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Research Article

Comparison of Reverse Nutech Functional Score with Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised to Evaluate Efficacy of Human Embryonic Stem Cell Therapy

Geeta Shroff*

Director, Nutech Mediworld, New Delhi, India

***Corresponding Author**: Geeta Shroff, Director, Nutech Mediworld, New Delhi, India.

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Abstract

Background: Amyotrophic lateral sclerosis (ALS) is a group of rare neurological diseases that mainly involve the nerve cells (neurons) responsible for controlling voluntary muscle movement. The present study aimed to evaluate the efficacy of hESC therapy using the Reverse Nutech Functional Score (RNFS) and ALS-Functional Rating Scale-Revised (ALS-FRS-R).

Materials and Methods: The study included 55 ALS patients. All the patients were investigated with routine diagnostic procedure for ALS. hESCs were administered via intramuscular, intravenous, supplemental routes including epidural and popliteal block, brachial plexus block, intrathecal, epidural catheter caudal and/or deep spinal muscle. Efficacy was assessed by scoring patients with RNFS and ALS-FRS-R.

Results: At the end of therapy, more patients with RNFS showed stability in affected parameters as compared to ALS-FRS-R. About 96.4% patients achieved stabilization when scored with RNFS and 89.1% patients achieved stabilization when scored with ALS-FRS-R with a single treatment session of stem cells.

Conclusion: hESCs may be beneficial in the treatment of patients with ALS as it stabilizes the condition. RNFS can be a unique tool to assess patients with ALS. Future studies are needed to substantiate the results.

Keywords: *Amyotrophic Lateral Sclerosis; Motor Neurons; Neurodegenerative Disorder; Single Photon Emission Computed Tomography*

Introduction

Amyotrophic lateral sclerosis (ALS), is a progressive condition that affects the brain and spinal cord. Due to the death of motor neurons (MNs), the patient loses ability to initiate and control muscle movements. This in turn affects the ability to eat, speak, move and breathe [1,2]. As the body starts getting non-functional, the patient develops symptoms that include muscles weakness, twitches and atrophy [2]. The common risk factors for ALS are family history, age and smoking, whereas there are less evidences for other risk factors like exposure to heavy metal, exposure to welding, heavy manual labor, military service, agricultural work, work in the plastics industry, repetitive muscle use, playing professional soccer, electrical shock and trauma [3,4]. The prevalence of ALS in the U.S. is estimated to be 3.9 cases per 100,000 persons [5]. The frequency of ALS in India is estimated to be 5 in 100,000 [5]. A study by Nalini., et al. elucidated that in Indians, the onset of ALS is at a younger age and the survival is prolonged indicating slow course of the disease among Indian patients [6].

Till date, researchers are unable to find a cure for ALS [7]. Riluzole is the only approved drug to treat patients with ALS. It can slow down the progression of symptoms and increase the life span of 57% patients with ALS by about 3 months [8,9]. Researchers have investigated a variety of stem cells in the treatment of ALS including embryonic stem cells (ESC), induced pluripotent stem cells (iPSCs), fetal brain tissue, neural stem cells (NSCs) and mesenchymal stem cells (MSCs) [10]. Human embryonic stem cells (hESCs) have the properties of self-renewal and differentiation in vitro [11]. In January 2009, the U.S. Food and Drug Administration (FDA) approved hESCs-based investigational new drug (IND) application to treat spinal cord injury (SCI).

We have previously published our studies in patients with different incurable conditions who showed remarkable improvement after hESC therapy. This study aimed at assessing the efficacy of hESC therapy in patients with ALS. The efficacy was assessed with the universally available scoring system, the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALS-FRS–R) [11] and the Reverse Nutech Functional Score (RNFS) developed at our facility (Unpublished data communicated to the journal). RNFS measures all the important parameters which needs to be measure in ALS patient but ALS-FRS-R only assess the present condition of the patient. Hence, it may be hypothesized that RNFS is a better tool than ALS-FRS-R for the assessment of efficacy of hESC therapy in ALS patients.

Methodology

Ethical statement

The study protocol was approved by an Independent Ethics Committee (IEC). The institutional committee for stem cell research and therapy of the institute reported the clinical study to the National Apex Body.

Cell Culture and differentiation

hESCs were obtained from a single, spare, expendable, embryo taken during natural *in vitro* fertilization (IVF) process with due consent. The cell lines were cultured and maintained as per our patented in-house technology (United States Granted Patent No US 8592, 208, 52) in a Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP) and Good Tissue Practice (GTP) compliant laboratory [12]. Safety and efficacy of these hESCs has been assessed in patients with various terminal conditions including CP, SPI, non-healing wounds and Becker's Muscular Dystrophy [12].

Study Characteristics

Patients (32 to 78 years) with ALS and those who agreed to give an informed consent were included in this study. The pregnant or lactating women were excluded. An approval to conduct the study was given by an Independent Ethics Committee (IEC).

All the patients were investigated with routine diagnostic procedure for ALS. The diagnosis of ALS was confirmed by an independent neurologist and supplemented with single photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI). All the patients were scored with RNFS and ALS-FRS-R, at baseline (BL) and at the end of therapy (ET). The RNFS and ALS-FRS-R scoring system evaluates the symptoms on the basis five ordinal grades that run in a direction 1 (good) →5 (bad) and 0 (bad) →4 (good), respectively. A grade of 1 for RNFS and a grade of 4 for ALS-FRS-R is the best possible grade (BPG) that can be achieved for a symptom.

Dosage Schedule

This study presents the results of a single treatment session with hESC therapy. We followed an already established treatment protocol for our patients [12]. To assess the hypersensitivity reactions of hESCs, all the patients were injected subcutaneously (s.c.) with 0.25 mL hESCs. After the evaluation of hypersensitivity reactions, the patients enter the treatment session that lasts for 8 to 12 weeks. hESCs were administered twice daily (0.25 ml) via intramuscular route to prime the body, twice every 7 days (1 ml) via intravenous route to help cells reach the homing area (injury site), once every 7 days via supplemental routes (1-5 ml) including epidural and popliteal block, brachial plexus block, intrathecal, epidural catheter caudal and/or deep spinal muscle. To enhance the absorption of hESCs to the brain, patients were also administered nasal sprays of 1 mL hESCs (3.5 million cells) daily, oral drops were given twice a week and intercostal injections were given daily.

Analysis

Two different criteria W1 and W2 were used to determine the improvement in the symptoms, where W1 = number of patients with symptoms that scored < best possible grade (BPG) at the time of admission or at BL and reached BPG at ET; and W2 = number of patients with symptoms that scored differently later by at least one grade of RNFS and ALS-FRS-R as compared to the scores at BL.

On the basis of affected parameters, the patient's scores were categorized. All the parameters were scored with RNFS and ALS-FRS-R at BL and at ET.

Results

A total of 55 patients were included in this study. Majority of the patients were men (n = 35).

Overall outcome in patients after the therapy

Parameters that scored < BPG at BL and reached BPG afterwards of RNFS and ALS-FRS-R

The RNFS and ALS-FRS-R scores of all the parameters are presented in table 1 and table 2. At BL, speech, a parameter that could be measured with both the scoring systems was affected in 38 and 37 patients with RNFS and ALS-FRS-R, respectively. Of these patients, two patients with RNFS and only one patient with ALS-FRS-R reached BPG at ET. At BL, swallowing was affected in 32 and 31 patients with RNFS and ALS-FRS-R, respectively. At ET, 10 patients with RNFS and five patients with ALS-FRS-R reached BPG. When scored with RNFS, almost all the affected parameters (n = 23) reached BPG at the ET except for muscle paralysis, memory and orientation. It was evaluated that both the scoring systems are beneficial in assessing the improvement in affected parameters, but RNFS is more beneficial as it helps in highlighting even the slightest improvement in the patient condition.

Parameters	RNFS				
	At Baseline	End of Therapy			
	Affected Patients	Reached BPG (%)	Changed by at least One RNFS Grade		
			Better (%)	No change (%)	Worse (%)
Balance - sitting	25	9 (36.0)	23 (92.0)	2 (8.0)	0 (0.0)
Balance - standing	46	6 (13.0)	36 (78.3)	8 (17.4)	2 (4.3)
Breathing difficulties	31	4 (12.9)	22 (71.0)	8 (25.8)	1 (3.2)
Chewing	12	5 (41.7)	6 (50.0)	6 (50.0)	0 (0.0)
Coordination	39	4 (10.3)	26 (66.7)	13 (33.3)	0 (0.0)
Depression	17	10 (58.8)	16 (94.1)	1 (5.9)	0 (0.0)
Fatigue	52	8 (15.4)	34 (65.4)	18 (34.6)	0 (0.0)
Irritability	12	7 (58.3)	11 (91.7)	1 (8.3)	0 (0.0)
Memory	1	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)
Muscle Paralysis	7	0 (0.0)	3 (42.9)	4 (57.1)	0 (0.0)
Muscle Weakness	55	7 (12.7)	40 (72.7)	15 (27.3)	0 (0.0)
Myalgia - pain intensity	40	11 (27.5)	31 (77.5)	9 (22.5)	0 (0.0)
Myalgia - pain area	40	11 (27.5)	30 (75.0)	10 (25.0)	0 (0.0)
Numbness	6	3 (50.0)	4 (66.7)	2 (33.3)	0 (0.0)
Orientation	1	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)
Sensation - pain	2	2 (100.0)	2 (100.0)	0 (0.0)	0 (0.0)
Sensation - touch	2	2 (100.0)	2 (100.0)	0 (0.0)	0 (0.0)
Sleep - Hypersomnia	7	2 (28.6)	5 (71.4)	2 (28.6)	0 (0.0)
Sleep - Hyposomnia	5	3 (60.0)	5 (100.0)	0 (0.0)	0 (0.0)
Speech	38	2 (5.3)	22 (57.9)	15 (39.5)	1 (2.6)
SPO_2	10	5 (50.0)	8 (80.0)	2 (20.0)	0 (0.0)
Stiffness	30	8 (26.7)	22 (73.3)	8 (26.7)	0 (0.0)
Swallowing	32	10 (31.3)	18 (56.3)	13 (40.6)	1 (3.1)
Tingling	2	2 (100.0)	2 (100.0)	0 (0.0)	0 (0.0)
Tremor	8	2 (25.0)	8 (100.0)	0 (0.0)	0 (0.0)
Walking balance	49	4 (8.2)	38 (77.6)	9 (18.4)	2 (4.1)
Walking distance	49	3 (6.1)	37 (75.5)	10 (20.4)	2 (4.1)

Table 1: *Number of patients who scored less than the BPG at BL and reached BPG or scored differently later by at least one grade of RNFS.*

Parameters that scored differently later by at least one score of RNFS and ALS-FRS-R

The data for the parameters who scored differently by at least one score at ET is presented in table 1 and table 2. When parameters were assessed with RNFS, 25 affected parameters showed an improvement except memory and orientation at ET (Table 1). With ALS-FRS-R, 12 parameters showed an improvement at ET (Table 2).

Patients that scored less than BPG at BL and reached BPG afterwards of RNFS and ALS-FRS-R

All the patients showed different number of affected parameters when scored with RNFS and ALS-FRS-R. When assessed with RNFS and ALS-FRS-R, 30 and 13 patients moved to BPG at the ET, respectively. When scored with RNFS at BL, two patients had 20 affected parameters at BL. At ET, both the patients showed an improvement in 19 parameters. When scored with ALS-FRS-R, 10 patients had 11 affected parameters. At ET, only two patients showed an improvement in one affected parameter (Table 3 and Table 4).

Patients that scored differently later by at least one score of RNFS and ALS-FRS-R

When scored with RNFS, 52 patients scored differently by at least one grade. Two patients had 20 affected parameters at BL and all the parameters improved by at least one grade at the ET. When scored with ALS-FRS-R, only 45 patients scored differently by at least

one grade. Only two patients had 12 affected parameters at BL. At ET, both patients showed an improvement in six and four parameters, respectively. Out of 55 patients, only two patients with RNFS and six patients with ALS-FRS-R showed worse condition at ET (Table 3 and Table 4). Majority of the patients showed improvement with RNFS as compared to ALS-FRS-R. This is because, ALS-FRS-R shows stability and only measure functional abilities but RNFS measures functional as well as other affected parameters which are important in ALS.

Parameters	ALS-FRS-R				
	At Baseline	End of Therapy			
	Affected Patients	Reached BPG (%)	Changed by at least One ALS-FRS-R Grade		
			Better (%)	No change (%)	Worse (%)
Climbing stairs	53	0 (0.0)	30 (56.6)	22 (41.5)	1 (1.9)
Cutting food and handling utensils	53	4 (7.5)	31 (58.5)	21 (39.6)	1 (1.9)
Dressing and hygiene	52	3 (5.8)	38 (73.1)	14 (26.9)	0 (0.0)
Dyspnea	33	1 (3.0)	19 (57.6)	12 (36.4)	2 (6.1)
Handwriting	48	3 (6.3)	29 (60.4)	19 (39.6)	0 (0.0)
Orthopnea	27	1 (3.7)	18 (66.7)	8 (29.6)	1 (3.7)
Respiratory support	11	1 (9.1)	9 (81.8)	2 (18.2)	0 (0.0)
Salivation	18	7 (38.9)	15 (83.3)	3 (16.7)	0 (0.0)
Speech	37	1 (2.7)	25 (67.6)	10 (27.0)	2 (5.4)
Swallowing	31	5 (16.1)	15 (48.4)	15 (48.4)	1 (3.2)
Turning in bed and adjusting bed clothes	51	3 (5.9)	37 (72.5)	12 (23.5)	2 (3.9)
Walking	50	0 (0.0)	36 (72.0)	12 (24.0)	2 (4.0)

Table 2: *Number of patients who scored less than the BPG at BL and reached BPG or scored differently later by at least one grade of ALS-FRS-R score.*

Patient no.	RNFS				
	Parameters at BL	Parameters at ET			
	Total	Reached BPG (%)	Changed by at least One RNFS Grade		
			Better (%)	No change (%)	Worse (%)
1	12	0 (0.0)	6 (50.0)	6 (50.0)	0 (0.0)
2	12	1(8.3)	6 (50.0)	6 (50.0)	0 (0.0)
3	10	0 (0.0)	9 (90.0)	1 (10.0)	0 (0.0)
4	8	0 (0.0)	7 (87.5)	1 (12.5)	0 (0.0)
5	11	0 (0.0)	8 (72.7)	3 (27.3)	0 (0.0)
6	9	0 (0.0)	5 (55.6)	4 (44.4)	0 (0.0)
7	9	0 (0.0)	7 (77.8)	2 (22.2)	0 (0.0)
8	12	0 (0.0)	8 (66.7)	4 (33.3)	0 (0.0)
9	11	0 (0.0)	6 (54.5)	5 (45.5)	0 (0.0)
10	13	0 (0.0)	13 (100.0)	0 (0.0)	0 (0.0)
11	13	0 (0.0)	13 (100.0)	0(0.0)	0 (0.0)
12	9	0 (0.0)	9 (100.0)	0 (0.0)	0 (0.0)
13	7	0 (0.0)	4 (57.1)	3 (42.9)	0 (0.0)
14	12	0 (0.0)	12 (100.0)	0 (0.0)	0 (0.0)
15	13	2 (15.4)	11 (84.6)	2 (15.4)	0 (0.0)
16	11	0 (0.0)	5 (45.5)	6 (54.5)	0 (0.0)
17	13	1 (7.7)	10 (76.9)	3 (23.1)	0 (0.0)

18	12	2 (16.7)	10 (83.3)	2 (16.7)	0 (0.0)
19	13	1(7.7)	11 (84.6)	2 (15.4)	0 (0.0)
20	13	0 (0.0)	10 (76.9)	3 (23.1)	0 (0.0)
21	10	0 (0.0)	2 (20.0)	8 (80.0)	0 (0.0)
22	10	0 (0.0)	2 (20.0)	8 (80.0)	0 (0.0)
23	15	2 (13.3)	14 (93.3)	1 (6.7)	0 (0.0)
24	16	3 (18.8)	15 (93.8)	1 (6.3)	0 (0.0)
25	12	1 (8.3)	11 (91.7)	1 (8.3)	0 (0.0)
26	12	3 (25.0)	10 (83.3)	2 (16.7)	0 (0.0)
27	11	2 (18.2)	9 (81.8)	2 (18.2)	0 (0.0)
28	6	1 (16.7)	6 (100.0)	0 (0.0)	0 (0.0)
29	12	1 (8.3)	7 (58.3)	5 (41.7)	0 (0.0)
30	12	8 (66.7)	12 (100.0)	0 (0.0)	0 (0.0)
31	16	1 (6.3)	15 (93.8)	1 (6.3)	0 (0.0)
32	11	1 (9.1)	10 (90.9)	1 (9.1)	0 (0.0)
33	11	2 (18.2)	11 (100.0)	0 (0.0)	0 (0.0)
34	12	0 (0.0)	8 (66.7)	4 (33.3)	0 (0.0)
35	12	0 (0.0)	11 (91.7)	1 (8.3)	0 (0.0)
36	11	1 (9.1)	2 (18.2)	9 (81.8)	0 (0.0)
37	17	0 (0.0)	16 (94.1)	1 (5.9)	0 (0.0)
38	7	1 (14.3)	5 (71.4)	2 (28.6)	0 (0.0)
39	12	10 (83.3)	12 (100.0)	0 (0.0)	0 (0.0)
40	16	16 (100.0)	16 (100.0)	0 (0.0)	0 (0.0)
41	16	12 (75.0)	16 (100.0)	0 (0.0)	0 (0.0)
42	13	9 (69.2)	13 (100.0)	0 (0.0)	0 (0.0)
43	20	19 (95.0)	20 (100.0)	0 (0.0)	0 (0.0)
44	20	19 (95.0)	20 (100.0)	0 (0.0)	0 (0.0)
45	13	1 (7.7)	1 (7.7)	6 (46.2)	6 (46.2)
46	5	0 (0.0)	3 (60.0)	2 (40.0)	0 (0.0)
47	9	3 (33.3)	3 (33.3)	6 (66.7)	0 (0.0)
48	5	0 (0.0)	0 (0.0)	5 (100.0)	0 (0.0)
49	8	1 (12.5)	0 (0.0)	8 (100.0)	0 (0.0)
50	7	0 (0.0)	1 (14.3)	6 (85.7)	0 (0.0)
51	6	1 (16.7)	2 (33.3)	4 (66.7)	0 (0.0)
52	13	0 (0.0)	1 (7.7)	9 (69.2)	3 (23.1)
53	7	3 (42.9)	5 (71.4)	2 (28.6)	0 (0.0)
54	7	0 (0.0)	0 (0.0)	7 (100.0)	0 (0.0)
55	5	2 (40.0)	2 (40.0)	3 (60.0)	0 (0.0)

Table 3: *Number of parameters that scored less than the BPG at BL and reached BPG afterwards or scored differently later by at least one grade of RNFS.*

SPECT scan

The SPECT scan findings before and after therapy are presented in figure 1 and 2. Before hESC therapy, moderate to severe hypoperfusion in bilateral parieto-temporal regions, bilateral basal ganglia and bilateral cerebellar regions was observed in all patients. After undergoing hESC therapy, the SPECT scan findings reported significant improvement (> 60%) improvement in the perfusion in cerebral and cerebellar regions. Hypoperfusion in other regions including bilateral parieto-temporal regions and bilateral basal ganglia also reduced to < 30%.

	ALS-FRS-R				
	Parameters at BL	Parameters at ET			
Patient no.	Total	Reached BPG (%)	Changed by at least One ALS-FRS-R Grade		
			Better (%)	No change (%)	Worse (%)
1	8	0 (0.0)	7 (87.5)	1 (12.5)	0 (0.0)
2	10	0 (0.0)	8 (80.0)	2 (20.0)	0 (0.0)
3	11	0 (0.0)	9 (81.8)	2 (18.2)	0 (0.0)
4	8	0 (0.0)	4 (50.0)	4 (50.0)	0 (0.0)
5	9	0 (0.0)	7 (77.8)	2 (22.2)	0 (0.0)
6	6	0 (0.0)	6 (100.0)	0 (0.0)	0 (0.0)
7	7	0 (0.0)	7 (100.0)	0 (0.0)	0 (0.0)
8	12	0 (0.0)	4 (33.3)	8 (66.7)	0 (0.0)
9	10	0 (0.0)	7 (70.0)	3 (30.0)	0 (0.0)
10	11	0 (0.0)	9 (81.8)	2 (18.2)	0 (0.0)
11	11	0 (0.0)	6 (54.5)	5 (45.5)	0 (0.0)
12	10	0 (0.0)	9 (90.0)	1 (10.0)	0 (0.0)
13	7	0 (0.0)	6 (85.7)	1 (14.3)	0 (0.0)
14	11	0 (0.0)	9 (81.8)	2 (18.2)	0 (0.0)
15	9	0 (0.0)	5 (55.6)	4 (44.4)	0 (0.0)
16	8	0 (0.0)	5 (62.5)	3 (37.5)	0 (0.0)
17	11	0 (0.0)	4 (36.4)	7 (63.6)	0 (0.0)
18	9	2 (22.2)	7 (77.8)	2 (22.2)	0 (0.0)
19	10	0 (0.0)	8 (80.0)	2 (20.0)	0 (0.0)
20	11	1 (9.1)	11 (100.0)	0 (0.0)	0 (0.0)
21	7	0 (0.0)	6 (85.7)	1 (14.3)	0 (0.0)
22	7	0 (0.0)	7 (100.0)	0 (0.0)	0 (0.0)
23	9	1 (11.1)	9 (100.0)	0 (0.0)	0 (0.0)
24	9	1 (11.1)	9 (100.0)	0 (0.0)	0 (0.0)
25	8	0 (0.0)	8 (100.0)	0 (0.0)	0 (0.0)
26	10	1 (10.0)	9 (90.0)	1 (10.0)	0 (0.0)
27	11	0 (0.0)	7 (63.6)	4 (36.4)	0 (0.0)
28	6	0 (0.0)	4 (66.7)	2 (33.3)	0 (0.0)
29	10	0 (0.0)	7 (70.0)	3 (30.0)	0 (0.0)
30	8	0 (0.0)	7 (87.5)	1 (12.5)	0 (0.0)
31	10	0 (0.0)	9 (90.0)	1 (10.0)	0 (0.0)
32	8	1 (12.5)	8 (100.0)	0 (0.0)	0 (0.0)
33	6	0 (0.0)	2 (33.3)	4 (66.7)	0 (0.0)
34	7	0 (0.0)	4 (57.1)	3 (42.9)	0 (0.0)
35	6	2 (33.3)	3 (50.0)	3 (50.0)	0 (0.0)
36	12	0 (0.0)	6 (50.0)	6 (50.0)	0 (0.0)
37	11	0 (0.0)	10 (90.9)	1 (9.1)	0 (0.0)
38	8	0 (0.0)	0 (0.0)	7 (87.5)	1 (12.5)
39	5	0 (0.0)	1 (20.0)	4 (80.0)	0 (0.0)
40	11	0 (0.0)	0 (0.0)	10 (90.9)	1 (9.1)
41	11	1 (9.1)	11 (100.0)	0 (0.0)	0 (0.0)
42	9	5 (55.6)	9 (100.0)	0 (0.0)	0 (0.0)
43	9	4 (44.4)	9 (100.0)	0 (0.0)	0 (0.0)
44	9	5 (55.6)	9 (100.0)	0 (0.0)	0 (0.0)
45	9	0 (0.0)	0 (0.0)	4 (44.4)	5 (55.6)

46	7	0 (0.0)	0 (0.0)	5 (71.4)	2 (28.6)
47	4	0 (0.0)	0 (0.0)	4 (100.0)	0 (0.0)
48	5	0 (0.0)	2 (40.0)	3 (60.0)	0 (0.0)
49	2	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)
50	7	0 (0.0)	0 (0.0)	7 (100.0)	0 (0.0)
51	6	0 (0.0)	0 (0.0)	5 (83.3)	1 (16.7)
52	7	0 (0.0)	0 (0.0)	5 (71.4)	2 (28.6)
53	8	0 (0.0)	0 (0.0)	8 (100.0)	0 (0.0)
54	9	3 (33.3)	5 (55.6)	4 (44.4)	0 (0.0)
55	4	2 (50.0)	2 (50.0)	2 (50.0)	0 (0.0)

Table 4: *Number of parameters that scored less than the BPG at BL and reached BPG afterwards or scored differently later by at least one grade of ALS-FRS-R score.*

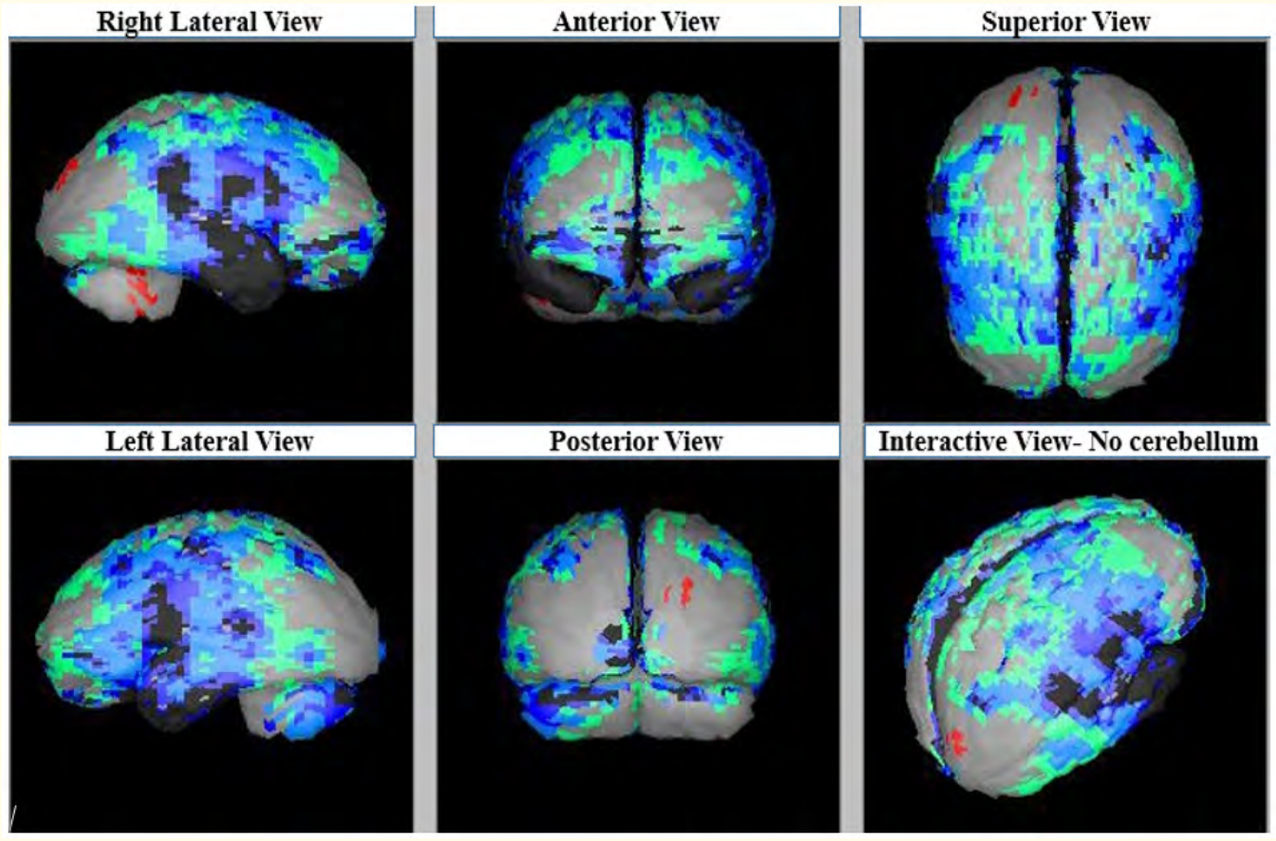

Figure 1: *SPECT scan of ALS disease patient's before therapy showing hypoperfused regions.*

Discussion and Conclusion

ALS is characterized by dysfunction and death of motor neurons (MNs) in the spinal cord, brain stem and cerebral cortex [13,14]. Currently, few treatment options are available to slow down the disease progression and neuronal degeneration in the patients [15]. Hence, there is a great need for effective treatment that can improve the symptoms, as well as cure ALS.

The proliferation and differentiating potential of hESCs into all tissue cell types has made this therapy an attractive option for therapeutic applications [16]. In most of the studies, hESC cell lines have been derived from 8-cell stage embryos not used clinically [17]. However, hESCs used in our study were derived from 2-cell staged fertilized spare ovum obtained after a regular IVF procedure. hESCs derived at this stage are free from immunogenicity [12]. In our previous studies, we have evaluated the efficacy and safety of hESCs therapy in various diseases like spinocerebellar ataxia, CP, and SCI [18,19].

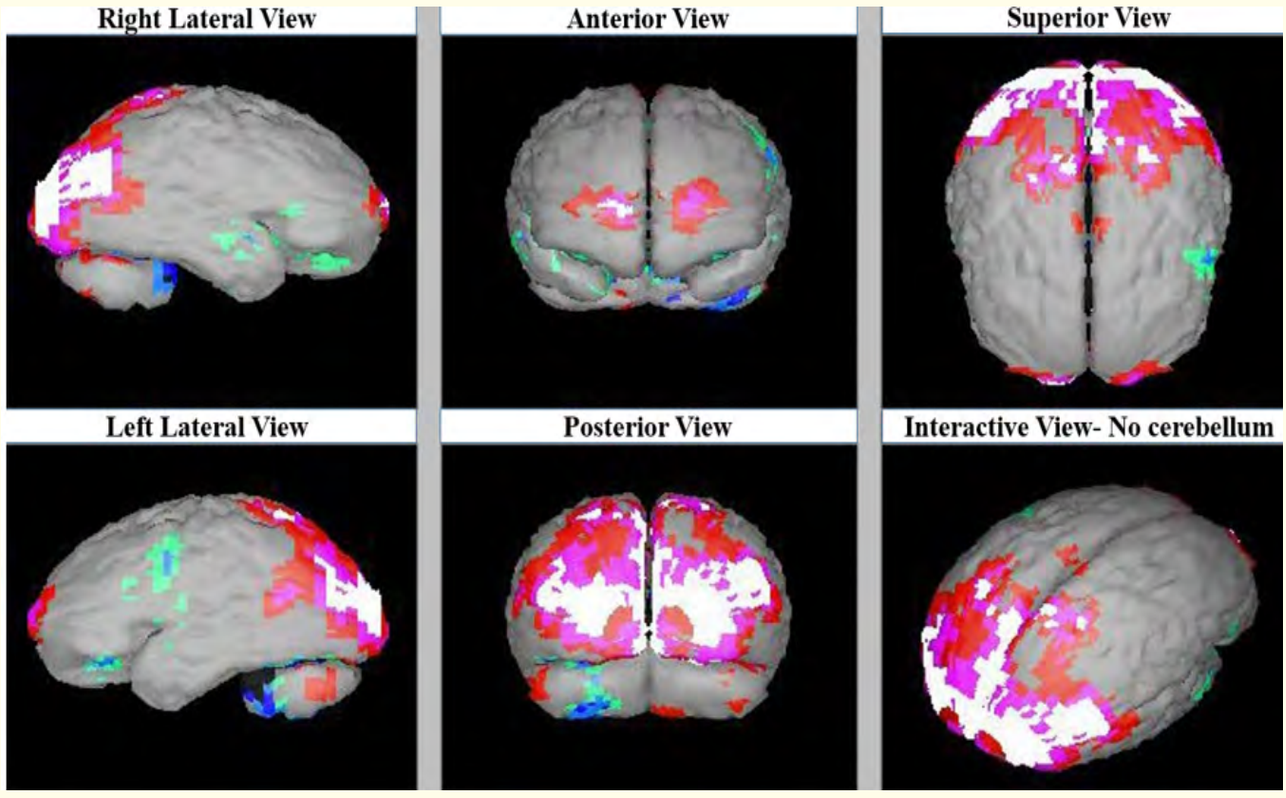

Figure 2: *SPECT scan of ALS disease patient's after therapy showing improved perfusion.*

Studies till date have focused on developing neural stem cells from hESCs, which are then differentiated into MNs *in vitro*. Then, these neurons are transplanted into animal models to evaluate the efficacy [20,21]. But, in the present study we directly injected the hESCs to ALS patients. This hESC line has neuronal (majorly) and non-neuronal progenitor cells [12]. In a separate study, we have demonstrated the mechanism of division and differentiation of a single neuronal progenitor cell into neurons, axons and neuronal tissue (Unpublished data communicated to the journal). These hESCs might have induced normal neurogenesis in the brain, correcting the abnormal functioning of astroglial cells, thereby, improving the overall condition of the patient.

ALS is a progressive disorder and the improvement depends on the clinical condition of the patient. In our study, we observed an improvement in patients with ALS after hESC therapy. No adverse events were reported in the patients after hESC therapy. The improvement in the condition of patients was also reflected in the SPECT scan which showed a decreased hypoperfusion in the affected part of brain after hESC therapy. The patients were stable while on hESC therapy and needed it regularly for stability. However, it is stipulated that hESCs should be transplanted regularly to stabilize the patients as the degenerative process is very aggressive in patients with ALS.

Further, we evaluated the efficacy of hESCs therapy with RNFS and ALS-FRS-R. ALS is a functional disorder and in ALS-FRS-R, the patient is graded in a single level that describes their present functional abilities. ALS-FRS-R can only assess respiratory difficulties and activities of daily life (cutting food, walking, climbing, dressing hygiene and ability to turn in bed) [22] whereas, RNFS developed by our facility can help in assessing these parameters and others including numbness, short-term memory, depression, orientation, sensation, sleep–hyposomnia, sleep–hypersomnia, stiffness, irritability, myalgia, fatigue and muscle paralysis. Also, RNFS grades can be added or subtracted, that can reveal even the slightest improvement in the patient. We have previously published our paper on RNFS as a scoring system in ALS (Unpublished data communicated to the journal). Since ALS-FRS-R assesses lesser parameters [4] as compared with RNFS; the assessment of the patients with ALS might be partial. As the diagnosis of ALS is majorly based on clinical signs and symptoms, it is crucial to take in to account all the associated symptoms.

Summarizing, the 96.4% patients with RNFS and 89.1% patients with ALS-FRS-R reported a stable condition after undergoing hESC therapy, which is difficult to achieve with the currently available therapies. Majority of the patients showed improvement with RNFS as compared to ALS-FRS-R. This is because, ALS-FRS-R shows stability and only measure functional abilities but RNFS measures functional as well as other affected parameters which are important in ALS. After undergoing hESC therapy, the SPECT scan findings reported significant improvement.

The evaluation of an improvement in patient's condition using RNFS seems to be much more accurate and RNFS could be a unique tool to assess the improvement of patients receiving hESC therapy. RNFS has only been used at our facility to assess patients. Extended use of this by other healthcare professionals will help in obtaining the evidences to support its use.

However, we have only assessed the scoring system in patients at our center undergoing hESC therapy. Future well designed studies with patients of different age groups and longer follow ups are needed to evaluate the efficacy of hESC therapy.

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Competing Interest

The authors declare no competing interest associated with the publication of this manuscript.

Informed Consent

Written informed consent was obtained from the patient for publication of any accompanying images.

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