

Cell Transplantation Technology For Spinal Cord Injury

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Abstract

The minimally manipulated cells from fetal nervous and hemopoietic tissues (gestational age 16-22 weeks) were subarachnoidally implanted into 15 patients (18-to-52 year old) with severe consequences of traumatic spinal cord injury (SCI) at cervical or thoracic spine level. The times after SCI were from 1 month to 6 years. The number of cell transplantations (CT) into a patient varied from 1 to 4. The time intervals between CT were 14-to-30 days. In 11 of 15 cases CT was combined with an operative partial disruption of a connective tissue cyst, followed by implantation into the spinal cord lesion of a spinal cord fragment together with olfactory ensheathing cells. Before CT the patients showed complete motor and sensory function disorder consistent with a grade A of SCI according to Frankel classification. With CT treatment, six patients improved their neurological status from A to C grade of SCI, exhibiting incomplete restoration of both motor and sensory function. The status of other five CT-treated patients became consistent with SCI grade B and was characterized by appearance of contracting activity in some muscles and incomplete restoration of sensitivity. The remaining four patients did not exhibit any clinical improvements. No serious complications of CT were noted. The results suggest a clinical relevance of the CT-based approach to treating severe consequences of SCI.

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INTRODUCTION

The human adult nervous tissue has very limited reparative potential and treatment of patients with severe injuries of the CNS frequently does not give desired results. In recent decades considerable progress has been reached in the understanding of the mechanisms regulating the cell reparative activity in CNS. The accumulating evidence clearly outlines two feasible approaches to improve reconstruction of injured CNS. The first is based on creation in CNS of conditions which are favorable to nerve fiber growth, whereas the second, on replacement of destroyed neurons by new functionally active neural cells. The transplantation of fetal-derived immature cells appears to unite both these approaches. In fact, it has been established that when grafted into adult CNS these cells are able both to elaborate the factors favoring axonal growth from recipient neurons and to provide the generation in CNS of new functionally active donor neurons [reviewed in ^{1,2} and ³]. In this paper we present the results of applying cell transplantation (CT) therapy in 15 spinal cord injury (SCI) patients.

MATERIALS AND METHODS

The study was performed in the exact accordance with the protocol approved by the Scientific Council and Ethics Committee at the Institute of Clinical Immunology. Informed consent was obtained from each subject who has been enrolled in the study.

The fetal brain neural and hemopoietic liver tissues were isolated from human fetuses (gestational age 16-22 weeks) after spontaneous or therapeutic abortion, and then prepared in the form of cell suspension, as described earlier [4]. The cells were further cryopreserved in the standard way in RPMI 1640 medium containing 90 % fetal bovine serum and 10 % dimethyl sulfoxide [5], and stored in liquid nitrogen until use. On the day of transplantation, the cell suspensions were thawed at 37°C, washed extensively, and assayed for cell viability by a trypan blue exclusion method in the routine way. The cell suspension designed for one transplantation was composed of equal numbers of cells obtained from three distinct donors. The overall number of viable cells in such suspension was 2.0×10^8 , whereas a ratio of cells from brain neural tissue to those from liver one was 10:1. The cells were grafted subarachnoidally via lumbar puncture.

Each patient underwent 1-to-4 CT. In 11 of 15 cases described in this paper subarachnoidal CT treatment was combined with an operative partial disruption of a spinal connective tissue cyst and implantation into a spinal cord lesion of a fetal spinal cord fragment together with olfactory ensheathing cells (2 x 10⁵). As previously reported [1], these cells are effective stimulators of nerve fiber growth and myelination.

The neurological status of the patients was determined in terms of modified Frankel scores [6]. For the Frankel score, a five scale subdivision was used: A, complete motor and sensory function disorder; B, motor complete, sensory incomplete function disorder; C, motor and sensory incomplete function disorder; D, useful motor function with or without auxiliary means; E, no motor or sensory function disorder.

All 15 patients enrolled in the study had an incomplete spinal cord transection. Their characteristics are shown in Table 1.

Figure 1

Table 1. Characteristics of SCI patients and results of their CT treatment in terms of Frankel definition.

No.	Patient, age (years)	Level of SCI	Time after SCI	Number of CT	Neurological status in terms of Frankel definition	
					before and after CT therapy	
1	K, 32	C6	1 month	2	A	C
2	Z, 24*	C6	2 months	3	A	C
3	G, 28*	Th11	3 months	2	A	C
4	T, 25*	Th6	4 months	3	A	C/D
5	B, 18	Th4	4 months	2	A	C
6	K, 34*	Th10	1.5 years	2	A	C
7	S, 18*	C5	1.5 years	2	A	B/C
8	T, 34*	C6	1.5 years	2	A	B/C
9	A, 48	Th3	2 years	2	A	A
10	Sh, 28*	C6	2.5 years	3	A	B
11	S, 32*	Th9	2.5 years	3	A	B
12	D, 32*	C6	3 years	1	A	B/C
13	M, 21	Th4	3 years	2	A	A
14	Kh, 46*	C4-6	4 years	4	A	A
15	O, 38*	Th6	6 years	1	A	A

*the case with operative cyst disruption.

RESULTS

The SCI patients were followed-up for 1.5-3.0 years after their CT treatment. As shown in Table 1, noticeable clinical improvements were noted in 11 of CT-treated 15 patients. The neurological status of 6 patients became clinically consistent with C grade of SCI. Of these five patients became able to move with crutches and one could walk sufficiently without any help. Other five CT-treated patients achieved grade B of SCI, characterised by incomplete restoration of sensitivity and appearance of contracting activity in some muscles. The patients 7, 8, and 12 from this

group could stand with support. The remaining 4 CT-treated patients exhibited no clinical improvements.

As can be seen in Table 1, the most clinical changes was observed in the 5 patients who have been CT-treated within 1 year after SCI. It might be proposed that the improvements observed in the SCI patients in this period of time could be due to traditional treatment more than CT. With understanding this, we followed-up for 1.5 year the random 5 patients not undergone CT who were comparable with the patients 1, 2, 3, 4, and 5 from the CT-treated group in SCI, surgery, age and sex characteristics. Both control and CT-treated patients have received the same conventional treatment. As shown in Table 2, only two of five control patients changed their neurological status from A to B grade of SCI, whereas remaining ones exhibited no significant clinical improvements.

Figure 2

Table 2. Characteristics of control SCI patients and results of their conventional treatment in terms of Frankel definition.

No	Patient, age (years)	Level of SCI	Neurological status in terms of Frankel definition	
			on admission	and 1.5 year after SCI
1.	B, 48	C5-6	A	A
2.	Ch, 22	C6	A	B
3.	A, 20	Th10	A	A
4.	O, 22	Th7-8	A	B
5.	A, 19	Th7-9	A	A

As a control, additional seven patients (24-to-56 years old) with SCI at cervical spine level may be also considered. These patients have initially demonstrated a syndrome of complete SCI consistent to A grade of SCI and received conventional treatment without CT. Within 1.5 year follow-up only three of them changed their status from A to B grade of SCI, while remaining others kept for yourselves the initial status (data not presented).

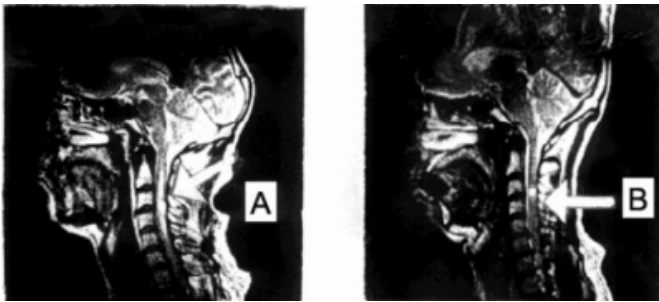
Four cases of applying CT are described in detail below.

Case 1. A 52-year-old male patient, K, was admitted to the Emergency City Hospital 6 hours after a vehicular accident. On admission the patient was in stuporous, although he followed instructions and correctly answered simple questions; his pulse rate was 110 bpm, arterial blood pressure 90/60; respiration was self-dependent at 22/ min and the functions of his cranial nerves were not compromised; there was tetraplegia and apparent muscle hypotonia; tendon and periosteal bone reflexes were flaccid in both upper and lower extremities (D=S), abdominal reflexes were absent; there was profound disorder of all kinds of sensitivity on both sides of the body lower Th1

level. The palpation of C3-to-C6 vertebrae was painful. X-ray examination failed to reveal any traumatic bone changes in cervical spine. Magnetic resonance imaging (MRI) showed a rounded area (0.7 x 0.5 cm) of hypointensity with clear-cut contours at C3-C4 junction (Fig.1A) and a centro-dorsal spindle-shaped 5.8 x 0.3 cm area giving signal of increased intensity at T2 regime along the whole length from C2 to C5 level. The diagnosis was cord contusion at the C3-C5 level and a syndrome of complete SCI.

Figure 3

Figure 1 (A,B). MRI scan of the patient K before (A) and 1 month after CT treatment (B). For description see text.

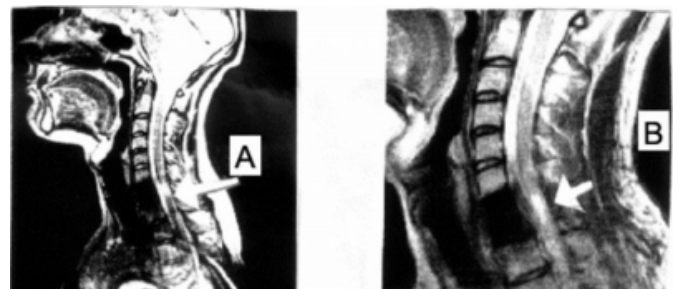


The standard therapy aimed for brain dehydration was started immediately after the cervical spine fixation. The cell suspension (10 ml) composed of cells obtained from neural and hemopoietic tissues was grafted subarachnoidally into the patient 4 days after trauma (day 0). The same cell grafting was done once again on 18 day. On 32 day after trauma the first signs of spinal function restoration were noted: the level of sensory disturbance lowered down to Th4 and some motor activity of the left foot appeared. On 44 day the patient exhibited a complete restoration of pain and touch sensitivity, kinesthesia restoration (S>D); the appearance of some sighs for vesical reflex, active leg motion with the strength of 3 and 2 points (according ASIA definition [6]) at the left and the right side, respectively. The muscle strength in arms was 2 points at the left side and absent at the right. Tendon and periosteal reflexes were active. MRI scan showed the intramedullary heterogeneous formation with indistinct contours (the cyst might presumably be embedded in neural cell graft) at C7, as well as the normal thickness and structure of the spinal cord below the level of SCI (Th1-Th3; Fig.1B). On 100 day after trauma, the complete restoration of all kinds of sensitivity and the recover of functioning pelvis organs were noted. Strength in arms and legs was found to reach for 4 and 5 points, respectively. The patient began walking with orthoses. Twenty-seven months later he could walk on crutches.

Case 2. A 24-year-old male patient Z with SCI at C7 was admitted to the neurosurgical department 6 days after a car accident. The bursting fracture of C7 vertebra and spinal cord compression was treated surgically by a partial resection of C7 vertebral body and ventral spondylodesis at C6-Th1 with a titan-nickel (Ti-Ni) implant. Seven weeks later patient was again admitted to the neurosurgery department for further management. On admission, the overall health status of the patient was of average severity. His consciousness was clear, cardiovascular and respiratory systems were without any pathological changes. Neurological parameters according to the ASIA scale were: inferior flaccid paraplegia; superior paraparesis (strength of arms at distal and proximal parts was 3 and 5 points, respectively); conductive type of disorders of all kinds of sensitivity lower Th1 level; tendon and periosteal reflexes active on upper extremities and flaccid on lower ones (D=S). Urination was via cystostoma. The patient's state was complicated by 26 x 18 x 5 cm necrotic pressure ulcer over the sacrum. MRI examination revealed deformation and size diminution of C6-C7 vertebral bodies. At C6-C7 level Ti-Ni implant was visualized. The spinal cord was thin at the injury level, but its continuity was not broken. The intramedullary cyst of 1.01 x 0.2 cm was clearly visualized at C7 segment (Fig. 2A). At Th1-3 level the spinal cord heterogeneity with the hyperintensive areas of up to 0.12 cm were detected in T2 regime.

Figure 4

Figure 2 (A,B). MRI scan of the patient Z before (A) and on 4 months after CT treatment (B). For description see text.



The patient was subjected to three subarachnoidal CT with 14 day intervals. The intermediate second CT was performed immediately after surgery: laminectomy at C7; partial extraction of an intramedullary cyst and implantation into the made cavity of a fetal spinal cord fragment together with olfactory ensheathing cells.

On 45 day after the last CT, the apparent clinical improvements in the patient were noted: complete restoration of sensitivity and vesical reflex; the presence of

strength of 5 points in arms from both sides and some motions in feet and in knee joints; complete healing of pressure ulcer. At 120 day after the CT treatment, on MRI scan in the field of a former cyst the areas of various densities with indistinct contours were seen (Fig. 2B). Those areas might be visible manifestation of reparative activity of the grafted cells. In the ten month after CT treatment the patient had complete control of pelvis organ functions. He was able to move with orthoses. Four months later he was walking on crutches.

Case 3. A 25 year-old male patient, T, suffered a bursting fracture of C7 vertebra with spinal cord compression, as a consequence of a road traffic accident. In a few days the patient underwent laminectomy at Th6-Th7. Four months later he was again admitted into the neurosurgical department for further management. On admission the patient was in a condition of middle severity. His consciousness was clear, cardiovascular and respiratory systems were without any pathological changes. Neurological status had the following characteristics: inferior spastic paraplegia; conductive disorders of all kinds of sensitivity lower Th5 level. Urination was via cystostoma. MRI scan showed deformation and size diminution of Th6 vertebral body. The spinal cord was thin at the injury level, but its continuity was not broken. At Th6, a 3.0 x 0.5 cm intramedullary cyst was clearly seen. The spinal cord heterogeneity with the hyperintensive areas of up to 0.7 cm at were also visualized in T2 regime.

The patient was subjected to two CT with a 30 days interval. The first CT was preceded by the surgery: repeated laminectomy at Th5-Th7 level, partial extraction of the intramedullary cyst and implantation into the made cavity of a spinal cord fragment with olfactory ensheathing cells. Four months later the patient demonstrated complete restoration of all kind of sensitivity, overall control over functions of pelvis organs and the evident improvements in motor sphere: he was able to stand with support. He underwent the third subarachnoidal cell grafting. After four months the patient could walk sufficiently without any help.

Case 4. A 18 year-old male patient, S, has received a wedge-shaped fracture-dislocation of C5 vertebra, owing to his diving. Consequently, a tetraplegia with disorder of all kinds of sensitivity lower Th1 level and with urinary retention have developed. In a few days the patient underwent the surgery: reduction and stabilization of vertebral column with a Ti-Ni implant. The patient got no benefit from the following conventional complex therapy. Twelve month

after the trauma, the intramedullary cyst overriding 2/3 spinal cord at C5-6 level was clearly visualized on a MRI scan (Fig. 3A). Fifteen months after the trauma the patient underwent the surgery: laminectomy at C5 level, partial extraction of the intramedullary cyst, implantation into the made cavity of a spinal cord fragment with olfactory ensheathing cells, and subarachnoidal CT. Next, two additional same CT were performed with 30 days interval. Twenty four months after the last CT the strength in patient's hands restored to 4 points, urination was self-dependent, recovery of both tactile sensation and musculoarticular sense was noted on the right. In addition, some contracting activity was found in femoral muscles. The patient became able to stand on his knees leaning against a floor by his hands. He was working with a computer. Disappearance of the intramedullary cyst, as well as restoration of his spinal cord integrity was noted on MRI scan (Fig. 3A).

Figure 5

Figure 3 (A,B). MRI scan of the patient S before (A) and 24 months after CT treatment (B). For description see text.

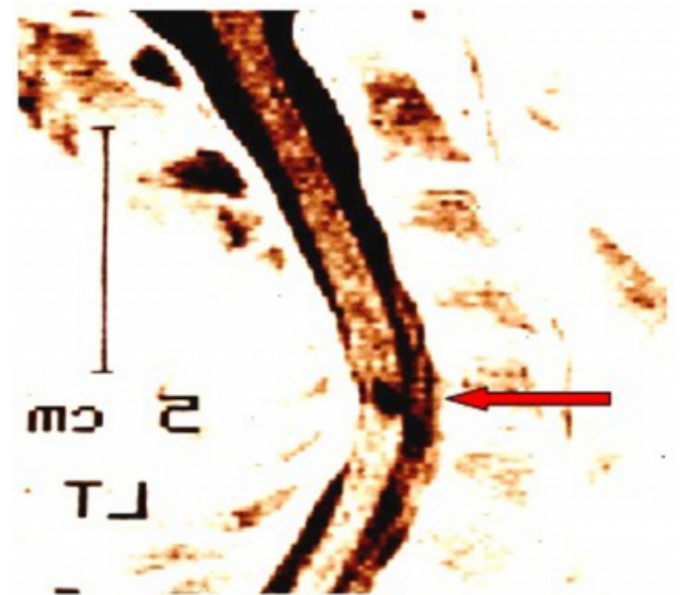


Figure 6



DISCUSSION

There is already a valid experimental basis for applying CT-based therapy in treating patients with CNS injuries [reviewed in 1-3]. It seems quite reasonable that realization of the reparative potential of grafted immature cells in such patients may greatly improve outcome of their disease. Importantly, novel techniques of preparation and propagation of immature multi- and unipotent cells, including those of patient's origin, which are being now actively developed, enable to solve not only technical, but also ethical problems confronting progress in cell transplantation [reviewed in 7,8] and, thereby, may promote widespread adoption of CT-based advances in clinical practice.

An effective CNS repair appears to require the presence in injured sites of not only neural cells potentially able to provide axonal growth, but also the other cells capable of creating the microenvironment favorable to both growth and myelination of nerve fibers. In our own investigation we transplanted into the SCI patients not only the cells isolated from immature nervous tissue, but also fetal liver cells. The human liver of gestational age of 16-22 weeks has been established to be a hematopoietic organ with relatively high contents of immature multipotent cells [9]. Evidence is accumulating that fetal and adult hematopoietic tissues contain the stem cells capable of differentiating into cells forming nervous tissue [10,11,12]; In addition, hematopoietic cells can elaborate the mediators able to support the growth

and viability of distinct cells including the cells constituting nervous tissue [reviewed in 7]; these cells possess a potent natural suppressor activity [13,14] that may be directed against developing cell transplantat-induced immune processes; and, moreover, they may contribute to neovascularization of ischemized tissues [15, 16]. There are also the publications indicating a capacity of those cells not only to inhibit but even to reverse the development of scar connective tissue [17, 18] that is known to represent a insuperable obstacle to axonal growth. Thus, it is reasonable to believe that the hemopoietic tissue-derived cells may be capable of extremely promoting CNS reparation.

In our view, CT into a SCI patient is most optimal before the formation in the injured site of the fibrous connective cyst that may be a major obstacle for restoration of spinal nerve communications. It is reasonable that in the cases with existing cysts, CT should be performed immediately after disruption of the cyst and restoration, as far as possible, of canals for nerve fiber growth.

The clinical success of CT is believed to be significantly defined by survival of the cells implanted in the body. In fact, the fetal neural cells have been previously demonstrated to be able to survive and function in major histocompatibility complex (MHC)- incompatible adult CNS for relatively long period of time [reviewed 1-3]. It should be had in mind, however, that immune privileges of CNS cannot yet guarantee immune unresponsiveness of the host to the allogeneic cells grafted into CNS. Therefore, we transplanted into a recipient only those cells whose alloantigens failed to induce a strong both proliferation of and macrophage inhibitory factor production by recipient's T lymphocyte in assays in vitro performed before CT. Moreover, to our opinion, the transplantation of cells from more than one donor may markedly lessen a risk for prompt immune-mediated rejection of all donor cells. Actually, such cell transplantation might lead to the situation when host's immune responses might be directed against only a part of the most antigenically incompatible cells, while another part of the cells might survive and be involved in CNS repair. Consistent with this proposition, we found that four of 12 patients with severe cranial traumas, who had undergone more than one subarachnoidal CT, developed both cell and humoral immune responses directed against some, but not all, transplanted cells (data not presented).

The cases reported herein indicate that the CT therapy of severe SCI patients may result in apparent clinical

improvements. The most changes were achieved in the patients with relatively short time after SCI (see Table 1). Since each of those patients had an incomplete spinal cord transection, it might be proposed that the observed clinical improvements were exclusively due to their spontaneous recovery, but not to the transplanted cells. However, it seems unlikely, because the patients with similar SCI, who have received in our department the standard rehabilitation treatment without CT, exhibited much less pronounced functional recovery. In support of the important role of the grafted cells in improving spinal cord functions may also be the data indicating the appreciable clinical improvements in six of ten CT-treated patients with times after SCI from 1.5 to 3 years. Before CT treatment these patients have received a complex standard rehabilitation therapy that, however, resulted in no clinical benefits. Generally, in term of conventional medicine such patients, at least in their most part, are considered as incurable and requiring only social rehabilitation.

The clinical improvements in those patients, who have been treated with CT not later 1.5 year after SCI, were associated with the visible corresponding changes in their MRI scans. CT treatment performed in more late time after SCI did usually not result in any detectable MRI changes (data not presented).

In all 15 cases described in this paper, CT therapy led to noticeable improvements in patient's psychological status, which were noted by both the patients, themselves, and their nearest relations.

CT into CNS appears to be safe and well tolerated. Meningisms, but also raises of body's temperature up to 38.5 C, were noted in some of patients during 24-to-48 h after CT. Those occurrences disappeared, by themselves, not requiring any additional serious medicament interventions. A long-term follow-up (range, 1.5-to-3.0 years) of CT-treated SCI patients revealed no complications which might be related to the grafted cells.

CONCLUSIONS

In conclusion the results presented herein suggest that CT-based therapy may be successfully applied in treating neurological sequences of SCI. Although much greater clinical experience is needed to determine a place and clinical relevance of this therapy in overall complex treatment of the patients with CNS injuries.

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