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# Cell Therapy of Brain Stroke

**S. S. Rabinovich, V. I. Seledtsov*, N. V. Banul*, O. V. Poveshchenko*, V. V. Senyukov*, S. V. Astrakov**, D. M. Samarin*, and V. Ya. Taraban***

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Cell suspension consisting of cells from immature nervous and hemopoietic tissues was subarachnoidally transplanted to 10 patients with brain stroke consequences. Clinical effect of different degree was attained in all patients. Six months after cell therapy functional activity significantly increased in contrast to clinically comparable control group. No serious complications of cell therapy were observed. Presumably, cell therapy is a more or less safe method of treatment, which can be effectively used in the treatment of brain stroke consequences.

**Key Words:** *cell therapy; brain stroke*

Cerebrovascular diseases are among the main causes of mortality and disability of elderly population. Annual incidence of brain stroke in Russia is 2.5-3 cases per 1000. The incidence of brain stroke in subjects aging over 50-55 years increases 1.8-2 times with every decade of life [2]. Measures aimed at restoration of cerebral blood flow and neuroprotection are effective at the acute stage of the disease. On the other hand, drug therapy of remote aftereffects of brain stroke is almost ineffective in the overwhelming majority of cases, because it virtually does not modulate reparative potential of the nervous tissue. Today the greatest (and justified) expectations in the treatment of severe neurological disorders are associated with the use of cell technologies. From immunological point of view, CNS is a privileged organ. It means that allogenic donor cells transplanted into CNS are protected from immune reactions. It was shown that donor cells derived from immature nervous tissue produce transmitters stimulating the growth and myelination of recipient nerve fibers and can be involved in the formation of new nervous communications [4,5]. Realization of the reparative potential of these cells can lead to appreciable reduction of neurological deficit caused by brain damage [4]. However, cell technologies are not yet widely used in neurological practice. This paper presents experience gained in the use of cell therapy for the treatment of remote aftereffects of brain stroke.

Novosibirsk State Medical Academy; *Institute of Clinical Immunology, Siberian Division of Russian Academy of Medical Sciences; **Municipal Clinical Hospital No. 34, Novosibirsk

## MATERIALS AND METHODS

Clinical studies were carried out in accordance with the protocol approved by the Academic Council and Ethic Committee of the Institute of Clinical Immunology, Siberian Division of Russian Academy of Medical Sciences. Each patient participating in the study gave his/her informed consent.

The tissues were obtained from human fetuses (16-22 week gestation) after spontaneous or prostaglandin-induced abortions. Cell suspension was prepared as described previously [8]. The cells were routinely cryopreserved in fetal calf serum with 10% DMSO and stored in liquid nitrogen. Cell suspension was defrosted at 37°C on the day of transplantation. Cell viability was evaluated using trypan blue exclusion test.

Cell suspension for one transplantation contained $2.0\times10^8$ viable cells (ratio of nerve cells to hemopoietic hepatic cells was 10:1). The cell suspension was injected into the subarachnoidal space of the recipient through spinal puncture.

Transplantation was carried out in 10 patients (5 men and 5 women) aged 35-56 years with aftereffects of hemorrhagic or ischemic stroke. The patients were

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hospitalized 4-24 months after cerebrovascular catastrophe. All patients had stable organic symptoms (memory disorders and decreased intellectual mnestic function). Nine patients presented with hemiparesis or hemiplegia, 5 suffered from sensorimotor aphasia, 4 had static and coordination disorders. One patient suffered from stable disuria (Table 1). Before hospitalization all patients received appropriate rehabilitative therapy, though virtually without effect.

The control group was randomly formed (retrospectively) and consisted of 11 patients aged 45-65 years. This group was comparable with the experimental group by the severity of cerebral involvement and duration of observation (Table 2). Patients of both groups received the same standard rehabilitative therapy.

The results were evaluated using the Karnovskii functional activity score. The data were statistically processed using Mann—Whitney nonparametric test.

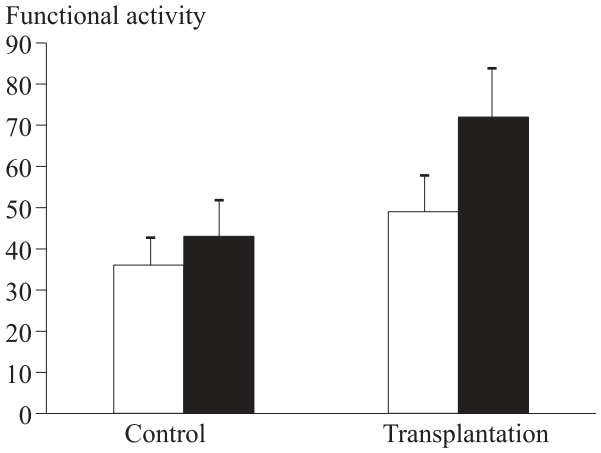


**Fig. 1.** Functional activity of patients with a history of brain stroke. Light bars: before treatment; dark bars: after treatment.

## RESULTS

Positive changes were observed in all patients after transplantation (5 patients received single transplantation, others received two transplantations): appreciable improvement of mental status and strength of limbs (by 1-2 points), recovery of speech and functions of pelvic organs. Positive shifts in the neurological status manifested during 2-3 weeks after transplantation and progressed during the subsequent 30-50 days. Func-

**TABLE 1.** Characteristics of Patients and Results of Therapy in the Study Group

| Patient, age, sex | Diagnosis | Psychoneurological deficiency | Period after stroke, months | Quality of life before/after treatment, % |
|---|---|---|---|---|
| M. O., 46, f | IS in MCA system and ACA on the left | Dementia syndrome, autonomic lability, episyndrome | 18 | 50/80 |
| N. S., 35, f | HS in MCA system on the left | Sensorimotor aphasia, 3 points force in the right hand and leg, frontal mentality, FPO disorders | 6 | 40/80 |
| S. V., 38, m | IS in MCA system on the right | Left-side hemiparesis (more severe in the hand), memory disorders, autonomic lability | 8 | 60/80 |
| S. K., 48, m | HS in MCA system on the right | Left-side hemiparesis (more severe in the hand), memory, behavior, and FPO disorders | 13 | 50/70 |
| G. O., 40, f | IS in MCA system on the left | Sensorimotor aphasia, 2 points force in the right hand and leg, frontal mentality | 10 | 40/70 |
| I. E., 49, f | IS in MCA system on the left | Right-side hemiparesis (more severe in the hand), sensorimotor aphasia, pronounced disorders | 8 | 60/90 |
| A. S., 56, m | HS in MCA system on the right | Left-side hemiparesis (more severe in the hand), memory disorders | 24 | 40/60 |
| M.va V., 52, f | IS in MCA system and ACA on the right | Left-side hemiparesis, Korsakov syndrome, autonomic lability | 18 | 40/50 |
| L. B., 48, m | IS in MCA system on the left | Korsakov syndrome, right-side hemiplegia, complete aphasia | 12 | 50/70 |
| T. V., 49, m | IS in MCA system on the left | Right-side hemiparesis, moderate sensorimotor aphasia | 4 | 60/80 |

**Note.** Here and in Table 2: HS: hemorrhagic stroke; IS: ischemic stroke; ACA: anterior cerebral artery; MCA: median cerebral artery; FPO: functions of pelvic organs.

**TABLE 2.** Characteristics of Control Patients and Results of Therapy

| Patient, age, sex | Diagnosis | Psychoneurological deficiency | Quality of life before/after treatment, % |
|---|---|---|---|
| P. V., 56, f | IS of MCA system on the right | Korsakov syndrome, right-side hemiparesis | 50/50 |
| D. A., 62, f | IS of MCA and ACA on the right | Left-side hemiparesis, aggression, severe mnemonic disorders | 40/40 |
| S. V., 58, m | IS of MCA system on the left | Dementia syndrome, right-side hemiparesis, FPO disorders, total aphasia | 40/50 |
| S. S., 67, f | IS of MCA system on the right | Left-side hemiparesis, severe mnemonic disorders | 40/40 |
| K. A., 65, m | HS of MCA system on the left | Korsakov syndrome, right-side hemiparesis | 30/30 |
| V. L., 48, f | HS of MCA system on the left | Dementia syndrome, right-side hemiparesis, FPO disorders | 30/40 |
| V. I., 51, f | IS of MCA system on the right | Left-side hemiparesis, aggression, severe mnemonic disorders | 30/50 |
| D. T., 47, f | HS of MCA system on the right | Left-side hemiparesis, complacency, severe mnemonic disorders | 30/30 |
| Sh. T., 39, f | HS of MCA system on the left | Right-side hemiparesis, disorders of FPO, feeble-mindedness | 40/60 |
| M. E., 63, f | HS of MCA system on the left | Dementia syndrome, right-side hemiparesis, FPO disorders, total aphasia | 30/40 |
| Ya. V., 45, m | IS of MCA system on the left | Dementia syndrome, right-side hemiparesis, FPO disorders, total aphasia | 40/40 |

tional status of the patients was evaluated using Karnovskii score 6 months after transplantation. The treatment significantly improved quality of life compared to the control group, where no improvement was attained (Fig. 1).

No serious complications of cell therapy were observed during the entire period of observation. Some patients developed fever (up to 38.5°C) and meningism during 48 h post-transplantation. These symptoms were arrested by appropriate drug therapy. Liquor cytosis persisted for 7 days after transplantation (increased content of live and dead mononuclear cells).

Fetal liver cells belonging mainly to hemopoietic differentiation lineages, were present in the transplant because, according to some reports, hemopoietic tissues contain stem cells capable of differentiating into cells forming the nervous tissue [6]. It is also worthy to note that immature hemopoietic tissue contains endotheliocyte precursors, which can provide neovascularization of ischemic tissues in the recipient [7].

The results are in line with previous reports [1,3] indicating the possibility of effective subarachnoidal cell transplantation in the treatment of discirculatory encephalopathies. We share the viewpoint [1,3] that cell therapy is justified in cases with severe disability and failure of vascular and neurotropic drug therapy and can be recommended for patients as an additional treatment. However, we admit that it is early to speak about wide introduction of cell technologies in practical neurology. Wide-scale clinical studies are needed in order to define clear-cut indications and contraindications for this treatment at medical research institutions with qualified specialists and appropriate laboratory equipment for manipulations with cell material.

## REFERENCES

1. A. Yu. Anikin, O. N. Dreval', and O. V. Akatov, *Byull. Eksp. Biol. Med.*, **126**, Suppl. 1, 32-35 (1998).
2. E. I. Gusev, *Zh. Nevrol. Psikhiatr.*, **9**, 3-7 (2003).
3. N. V. Mironov, V. I. Shmyrev, V. S. Bugaev, and A. Yu. Anikin, *Transplantation of Human Fetal Tissues* [in Russian], Moscow (1996), pp. 50-52.
4. V. V. Semchenko, S. I. Erineev, S. S. Stepanov, and G. G. Sergienko, *Transplantation of Immature Nervous Tissue in Experimental and Clinical Neurology* [in Russian], Omsk (2000).
5. J. W. Faucett, *Spinal Cord*, **36**, 811-817 (1998).
6. Y. Li, Chen J., and M. Chopp, *Cell Transplant.*, **10**, 31-40 (2001).
7. T. Murohara, H. Ikeda, J. Duan, *et al.*, *J. Clin. Invest.*, **105**, 1527-1536 (2000).
8. V. I. Seledtsov, I. V. Avdeev, A. V. Morenkov, *et al.*, *Immunobiology*, **192**, 205-217 (1995).