4	4	4
			Wrist			
4	4	4	Flexor	4	4	4
4	4	4	Extensor	4	4	4
