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Functional Recovery After Wharton's Jelly-Derived Mesenchymal Stem Cell Administration in a Patient with Traumatic Brain Injury: A Pilot Study

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ABSTRACT

AIM: To introduce a traumatic brain injury (TBI) patient who underwent stem cell transplantation (SCT) in order to minimize the remaining injury deficiencies.

MATERIAL and METHODS: This study included a 29 years old male who had TBI resulting from a vehicle accident which took place one and a half years ago. The participant received six doses of intrathecal, intramuscular, and intravenous transplantation of Wharton's jellv-derived mesenchymal stem cells (WJ-MSCs) at a goal dose of $1xl0^6$ / kg respectively for each route of administration for six months.

RESULTS: No important negative effects were reported. The patients' speech, cognitive, memory and fine motor skills were improved. The efficacy of treatment with SCT was assessed with cranial magnetic resonance imaging (MRI), computed tomography (CT) screening, and electroencephalography (EEG).

CONCLUSION: SCT can have a promising future as a medical approach in recurrent TBI.

KEYWORDS: Stem cell, Brain injury, Umbilical cord, Transplantation

ABBREVIATIONS: a.f.i.: After the first intervention, **CNS:** Central nervous system, **CT:** Computed tomography, **DC:** Decompressive craniectomy, **EEG:** Electroencephalogram, **FIM:** Functional independence measure, **i.m:** Intramuscular, **i.t:** Intrathecal, **i.v.:** Intravenous, **MRI:** Magnetic resonance imaging, **MRC:** Medical Research Council, **MSCs:** Mesenchymal stem cells, **NeDs:** Neurological disorders, **Pre-t.p:** pre-transplantation, **PTH:** Post-traumatic hydrocephalus, **SCT:** Stem cell therapy, **VP:** Ventriculoperitoneal, **WJ-MSCs:** Wharton's jellv-derived mesenchymal stem cells

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INTRODUCTION

Traumatic brain injury (TBI) is a prominent public health and socioeconomic issue (12). It is described as "a brain function change or other signs of brain pathology that is induced by an external force" (15). It may lead to brain parenchyma after a head trauma and result in neurological deficiencies (5). It is regarded as a "silent disease" since the severity of the outcomes of this disease is not entirely understood yet (17). Nearly 50% of TBIs were reported to source from motor vehicle accidents.

TBI is also caused by acts of violence, explosions, falls and sports injury (10). TBI is usually related to short period of concentration, mood disturbances, bad decision-making and physical disability (17). Cerebral injury following TBI causes immediate harm to the tissue and changes cerebral blood flow control and metabolism and this provokes a series of neurochemical alterations and leads to apoptosis (25). Focusing on a multidisciplinary strategy is crucial because of insufficient treatment methods of persistent TBI. Stem cell therapy (SCT) is an inventive procedure capable of supplementing or substituting medicinal and surgical therapies (3). This innovative technique seeks to prevent neuronal degeneration and replace the damaged neurons. Stem cells are capable of differentiating and transforming into mature cells, thereby restoring the damaged cells (9, 24). Several preclinical studies indicated the SCT to be secure and effective in the management of TBI (2,13). In addition, numerous sources of cells for transplantation, such as mesenchymal stem cells; were used in clinical studies for TBI (MSCs; e.g., Wharton's jelly-derived MSCs [WJ-MSCs]). MSCs help recover the injured tissues which occur due to TBIs resulting from the bystander effect. MSCs may be led by chemotaxis or an inflammatory element, move to the region of lesion, preferably let go the nutritional factors and perform the role of antiapoptosis. Simultaneously, WJ-MSCs have unique benefits such as being plentiful, simple to acquire with minimum invasiveness, and readily cultured to a reasonable amount for transplantation without the ethical problems which are characteristic to allografting. We formerly assessed the security and usefulness of both the triple route and multiple WJ-MSC implantations in treating a patient with hypoxic-ischemic encephalopathy (HIE) (7). In the present study, we introduced an incident of a 29-year-old male who was struggling with TBI as a consequence of a road accident. The patient underwent intrathecal (i.t.), intramuscular (i.m.), and intravenous (i.v.) WJ-MSC transplantation one and a half years following his TBI to minimize the remaining injury deficiencies.

CASE PRESENTATION

The pilot study introduced was a prospective, longitudinal medical experiment. The study was conducted in Health Sciences University, Gaziosmanpaşa Training and Research Hospital, Istanbul, Turkey. The Turkish ministry of health approved the MSC trial (protocol number: 56733164-203-E.2569). Legal counselors of the patient were informed of the operation, and a written informed consent form was acquired according to the Helsinki Declaration. The general data gathered prior to the experimental therapy included age, sex, reasons for TBI, span of time after the TBI, previous TBI medical care and medical history.

Medical History

The patient was a 29-year-old man that experienced a motor vehicle crash and had a serious TBI in March 2017. He underwent decompressive craniectomy (DC) and ventriculoperitoneal (VP), and a couple months after, his craniectomy flap was placed back on his skull. He was conscious but did not respond, tetraplegic with high-degree muscle spasms, and could not speak, control his sphincter and communicate. He completed almost a year in a rehabilitation clinic but did not show much progress. Injections of botulinum toxin against muscle spasms provided only partial relief. His upper extremities were hyperflexed in a decorticated pose, and his lower extremities stretched. His muscle tone was improved, and the everyday tasks such as mobilization and bathing became considerably difficult. At this point, the patient was referred for the MSC trial at our tertiary-level hospital.

Enrollment Criteria

The participant, whose TBI was verified by imaging tests (including a computed tomography (CT) scan), neurological examination, and neurophysiological observations electroencephalography (EEG); was included the pilot study. Those who had focal central nervous system (CNS) lesions (e.g., neoplastic lesions) and chronic disorders (e.g., systemic disorders) involving long term pharmacotherapy were excluded from the study. The patient was assessed by the physicians in the units of neurosurgery and physical therapy and rehabilitation. The WJ-MSC implantation process was conducted when the patient was stable, without potential side effects for sedo-/general anesthesia in terms of internal medicine and any significant infectious illnesses including sepsis.

PROCEDURE

Umbilical cords were collected from LivMedCell's (Istanbul, Turkey) Good Manufacturing Practice facility. Upon receiving informed consent, all the umbilical cords were collected from different donors, as authorized by the LivMedCell institutional regulatory board. Postnatal umbilical cords were collected from patients who underwent full-term gestation. Our recent publications included the processing and quality testing of umbilical cords, description of WJ-MSCs by flow cytometry, cell differentiation and karyotyping, the pre-transplantation process, and surgical and WJ-MSC transplantation (Table I) (7,16).

CLINICAL ASSESSMENT

Pre-treatment Neurological Investigation

The pre-treatment evaluation required a thorough review by a group of medical and rehabilitation professionals **(Suppl. Video 1)**. For each phase of the protocol, comprehensive neurological and functional assessments were recorded. Spasticity was evaluated through the Updated Ashworth Scale (MAS), and quality of life was evaluated according to the

Table I: WJ-MSC Administration Schedule

Date	Route	WJ-MSC
Round 1		
24.09.2018	IT	1x10^6/kg in 3 ml
24.09.2018	IV	1x10^6/kg in 30 ml
24.09.2018	IM	1x10^6/kg in 20 ml
Round 2		
09.10.2018	IT	1x10^6/kg in 3 ml
09.10.2018	IV	1x10^6/kg in 30 ml
09.10.2018	IM	1x10^6/kg in 20 ml
Round 3		
09.11.2018	IT	1x10^6/kg in 3 ml
09.11.2018	IV	1x10^6/kg in 30 ml
09.11.2018	IM	1x10^6/kg in 20 ml
Round 4		
17.12.2018	IT	1x10^6/kg in 3 ml
17.12.2018	IV	1x10^6/kg in 30 ml
17.12.2018	IM	1x10^6/kg in 20 ml
Round 5		
07.01.2019	IT	1x10^6/kg in 3 ml
07.01.2019	IV	1x10^6/kg in 30 ml
07.01.2019	IM	1x10^6/kg in 30 ml
Round 6		
07.02.2019	IT	1x10^6/kg in 3 ml
07.02.2019	IV	1x10^6/kg in 30 ml
07.02.2019	IM	1x10^6/kg in 30 ml

IT: *Intratekal,* ***IV:*** *Intravenous,* ***IM:*** *Intramuscular,* ***WJ-MSC:*** *Wharton's Jelly-Derived Mesenchymal Stem Cell.*

parental assessment of Functional Independence Measure (FIM) scale.

Safety Assessment Criteria

The patient required to be free of inflammation, fever, elevated rates of C-reactive protein, elevated leukocytosis, allergic reactions / shock, and perioperative complications (anesthesia-and analgesia-related problems and/or wound infections) for seven to 14 days following the procedure to be safe for the transplantation. WJ-MSC could be used only if infection, neuropathic discomfort, cancer growth and cognitive impairment was absent and these criteria were evaluated for one year after the procedure.

Follow-up Evaluation of Treatment Success

The follow-up assessment comprised of a neurological test of muscle control, spasticity and quality of life. The muscle activity was measured by the Medical Research Council (MRC) Muscle Strength Scale. Spasticity was evaluated with the Updated Ashworth Scale and the quality of life was assessed based on the functional healing calculated by the FIM Scale (21). The incidence of neuropathic pain, secondary infections, urinary tract infections, and/or pressure ulcers on the skin were also assessed.

RESULTS

Safety and Adverse Effects

The participant endured the process excellently and did not have any serious injection related side effects. Our patient had only early, temporary complications such as subfebrile fever, moderate headache, and muscle pain related to i.m. injection which was settled by symptomatic medical care within 24-48 hours (Table II). No other safety problems or negative effects were identified during the one-year follow-up (Figure 1A, Table IV).

FIM Scale Score

The six item FIM Scale (e.g. self-care, along with the motor and cognitive ratings) showed important developments in the participant's quality of life. The total FIM Scale score changed from 22/126 at baseline to 76/126 in 12 months.

Modified Ashworth and MRC Muscle Strength Scale

The Modified Ashworth Scale total score was similar on both sides. This scale was used to assess the shoulders, elbows, hips, knees and ankles which improved from 44 at baseline to 16 in 12 months. Likewise, the total score for the MRC Muscle Strength Measure also increased on both sides including the hands, arms, elbows, wrists, knees and ankles, from 22 at baseline to 44 during the one-year follow-up (Figure 1B, C; Table III).

Neuroradiological and Neurophysiological Findings

The former postoperative cranial CT and MRI demonstrated encephalomalacic sequelae and hydrocephalus with VP shunting. Prior to and following each transplantation, we carried out repeat cranial CTs to test the advancement of the patient's hydocephalus thoroughly.

No substantial difference was found between the current and past cranial CT results 12 months after the first intervention (a.f.i.) (Figure 2A-E; Table V). The pre-transplantation EEG showed unorganized waveform patterns which suggested widespread brain injury. Following the 6th transplantation, the patient's EEG additionally showed disorganized waveform patterns (Table V).

Physical Therapy and Rehabilitation

There was a significant clinical development in the patient's reaction to physical therapy during the follow-up. He underwent in-depth neurorehabilitation with physiotherapy a.f.i. he was

Table II: Early and Late Complications of the Procedures

Date	24.09.2018	09.10.2018	09.11.2018	17.12.2018	07.01.2019	07.02.2019
Early						
Infection	–	–	–	–	–	–
Fever	+	+	–	+	–	–
Pain	+	–	+	+	-	-
Headache	+	+	–	–	–	–
Increased level of C-reactive protein	–	–	–	–	–	–
Leukocytosis	–	–	–	–	–	–
Allergic reaction/shock	–	–	–	–	–	–
Perioperative complications	–	–	–	–	–	–
Late						
Secondary infections	–	–	–	–	–	–
Urinary tract infections	–	–	–	–	–	–
Deterioration of neurological status	–	–	–	–	–	–
Neuropathic pain	–	–	–	–	–	–
Carcinogenesis	–	–	–	–	–	–

Table III: Quality-of-Life Improvement (Motor and Cognitive Scores), Spasticity, and Motor Function Evaluated with the Use of the FIM Scale, Modified Ashworth Grading and MRC Muscle Strength Scale

Evaluation Periods (Pre and Post-transplantation)	FIM Scale		Modified Ashworth Scale												MRC Muscle Strength Scale											
			Shoulders		Elbows		Wrists		Hips		Knees		Ankles		Shoulders		Elbows		Wrists		Hips		Knees		Ankles	
	Motor	Cognitive	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
Pre-Transplantation	13	9	3	3	4	4	4	4	4	4	4	4	3	3	2	2	2	2	2	2	2	2	2	2	1	1
1st week	14	15	3	3	3	3	3	4	4	3	3	4	3	3	3	2	2	2	2	2	2	2	3	3	2	2
1st month	19	18	2	3	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	2	3	3	3	3	3	3
2nd month	30	22	2	2	2	2	2	3	2	3	2	3	2	3	3	3	4	3	3	3	3	3	4	3	3	3
3rd month	40	27	1	2	2	2	2	2	2	2	1	2	2	2	4	4	4	3	4	3	4	4	3	3	3	3
12th month	46	30	1	1	1	2	1	1	1	2	1	1	2	2	4	4	4	4	4	4	4	4	3	3	3	3

FIM: *Functional Independence Measurement,* ***MRC:*** *Medical Research Council,* ***R:*** *Right,* ***L:*** *Left.*

prescribed a target exercise schedule that stressed methods to improve mobility and the multiplication of the injected stem cells, hence, he had better outcomes. The target schedule lasted 50 minutes per day, repeated five times a week and contained posture, balance, range of motion, strength, and stretch exercises. The exercise program was discontinued on the days of stem cell administration. The patient responded upon the first transplantation to external stimuli and such an improvement was highly valued by his mother and the caregivers. He could stand on his feet with support, move one foot backwards to enhance his balance and his muscle spasms were reduced after the third transplantation **(Suppl. Video 2)**. His social skills and independent movements (e.g. independently kissing the hands of a caregiver) were improved after the fourth transplantation. Moreover, he could stand on his feet with less support after the intensive exercise program

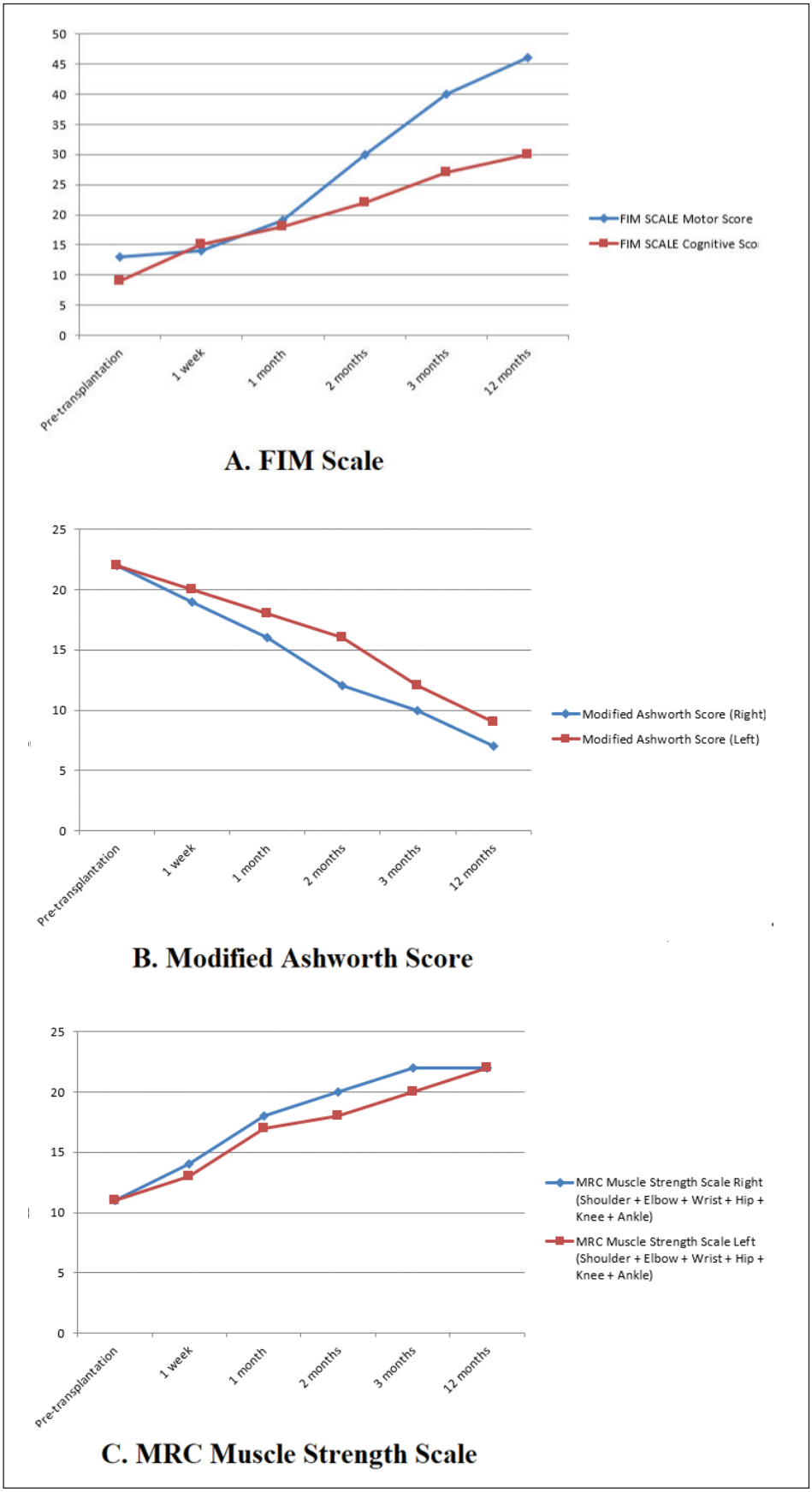

Figure 1: The progress of patient's quality of life (motor and cognitive scores), spasticity, and motor were assessed through FIM **(A)**, Modified Ashworth Grading **(B)**, and MRC Muscle Strength **(C)** scale in graphics, respectively.

Table IV: Quality-of-life Improvement Evaluated with the Use of the FIM Scale

Measurement	Pre-Transplantation	After 1st Administration	After 2nd Administration	After 3rd Administration	After 4th Administration	After 6 months from the final application
1. Self-Care						
Eating	1	1	3	5	5	6
Grooming	1	1	1	3	4	4
Bathing	1	1	2	3	4	4
Dressing-Upper body	1	1	1	2	3	4
Dressing-Lower body	1	1	1	1	2	3
2. Toileting (Sphincter Control)						
Bladder Management	1	1	1	1	3	4
Bowel Management	1	1	1	1	2	2
3. Transfer						
Bed, Chair, Wheelchair	1	1	3	5	5	5
Toilet	1	1	1	2	3	4
Tub, Shower	1	1	1	1	2	3
4. Locomotion						
Walk/Wheelchair	1	2	3	5	5	5
Stairs	1	1	1	1	2	2
Motor Subtotal Score	**13**	**14**	**19**	**30**	**40**	**46**
5. Communication						
Comprehension	3	5	5	6	7	7
Expression	2	3	4	4	5	5
6. Social Cognition						
Social Interaction	2	3	4	5	6	7
Problem Solving	1	1	2	3	4	5
Memory	2	3	3	4	5	7
Cognitive Subtotal Score	**9**	**15**	**18**	**22**	**27**	**30**
Total FIM Score	**23**	**29**	**37**	**52**	**67**	**76**

FIM: *Functional Independence Measurement.* ***FIM scale in detail: 7 Points*** *= Complete Independence,* ***6 Points*** *= Modified Independence,* ***5 Points*** *= Supervision,* ***4 points*** *= Minimal Assistance,* ***3 Points*** *= Moderate Assistance,* ***2 Points*** *= Maximal Assistance, and* ***1 Point*** *= Total Assistance or not Testable.*
Total motor score: *91 points,* ***Total cognitive score:*** *35 points, and* ***Total FIM score:*** *126 points.*

following the fifth transplantation **(Suppl. Video 3)**. He tried to talk and utter following the sixth transplantation sounds **(Suppl. Video 4)**. The patient had follow-ups every six months to evaluate his progress further.

DISCUSSION

Cerebral injury following TBI leads to ischemia of the cerebral tissue, thereby, results in anaerobic glycolysis. Such incidents cause membrane deterioration of vascular and

Table V: Summary of the Neuroradiological and Neurophysiological Findings Using Cranial CT and EEG Before and After the Treatment

CT	Date	CT Appearance of Cranium
	Pre-t.p.	Dilation in the lateral ventricle. Focal encephalomalacic appearance in the right temporal and bilateral frontal lobe.
	Post-t.p.	No significant difference between the findings compared to the previous CT.
EEG	**Date**	**EEG Findings**
	Pre-t.p.	Disorganized waveform pattern.
	Post-t.p.	Disorganized waveform pattern.

CT: *Computed tomography,* ***EEG:*** *Electroencephalogram,* ***t.p:*** *Transplantation.*

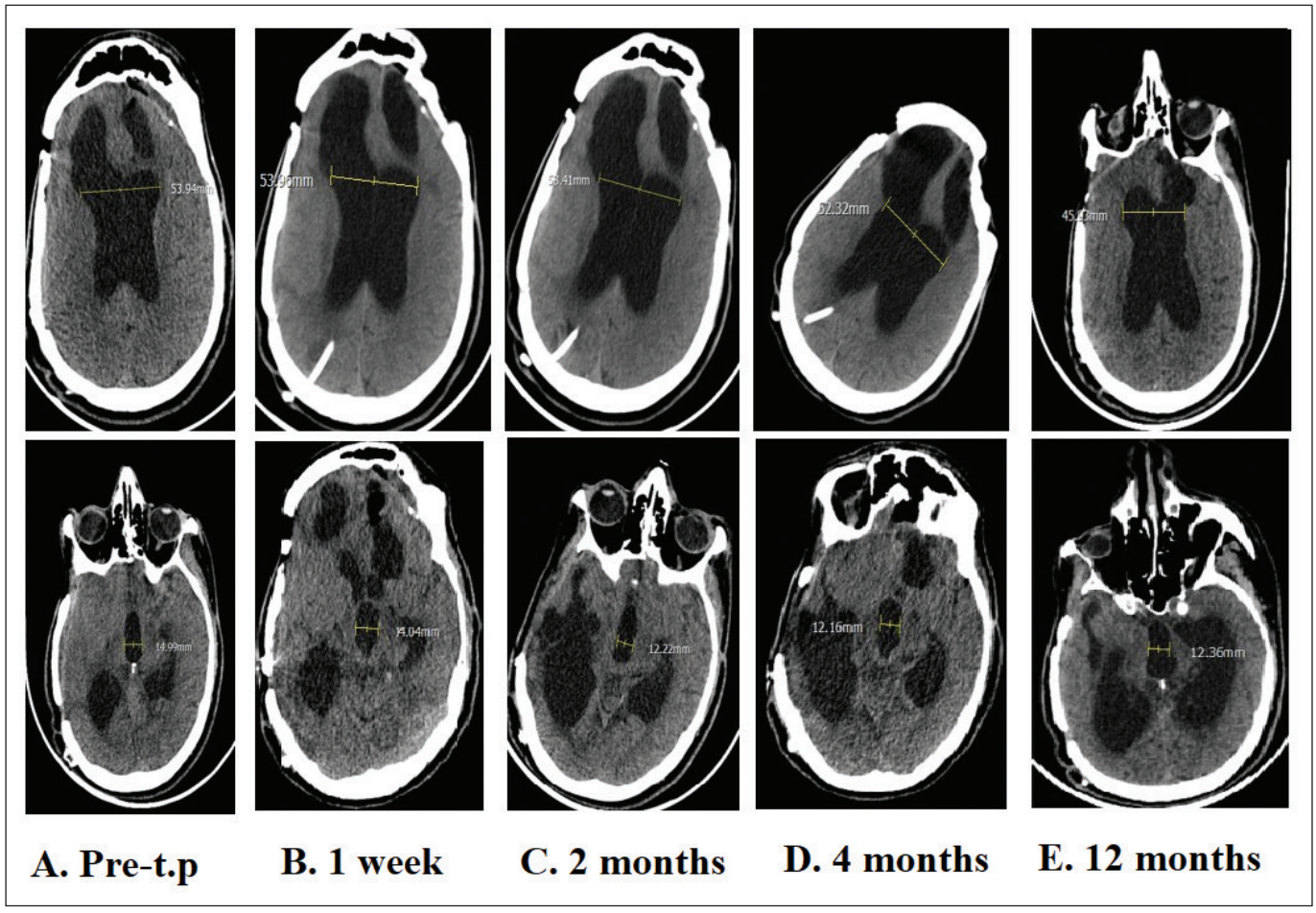

Figure 2: The former postoperative cranial CT demonstrated encephalomalacic sequelae and hydrocephalus with VP shunting **(A)**. Repeated cranial CTs on the first week **(B)**, second month **(C)**, third month **(D)**, and 12th month **(E)** after the first intervention.

cellular forms in the cerebral tissue, consequently, cause necrosis and apoptosis (22). DC treatment and diverse pharmacological medications are recommended to manage TBI (4,14). Regardless, such therapeutic interferences do not cease the neuronal deterioration. In other respects, SCT has a rare ability to change the development of the illness, as stem cells can alter and grow into mature and multipotent cells (24). TBI includes diffused axonal injury and the myelin sheath is interrupted, therefore, it has an effect on the neurotransmission (26). Stem cells home in on and migrate to the injury site, thereby reducing inflammation by mediating inflammatory markers (19). Moreover, these cells change and generate into neural cells and oligodendrocytes that lead to remyelination of the damaged axons and enhance neural pathways (18). Neuroprotection and neuroangiogenesis are caused by the release of numerous elements such as brain-derived neurotrophic factor (BDNF) from these stem cells (20). Additionally, immune cells and cytokines caused

by cerebral inflammatory responses TBI can be modulated by MSCs. Hence, SCT provides fresh perspectives into the immunomodulatory mechanisms that are caused by MSC transplantation by implying useful neurological healing following TBI (26). Preclinical studies utilized numerous kinds of stem cells and various routes of administration while treating TBI (2,13). Therefore, cell transplantation may enhance functional results following TBI.

In the present study, we applied triple route (i.v., i.t, and i.m.) and multiple WJ-MSCs to the patient. WJ is a valuable source of stem cells that are utilized in various animal models of neurological disorders (NeDs). WJ-MSCs were preferred since they were safe and could be isolated without difficulty. WJ-MSCs which is a rich source of HLA-G has an immunosuppressive effect on natural killer-cells and T-cells. This expression profile is significant when preventing maternal immunity against the fetus during gestation and supplying superior graft acceptance in SCT. WJ-MSCs are excellent cell sources for third-party/ allogeneic administrations due to HLA-G secretion. The latest clinical trials suggest the administration of WJ-MSC is favorable for patients with NeDs such as TBI (7).

There are numerous clinical studies conducted worldwide indicating the cellular therapy to be secure and efficient in TBI. Nonetheless, the targeted route stem cell transplantation becomes increasingly popular. Stem cells in the target area should be highly concentrated to magnify the advantages of cellular transplantation. So, cells should be transplanted in the regional routes (20). Intracerebral transplantation may be optimal in TBI however, this intrusive procedure may also cause secondary harm to the cerebral tissue. Administration of stem cells through i.t. enhances neural connectivity, reduces pro-inflammatory mediators in the brain and spinal cord, and increases the movement and distinction of neural precursors (22). Moreover, Sharma et al. found that i.t. transplantation of autologous bone marrow MSCs helped the functional healing of neurological deficiency and increased the living standards of those who suffer from TBI (18). Additionally, numerous studies indicated that only i.v. transplantation was completely effective while treating TBI (11,20). Nevertheless, i.v. transplantation may confine the administrated cells in the lungs and cause inadequate number of cells in the target area to deliver favorable TBI outcomes (1). We formerly discussed the security and usefulness of the triple route and multiple WJ-MSC implantations in HIE and cerebral palsy. In this pilot study, the patient received combined (i.v., i.t., and i.m.) WJ-MSC transplantation that lasted six months. These routes are minimally intrusive and targeted the favored area.

The participant demonstrated changes in his speech, mental skills, ability to focus, concentrating, short-term memory and fine and gross motor movements in our present case report. His degree of autonomy has increased, as demonstrated by the one-year follow-up improvement of his FIM motor scale score from 13/91 at baseline to 46/91. His cognitive score progress was much higher than his motor score, improving from 9/35 at baseline to 27/35 on the third month follow-up. His cognitive score was 30/35, at the last follow-up. While this was a pilot study, as reported in trials of MSC-treated HIE and CP patients, the clinical results of MSCs indicated that they affected cognitive functions before motor functions (7, 16). In fact, care including SCT along with physiotherapy has astounding benefits for people with neurological conditions due to incidents such as TBI. The therapy alone may stop the progression of muscle atrophy and joint stiffness; however, the impaired nerve function cannot be restored (8). It is believed that such a change could be due to the transfer of MSCs to the injury site and the development of neuroregenerative mechanisms there. Additionally, findings also suggested that successful therapy practices could partly recover the impaired nerve activity within the first year of TBI. Nonetheless, the latest standard therapy procedures have minimal advantages for individuals who lived with TBIs over a year (23). In the present report, we provided both subjective (physical therapy and rehabilitation reports) and objective (FIM, Modified Ashworth and MRC Muscle Strength Scales scores) tests to show that the participant achieved an increase in neurological and functional performance after a reaching a plateau of spontaneous improvement one and a half years post-injury.

The patient's neurophysiological follow-ups showed abnormal waveform patterns which suggested extensive brain injury in the EEG similar to the findings before the procedure, however there was no increase in epileptic attacks of the patient; rather, the patient had less epileptic attacks and the dosage of antiepileptic treatment was decreased in the follow-ups. Particularly, MSC implantation usually decreases seizures and protects the neurons more excellently (6). Therefore, while the EEG monitoring of the patient did not dramatically change, the decrease in the epileptic attacks may prove the advantages of treatment with MSC.

Post-traumatic hydrocephalus (PTH) has an effect on 19-36% of patients undergoing DC and is a significant reason for morbidity following TBI. Hydrocephalus usually occurs about a month after a patient has DC and can be linked with worse results. Early detection and care of PTH (through, for example, VP shunting) in patients recovered from TBI will stop more neurological deterioration (22). There were no studies on the impact stem cells had on hydrocephalus. So, intracranial hypertension might be increased by stem cells but as it's observable in the cranial CT follow-up results, such an incidence did not take place in our case. Particularly, the patient's adjustable shunt pressure did not require any alterations in the follow-up. So, these findings indicated that SCT did not have a direct effect on the progression of hydrocephalus.

CONCLUSION

This case study demonstrated that cell transplantation might be greatly beneficial in the treatment of TBI. Through such a method, the feasible neurons might be protected and the damaged ones could be changed by the neuroprotection and neuroangiogenesis mechanisms. Cellular transplantation, in addition to neurorehabilitation, has a significant role in the functional healing of chronic TBI patients and increasing their standard of living. A thorough comparative study including

different types of cells and routes of transplantation should be carried out. Methodologically rigorous studies with randomization, blinding strategies, and control groups should be carried out to reach more definite results.

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