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Effect of fetal cerebellum tissue transplantation on the spasticity and chronic pain syndrome after spinal cord injury in rats



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ABSTRACT

The syndromes of spasticity and chronic pain are diagnosed in the majority of patients in different periods of recovering from spinal injury. Current synthetic or semi-synthetic matrixes, tissue and cell transplants, which are used in the treatment of spinal cord injuries, can affect the development of the syndrome of spasticity and chronic pain.

OBJECTIVE. To examine the effect of fetal cerebellum tissue transplantation (FCTT) on the course of the spasticity and chronic pain syndrome after experimental spinal cord injury.

MATERIALS AND METHODS. Animals – albino outbred male rats (5.5 months, 300 grams, inbred line, the original strain – Wistar); main experimental groups: 1 – spinal cord injury only (n = 16), 2 – spinal cord injury + immediate homotopical implantation of a fragment of the fetal cerebellum tissue (n = 15). Model of injury – left-side spinal cord hemisection at T₁₁ level; verification of spasticity – by Ashworth scale and electroneuromyography, severe pain syndrome – by autophagy.

RESULTS. FCTT does not affect the frequency of severe neuropathic pain syndrome, is accompanied by early (1st week) debut of spasticity signs, significantly increases the level of spasticity (1st-3rd weeks), which is most likely due to glutamatergic effect of descendants of immature transplant cells – cerebellar granular neurons precursors. The maximum increase of the spasticity in the case of FCTT was observed at the 3rd week, in the control group – within the 1st and 4th weeks; from the 4th week after FCTT till the end of the experiment stabilization of spasticity rate in the range of 1.8-2.1 points was observed, which is probably due to the autoimmune motoneurons loss in the perifocal area. At the 24th week the level of spasticity in the case of FCTT succumbed to 2.1 ± 0.3 points, in the control group – 2.6 ± 0.4 Ashworth's points (p > 0.05).

CONCLUSION. Immediate fetal cerebellum tissue transplantation in rats with spinal cord injury causes early pro-spastic effect, in the long term – stabilizes spasticity level.

KEYWORDS: spinal cord injury; fetal cerebellum tissue transplantation; motor function recovery; posttraumatic spasticity syndrome; chronic pain syndrome

Overcoming the effects of the vertebral-spinal injury is one of the important applied and fundamental problems of modern biomedical science that has significant socio-economic importance [1]. Improving the quality of life for spinal patients, returning them to active work remains an important priority of modern restorative neurosurgery. The solution to this problem is associated with the development of biogenic and abiogenic means of motor function recovery. The technology of «exo-

skeletonization» is thriving and by productivity is currently ahead of biogenic ways of motor function restoration, but has features that hinder widespread introduction. In particular, in this case it is important to have minimum of conscious motor activity of paretic limbs, to save a certain amount of downward supraspinal fibres, to maintain a certain level of pelvic organs functions, i.e. the minimum downward innervation of lumbosacral autonomic centers; to eliminate the syndromes of spasticity and chronic

pain. Thus, achievement of significant progress in the treatment of spinal cord injury consequences is possible under conditions of complex use of two directions - neural tissue engineering and bionic prosthetics, against the elimination of spasticity and chronic pain syndromes.

Spasticity syndrome is diagnosed in 45-78 % of patients in different periods of recovering from spinal injury [2, 3], chronic pain – in 60-80 % [4, 5]. All currently known synthetic or semi-synthetic matrixes, tissue and cell transplants could affect the development of spasticity [6] and chronic pain [7-15] syndromes.

The manifestation of spasticity and neuropathic pain syndrome during spinal cord injury is associated with an increased excitability of neurons and formation of pathological neuronal network at the posterior horn. [16] The main mechanism of the positive impact of biogenic means of the nervous system pathology rehabilitation is to stimulate neuroplastic process. Most growth factors, which tissue grafts or transplanted cells express, activate neuroplastic process [16]. The leader in content of immature neuroectodermal cells is cerebellum tissue at the later stages of gestation [17-22]. In this regard, it is important to study the effect of neural tissue transplantation in the course of spasticity and chronic pain syndromes at spinal cord injury. This paper deals with the impact of immediate tissue allotransplantation of fetal rat cerebellum in the area of hemisection of the spinal cord in course of these two complications of spinal cord injury.

MATERIALS AND METHODS

The research was conducted in compliance with current Bioethics regulations according European Communities Council Directives of 24 November 1986 (86/609 / EEC), the European Convention for the Protection of vertebrate animals used for experimental and scientific purposes (Strasbourg, 1986), the Law of Ukraine №3447-IV «On protection of animals from cruelty» (2006). For the study we used white mongrel male rats of the vivarium State institution «Institute of neurosurgery n. acad. A. P. Romodanov NAMS Ukraine», age 5.5 months, weighing about 350 grams, held under standard conditions with the usual diet.

We formed 3 experimental groups:

1) control group («Control»), animals with simulated spinal cord injury – left-sided hemisection of the spinal cord at T₁₁ (n = 16, 9 of the animals involved in electroneuromyography, the maximum observation period – 26 weeks);

2) group of fetal cerebellum tissue transplantation (FCTT) animals with similar simulated injury of the spinal cord and immediate transplantation of allogenic tissue of fetal cerebellum in the affected area (n = 15, 9 of the animals involved in electroneuromyography, the maximum observation period – 26 weeks);

3) group of mature (3 months) intact animals (n = 7) for comparing the data of electroneuromyography.

Protocol of spinal cord injury modelling by left-sided cross section of the spinal cord and FCTT are described in detail in previous studies [23, 24]. After anesthesia (intraperitoneal administration of 15 mg/kg xylazine («Sedazin», *Biowet*, Poland) and 70 mg/kg ketamine («Calypsol», *A. Gedeon Richter*, Hungary) and fixing animals, we performed back access to spinal cord at T₁₁ and crossed its left half. Fetal cerebellar tissue was removed from rat fetuses 18 days of gestation (E18) obtained from deeply anesthetized (see above) pregnant females. One of the fragments was used to calculate the proportion of viable cells, which was 76 ± 5 %. We placed a fetal cerebellum fragment size of ~ 2 mm³ in the spinal cord wound of «FCTT» group animals. In animals of all experimental groups, the window of access to the spinal canal was covered with a fragment of subcutaneous fascia layers. Soft tissue and skin were sutured. Solution bacyllin-5 ~150-200 thousand U per animal (*Kyivmedpreparat*, Ukraine) was injected subcutaneously in the back neck area, intraperitoneally – 6 mg/kg of dexamethasone (*KRKA*, Slovenia).

Level paretic limb spasticity was assessed by B. Ashworth scale (Table. 1) [25, 26] at the ankle and knee joints, fixing the highest value.

Measurement of limbs spasticity in each animal group «FCTT» was performed at 1, 3, 5, 7, 10, 17, 26 weeks of observation. In connection with asynchronous testing of individual cohorts of animals from experimental groups, in this and previous studies [16, 23, 24], the raw data of each animal were led to standard timeline using interpolation method as displayed in the work. The reliability of differences between groups was assessed by comparing test results obtained at similar terms of observation.

To assess the excitability of neuronal structures below the level of the injury we used electromyographic study of H-reflex values ('Hoffmann-reflex') – a phenomenon which is caused by pulsed electrical stimulation of proprioceptive Ia-fibers of sciatic nerve, monosynaptic excitation transfer to motoneurons and electrical excitation of gastrocnemius muscle (H-wave) [27, 28]. To electromyographic study we involved animals with SI IHL no less than 1 point Ashworth (n = 9, group of «control»; n = 9, group «FCTT»). Under general anaesthesia (see. Above) we performed the main access to the shaft of sciatic nerve at the upper and middle thirds of the thighs of both hind limbs. Then we installed stimulating hook-shaped platinum bipolar electrode 5 mm from the exit point of the pelvic nerve and generated electrical pulses of 5 ms by digital electroneuromyograph Neuro-MVP Micro (*Neurosoft*, Russia) with a frequency of 0.2 Hz and automatic jump-like increase in amplitude of each subsequent pulse for 1 mA (starting at 1 mA – to a significant reduction in the amplitude of the H-wave) [32]. A concentric needle electrode recorded electrical responses in the thickness of gastrocnemius muscle. After the study, deeply anesthetized animal was euthanized using cervical dislocation. The value of recorded amplitude of H and M-wave was measured by analogue method, the ratio of H to M-wave was calculated in percentage.

The frequency of severe pain syndrome in groups was evaluated counting the number of animals with autophagy towards paretic limbs – manifestation of severe regional pain [32-34]. The animal with signs of autophagy as biting and biting off a paretic foot parts was taken out of the experiment with ethical considerations.

Statistical processing of digital data was performed using the software package STATISTICA 10.0 (*StatSoft*, USA). The difference between levels of paretic limb spasticity in animals of experimental groups was assessed using Mann-Whitney U-test and checked by direct data comparison for cohorts of animals at synchronous terms of observation. The difference of similar indicator at various standardized periods of observation was assessed within each group by Wilcoxon. The results of ENMG were assessed using Mann-Whitney U-test. Nonparametric Fisher's exact test was used to establish differences in the frequency of manifestation of severe pain between the experimental groups. The reliability of difference of compared values was associated with values of p < 0.05. Calculated values were represented as (M ± m), where M – mean, m – standard error of the mean.



Tab. 1. Ashworth scale to assess the level of paretic limb spasticity

POINTS	CLINICAL EQUIVALENT
0	Increase of muscle tone is missing
1	Slight increase in muscle tone, minimum tension at the end of a passive movement in the joint
2	The noticeable increase in muscle tone throughout the range of passive movement; passive movements are fully possible
3	Significant increase in muscle tone; passive movements are complicated and limited
4	Failure to exercise passive movements in the joint, a condition of severe rigidity, bending or extensor contracture

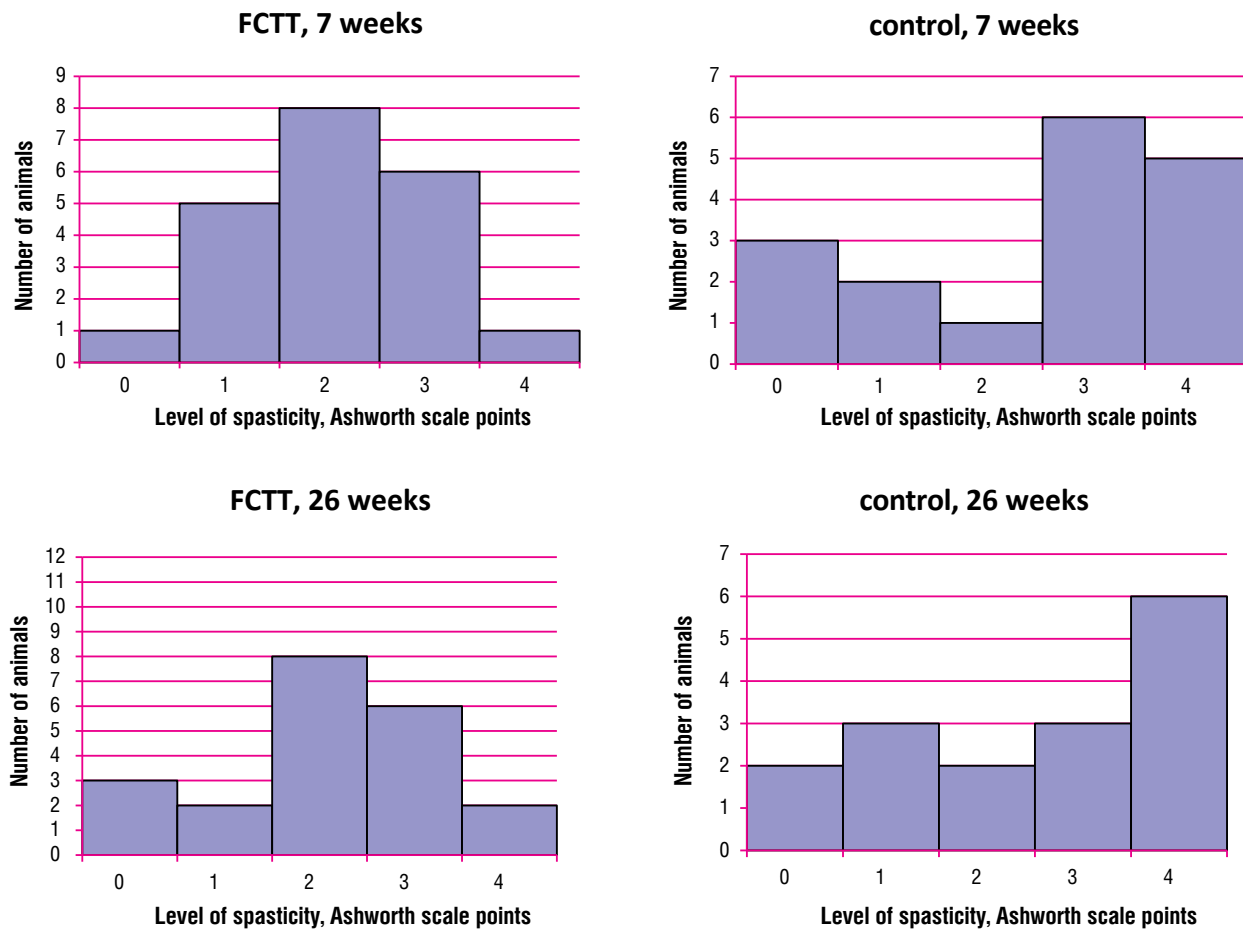


Fig. 1. Average values of paretic limb spasticity level of animals from experimental groups at the 7th and 26th weeks of observation.

Note: when registering a fractional value of the index, the number of animals that accounts for the next two integer values was increased by one.

RESULTS AND DISCUSSION

Group of animals after transplantation of fetal cerebellar tissue, unlike the control group throughout the observation period was characterized by a normal distribution of individual values of paretic limb spasticity (Fig. 1). At the 7th day the average level of paretic limb spasticity in the «FCTT» amounted to 1.1 ± 0.2 Ashworth points, by the end of the 3rd week the figure of the «control» significantly surpassed ($p < 0.05$; Mann-Whitney U-test; Fig. 2). Within 1-3 weeks we revealed a statistically significant increase in the level of spasticity to 1.8 ± 0.8 Ashworth's points ($p = 0.006$; Wilcoxon); further we noted unreliable ($p > 0.05$; Wilcoxon) fluctuations of the indicator at around 2 Ashworth points (26th week – 2.1 ± 1.1 points). Intersection with the midrange dynamics curve of paretic limb spasticity of «control» animals accounted for 4-6th week of observation, by the end of the experiment the preference of the «control» group indicator remained unreliable (maximum – 20 weeks, $p = 0.204$; Mann-Whitney U-test).

Direct distribution of generated impulse along sciatic nerve to the gastrocnemius muscle leads to the formation of M-wave preceding the H-wave [25]. The increase in ratio of amplitudes H-wave and M-wave (H/M-ratio) is typical for spasticity [29-31]. There is a weak positive correlation ($r = 0.51$) between the level of spasticity, measured by Ashworth scale, and H/M ratio [25]. Comparison of average values M and H amplitude response for both hind limbs of «FCTT» animals at the 26th week of the experiment showed no significant differences (Fig. 3). The amplitude of M-response prevailed H-response amplitude of the researched muscle of both hind limbs ($p < 0.035$; Mann-Whitney U-test).

Significant ($p < 0.007$; Mann-Whitney U-test) difference of the value we revealed for the amplitudes of M and H responses, H/M index of both hind limbs when compared to intact animals, excluding amplitude of M response of back contralateral to the place of the injury limb. The value of H/M index for the studied paretic muscle and contralateral to limb in the «FCTT» group was $66.4 \pm 11.8\%$ and $65.7 \pm 7.5\%$, respectively, in the «control» – $66.8 \pm 9.8\%$ and $66.5 \pm 15.4\%$, in the group of intact animals – $34.1 \pm 3.2\%$. No significant differences in investigated ENMG indicators when comparing groups of «control» and «FCTT» were found ($r \geq 0.05$; Mann-Whitney U-test).

In «control» group the phenomenon of autophagy as biting and biting off parts of paretic foot was characteristic of 18.6% animals, in the «FCTT» group we revealed in 1 animal (6%), the difference of manifestation frequency between the two groups was unreliable ($r \geq 0.05$; Fisher's exact test).

Rat cerebellum in the final period of ontogenesis contains a large population of precursor glutamatergic cells [17, 35-37], which, in our opinion, in the case of transplantation of immature cerebellar tissue are able to have a stimulating effect on neuronal network of adjacent areas of the spinal cord. Furthermore, neural transplant is a trigger of immune response series [38-42], while a number of inflammatory cytokines show excitatory effect on motoneurons [43, 44]. In the short time periods (10 days), a number of inflammatory cytokines (TNF α , IL-1 α , IL-6, MIP-1 α) show neuron protective effect [43]. Excitatory effect of TNF α on motoneurons is considered one of the factors of glutamate-mediated formation of spasticity. In addition, tropic glutamate receptors, determining stimulant effect on neurons, are found among the series of antibodies specific to various immunogenic processes in brain tissue [45-48]. Probably, these

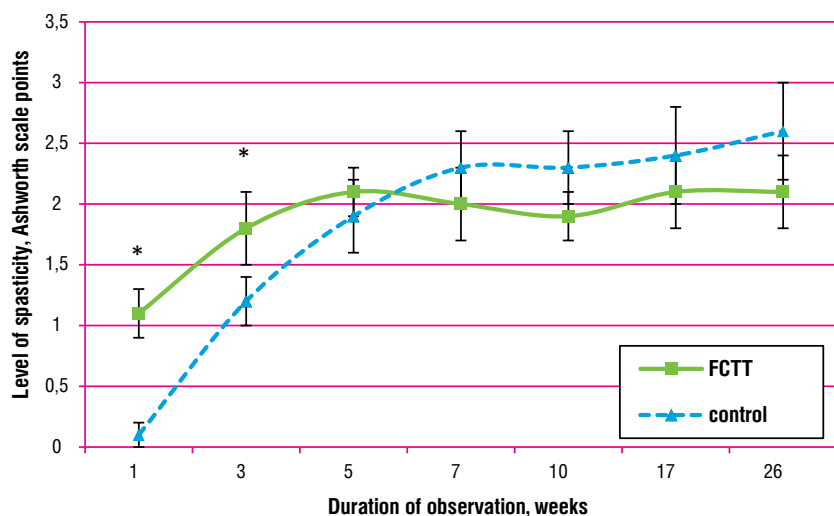


Fig. 2. The dynamic pattern of the paretic limb spasticity in animals from experimental groups. FCTT – fetal cerebellum tissue transplantation.

Note: * – significant difference compared with the control group ($p < 0.05$).

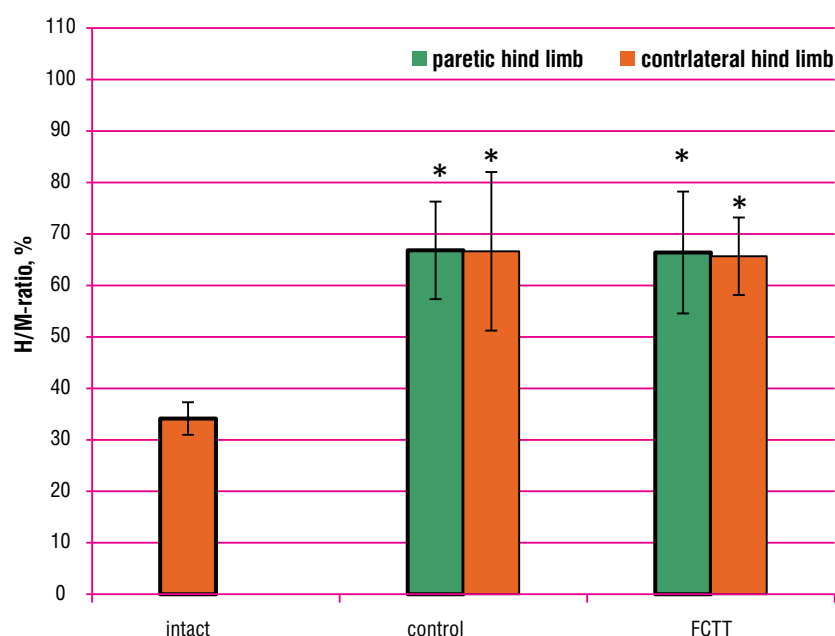


Fig. 3. Value of H/M for the hind limbs of experimental groups animals at the 26th week of observation. FCTT – fetal cerebellum tissue transplantation.

Note: * – $p < 0.05$ compared to intact animals (Mann-Whitney U-test).

factors cause the early debut of paretic limb spasticity in the «FCTT.» The reason for limiting further growth of paretic limb spasticity in the «FCTT», in our opinion, is the gradual death of excessively excited motor neurons («excitotoxic death») [16, 49-54]. Glutamate, inflammatory cytokines, neurotoxic and tropic to glutamate receptors autoimmune antibodies, causing quick demonstration of spasticity syndrome at the early stages of a traumatic process, for a longer time intervals after transplantation induce elimination of excessively excited motor neurons and stabilization of spasticity dynamics in the «FCTT.»

The above pathophysiological mechanisms probably relate to excessively excited spinothalamic neurons – a substrate of chronic pain. In the case of tissue transplantation of fetal cerebellum (group «FCTT»), the frequency of this complication may not exceed the characteristic of «control».

Thus, despite the substantial content of neural progenitors in the tissue of fetal cerebellum, the use of its transplantation at spinal cord injury is possible only in the experiment, due to the potentiate effect on spasticity syndrome.

CONCLUSIONS

1. Transplantation of fetal cerebellum tissue in the area of hemisection of the rat spinal cord significantly increases the level of paretic limb spasticity for the first three weeks of observation compared with the control group and did not affect the frequency of severe neuropathic pain.
2. After transplantation of fetal cerebellar tissue, changes in the excitability of motor neurons of the spinal cord below the level of its hemisection have bilateral nature.

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