



Research Article

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## Treatment Options for Developmental Delay in Children with Perinatal Damage of Nervous System

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### Abstract

**Objective:** Improvement of treatment in children with developmental delay (DD) resulting from perinatal affection of CNS using combination with conventional therapy and administration of fetal stem cells (FSCs) in suspensions containing stem cells extracted from human fetal liver and brain.

**Materials and methods:** Our study allocated 14 children diagnosed with developmental delay and perinatal damage of CNS including 4 boys aged 1.5 to 14 years, with their mean age  $4.23 \pm 0.31$  yrs. and 3 girls - from 3.5 to 13 yrs (mean age –  $3.92 \pm 0.21$  yrs.) (Allocated to the MG) where along with conventional therapy were administered fetal stem cells. Control group (CG) included 7 patients with Developmental delay (DD) – children treated with conventional methods only, including 4 males (aged 3 to 14 yrs. and average age –  $4.11 \pm 0.14$  yrs.) and 3 females (aged from 3 to 15 yrs. and mean age  $4.02 \pm 0.15$  yrs.).

**Results:** Our research revealed that fetal stem cell therapy, irrespective of developmental delay severity in children with CNS damage during perinatal period, can favorably influence the course of development and their immunological markers in particular. Procedure of fetal stem cell administration is simple and non-invasive (no potential causes of complications or allergy reactions in the patients). To promote substantial effects of fetal stem cells we additionally recommended a complex treatment with medicines; different supplementary methods were used for the patients. Aspects of fetal stem cells effect in children with developmental delay are not fully understood and do need a thorough scientific research. In particular, future in-depth study is demanded, as well as the larger randomized and placebo-controlled trials to identify a potential of fetal stem cells-related advantages in children with developmental delay (DD).

**Conclusion:** Fetal stem cells (FSCs) use in complex treatment of patients with developmental delay tends to improve cognitive functions along with motor development of children with nervous system affection; such patients also revealed increased immunology findings.

### Keywords

Perinatal damage; Nervous system; Conventional therapy; Mechanotherapy

### Introduction

Perinatal injury of central nervous system (CNS) belongs to a large group of pathology states in early aged children stipulated by influence of harmful factors on nervous system in the period from 28<sup>th</sup> week of gestation up to the 7<sup>th</sup> day of neonate's life [1-3].

Nowadays, in conformity with the authors, [4,5] cases with perinatal damage of CNS occurrence among the neonates can range over 45 to 80%. It is hardly surprising, that such a high percent of prevalence of nervous system pathology can promote a great scientific and practical interest.

Importance of likely study for perinatal damage of CNS is also because of a great variety of outcomes of this lesion, starting from minimal deadaptation with mild psychomotor deficit and up to severe invalidity in children [1].

There are many unclear and contradictory points for perinatal neurology, despite of many years of scientific studies.

In particular, this refers to significant reliability in diagnostics of any sort of nervous system defects in the newborns, along with mere interpretation of the data obtained; that is stipulated by a major difficulty in identification of neurology deficits at the initial stages of post-natal ontogenesis [6].

While studying perinatal pathology of nervous system one can emphasize several main aspects. Firstly, until presently scientists have not developed a single concept on terminology and background for this state (both from native and foreign perinatal neurology school); specifically, no single opinion about terminology and systematic classification of this condition exists as well as no evidence on precise diagnostic criteria for CNS affection among the neonates and infants [2,7,8].

For the second, in order to significantly highlight this pathology, one must have a clear understanding of "neurology normal ranges". In domestic contemporary literature and practical neurology, standardized scales for assessment of psychomotor skills are the most commonly used [9]. Necessity of establishing the new scale is stipulated by the high percentage of perinatal CNS suffering that might be a sequel of hyper-diagnostics or changed standardized scopes for recovery of psychomotor skills recorded within the last 15-20 years. In addition, with all variety of existing scales to assess early age infants, at present day; there is no unified method for examination of children at their first year of life which does not allow to reliably assess the levels of cognitive or motor development and, subsequently, to provide evidence on prevalence of neurology pathology among children [2,4].

So-called risk factors can play a certain role in occurrence of perinatal CNS pathology. Significance of these or the other factors for development of likely states is still disputable. In the studies of foreign authors, a great attention is concentrated on the status of newborns over the first day after birth [10,11]. However, one cannot miss the factors like: mother's overall health during pregnancy, a course of pregnancy and delivery, the same as complications resulting from them [12-15].

Not less important aspect in study of the problem of perinatal damage of CNS is determining the new pathogenetic mechanisms

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resulting in nervous system suffering. From within a plenty of perinatal factors; hypoxia takes the leading role in regard to a genesis of perinatal CNS pathology [10,16]. Hypoxia cannot only trigger metabolic destruction in the neurons under the circumstances of oxygen deficit, but also is able to accumulate toxic metabolites there; it can also predetermine pathological changes in cerebrovascular hemodynamics. Therefore, search for the new guidelines in a cascade of intracellular reactions; particularly, peroxidation of lipids and destruction of cellular membranes would allow not only evaluating severity of CNS damage, however, it can become a pre-requisite for further search for the new and effective medical resources with antioxidant effects.

All directions concentrated at learning a sequela of perinatal damage of nervous system consist in a single ultimate aim at higher effectiveness of contemporary therapy options as well as adequate treatment that might facilitate a compensation for psychomotor defect and, subsequently, to improve social and psychological adaptation of the suffering children in future.

The main strands in complex recovery treatment for perinatal CNS damage include the following [17-20]:

1) Medical rehabilitation (medical therapy, kinesiotherapy – medical physiotherapy and massage; treatment with application of medical loading and “positive pressure suits”; physical therapy as well as orthopedic surgery options; orthotherapy approaches etc.)

2) Social environment adaptation to children.

3) Psychologic and pedagogic along with speech therapeutic corrections in infants (psychic repair, sensoric learning, classes with speech therapist and special-needs expert, by application of Montessori education, occupational therapy, active work with the family etc.)

In the field of medical rehabilitation and correcting consequences after perinatal affection of CNS, doctors most commonly use methods of Kinesiotherapy, medicamental treatment and physiotherapeutic approach. Kinesiotherapy – is a treatment regimen directed at some positive effects [20,21] by accomplishing proper motor exercising; which are also concentrated both on correction of the motor defects as well as reduction of unfavorable sequela of hypodynamia in children.

The modes of physical exercising listed below are actively put into practice by the doctors:

- Gymnastics (exercises targeted at training for muscles power, recovery of mobility in the joints, development for coordination in motions (both passive and active movements));
- Additionally – due to a character of muscle groups involved – doctors recommend static exercising for isometric constriction along with dynamic tension tasks upon isotonic muscular involvement);
- Sports-applied methods for treatment (concentrated on restoration of complex motoric skills);
- Therapeutic gymnastics (learning of voluntary and standardized strain and relaxation on the muscles, stabilization of coordination and balance reduction for increased muscle tone and elimination of pathological synkinesis, raise of muscle power, mobility in the joints; methods directed at better coordination of motions,

reinforcement of articular and muscular sensations; recovery of fine motor skills);

- Mechanotherapy (exercises with application of training systems and special simulator facilities. Massage is particularly concentrated on stabilization of functions in the organism, this method contributes to blood supply and lymphatic outflow; simultaneously with all processes for oxidation-reduction inside the muscles.

Medical therapy takes a major place in restorative treatment on all consequences after perinatal lesions of CNS with application of the following groups of medical drugs [22-24]:

- 1) Preparations inducing neurotrophic and nootropic action;
- 2) Medicines to promote overall cerebral hemodynamics and microcirculation;
- 3) Drugs maintaining metabolism in nervous system; preserving reparative and resorbable effects;
- 4) Medical agents which aim at cerebral hypertension decreasing;
- 5) anticonvulsants;
- 6) preparations stabilizing muscle tone (if muscles hypertonia is assessed);
- 7) medicines inhibiting hyperkinesia signs;
- 8) Vitamins.

Improvement of motor, speech and cognitive functions by virtue of contemporary intense technologies application for likely categories of patients is considered as the principal task of medical rehabilitation for infants. For this reason, many researchers started launching various experiments with novel methods of treatment and stem cells therapy remains among the similar options of therapy. Fetal stem cells treatment opens a modern therapeutic possibility for children with developmental delay due to perinatal CNS lesions; however, it is still at the early terms of facilitated research. Scientists Sych et al. [25] managed to give evidence about effectiveness and safety of fetal stem cells transplantation on children with cerebral palsy (CP).

## Material and Methods

This study allocated 14 children who were diagnosed with developmental delay following perinatal CNS affection including 4 boys in their age of 1.5 to 14 years, (average age  $4.23 \pm 0.31$  yrs.) and 3 girls aged from 3.5 to 13 years (mean age was  $3.92 \pm 0.21$  yrs.). All children under study were referred to the main group (MG), where all of them (along with conventional therapy) underwent treatment by use of fetal stem cells suspensions. Control group (CG) was constituted of 7 children suffering from perinatally induced developmental delay and treated by use of conservative options only. Our CG allocated children with inclusion of 4 males (aged 3 to 14 years and mean age  $4.11 \pm 0.14$  yrs.) and 3 females (in age from 3 to 15 years;  $4.02 \pm 0.15$  yrs. on average).

All children underwent general inspection and neurology examination, with addition of general blood tests including immunology results - those were conducted prior to treatment, over 3 and 9 months following fetal stem cells transplantation.

Such children were performed immunology profile testing [B-lymphocytes: CD<sup>19+</sup>, T-lymphocytes: CD<sup>3+</sup>, T-helpers: CD<sup>4+</sup>,

T-suppressors: CD<sup>8+</sup>, natural killer (NK): CD<sup>16+</sup>, and apoptosis factors: CD<sup>95+</sup>] prior to treatment, over 3 and 9 months after fetal stem cells administered to this group of children. Tests with the corresponding findings were made on the base of specialized laboratory at EmCell (Kyiv, Ukraine) with application of cytofluorimetry (wavelength 464-480 nm, by use of cytofluorimeter FASTER 2010, Beckton Dickinson, North Ryde, NSW, Australia). Parents of all children signed informed consent before the patients could receive their therapy by use of fetal stem cell preparations.

Gross motor functions and classification system (GMFCS) featured a five-level ordinal scale reflecting the order which decreases; all values of independence and functionality in children suffering from developmental delay and perinatally affected CNS [26].

The above study on developmental delay patients has been conducted in accordance with good clinical practice, Helsinki declaration and ethical standards of work with embryonic tissues of human (approved by the Ministry of Public Health of Ukraine).

### Stem cells procedure

Two preparations are produced in the form of cryopreserved suspensions of fetal stem cells including stem cells of fetal liver (preparation 1) and suspended fetal stem cells of human fetal brain (preparation 2). For this purpose, in conditions of a surgery room, and in compliance with the rules of aseptic and antiseptic we received the fetal material, specifically: the tissues of liver and fetal brain – extracted from the human fetus of 8 weeks of gestation; died as a result of medical abortion and in cases when pregnancy was interrupted due to social indications; with absence of developmental pathology or infection in a woman-donor who signed her informed consent. Obtained fetal tissues are placed to the sterile transport medium with Hanks' balanced salt solution (HBSS). Fetal tissues are separated and homogenized using HBSS in the sterile conditions. Suspensions received are exposed to filtration and cryopreservation. Dimethylsulphoxide (DMSO) is used as cryoprotector. Readymade suspensions are furtherly dispensed to the cryovials in a volume of 0.1-1.0 mL. Cryopreservation of cell suspensions is performed in the chamber with programmed freezing and according to a specially adjusted program. Suspensions containing stem cells of fetal liver and brain are cryopreserved using liquid nitrogen at the minimal temperature of -196°C.

For the aim of maintaining safety, both women-donors as well as ready-made fetal stem cells were tested for bacterial and viral infections, parasites and mycotic infections such as syphilis (*Treponema pallidum*), human immunodeficiency virus 1 and 2, hepatitis B and C viruses, toxoplasmosis (*Toxoplasma gondii*), rubella, cytomegalovirus, *herpes simplex* virus 1 and 2, Epstein-Barr virus, *Mycoplasma genitalium*, *Ureaplasma urealyticum*, *Ureaplasma parvum*, and *Chlamydia trachomatis*.

Our stem cell procedure consisted in transplantation of the suspensions containing cryopreserved fetal stem cells following a conventional premedication by use of 10 mg diphenylhydramine infusion and 15 mg prednisone during the treatment day 1, whereas a specially prepared solution was administered during the 2<sup>nd</sup> day of therapy. For the first day, all children in the MG were injected suspensions made of fetal liver (drip feed intravenous infusion) in a volume of 0.5-3 mL maintaining the nucleated cells count from 1.0 to 54×10<sup>6</sup>/mL, and a range of CD<sup>34+</sup> progenitor cells making up from 1 up to 20×10<sup>5</sup>/mL, whereas the number of mixed-lineage colony-forming units (CFU) in the suspension – constituted from 0.05 to 0.82×10<sup>6</sup>/mL.

### Statistical analysis

For study, we made use of the package of software program *Statistica 7.0* (StatSoft, USA). Sampling of the results was evaluated for the normal distribution by means of Kolmogorov-Smirnov test. On account for all study, data revealed different laws for distribution, an average value and sampled standard deviation were applied for featuring presentation. In a process of calculation we used both parametric (Student's t-test with normal distribution) and non-parametric methods: U - Mann-Whitney rank-sum test (for independent samples), W- Wilcoxon signed-rank test (for dependent samples) in distribution which were different from the standard one. Fischer's Exact test was employed during assessment on the ranges of significance with various qualitative signs. In all cases likely differences were regarded as reliable and maintained a significance that constituted less than 0.05.

### Results

In 78.57% of patients we observed a syndrome of early post-infusion improvement: children revealed improved physical and emotional state. Following administration of suspensions containing cryopreserved stem cells of fetal liver, we did not observe a single case of complication or adverse effects; no evidence of "graft-versus-host disease" (GVHD) recorded.

Immediate and remote results showed effectiveness of the suggested method of treatment in children.

Prior to fetal stem cell treatment (FSCT), the mean score by GMFCS scale was 3.5 ± 0.01 among the patients of the MG, whereas in the CG patients it made up 3.48 ± 0.03 scores. Over 3 months after therapy the average score by GMFCS constituted 3.21 ± 0.02 scores in the MG patients; simultaneously, patients of the CG revealed on average – 3.35 ± 0.03 scores. Over 9 months after treatment we observed significant improvement in children; that is, reduction in the average scores by GMFCS recorded in the MG (2.78 ± 0.04 scores), p<0.05. Simultaneously, among the patients of the CG an average score by GMFCS composed 3.12 ± 0.03 scores, p>0.05.

In 64.29% of children, we recorded improved communication, among them 71.43% of patients represented the MG and 57.14% children of the CG respectively. Sociability increased in 71.43% of children, whereas among children of the MG we recorded improvement in sociability by 57.14%, and patients of the CG revealed the parameter of sociability within a range of 42.85%. In addition, we also noticed improvement in respect to behavior in 85.71% of the MG children, as well as 57.14% of patients showed better behavior in the CG.

We also made an evaluation of immunology laboratory results for the children with developmental delay and perinatal damage of CNS (Table 1).

According to the Table 1, over 3 months after FSCT, B-lymphocyte (CD<sup>19+</sup>) count reduced significantly. This parameter was indicative of improved cell-mediated immunity in children, which was confirmed by the significant increase of CD<sup>3+</sup> and CD<sup>4+</sup> counts 3 and 9 months after FSCT. Again, no side effects were observed among the developmental delay patients during this period of observation.

There are signs of several effective mechanisms involved following FSCT, including regeneration of the neural cells, direct stimulation of the neurons, the endogenous stem cells as well as trophic paracrine mediators and neovascularization. Among the potential mechanisms

Table 1: Immunology laboratory findings.

Parameters	Before FSCT	After FSCT	
		3 Months	9 Months
B-lymphocytes: CD <sup>19+</sup> , % ×10 <sup>9</sup> /L	19.85 ± 0.61 0.3507 ± 0.22	10.58 ± 0.52* 0.2587 ± 0.31	10.19 ± 0.60** 0.3067 ± 0.19
T-lymphocytes: CD <sup>3+</sup> , % ×10 <sup>9</sup> /L	49.65 ± 0.12 1.4870 ± 0.27	51.20 ± 0.17 1.2429 ± 0.25	54.15 ± 0.31** 1.2602 ± 0.30
T-helpers: CD <sup>4+</sup> , % ×10 <sup>9</sup> /L	29.56 ± 0.50 0.8142 ± 0.42	32.43 ± 0.42* 0.7915 ± 0.33	35.71 ± 0.41** 0.8721 ± 0.41
T-suppressors: CD <sup>8+</sup> , % ×10 <sup>9</sup> /L	24.56 ± 0.41 0.562 ± 0.22	19.63 ± 0.51 0.4523 ± 0.17	22.10 ± 0.50 0.5680 ± 0.22
Natural killer (NK): CD <sup>16+</sup> , % ×10 <sup>9</sup> /L	13.26 ± 0.15 0.2888 ± 0.17	11.80 ± 0.11 0.3261 ± 0.15	10.81 ± 0.12 0.3262 ± 0.11
Helper-suppressor ratio CD <sup>4+</sup> /CD <sup>8+</sup>	1.44 ± 0.15	1.75 ± 0.13	1.32 ± 0.12
Leukocytes, ×10 <sup>9</sup> /L	9.1 ± 0.41	7.7 ± 0.44	5.7 ± 0.31
Lymphocytes, %	27 ± 0.60	32 ± 0.57	27 ± 0.51
Absolute lymphocytes, ×10 <sup>9</sup> /L	2.38 ± 0.21	2.38 ± 0.22	3.16 ± 0.22

**Note:**

\*\*p<0.05 between results before therapy and over 3 months after FSCT

\*\*\*p<0.05 between results before therapy and over 9 months after FSCT

of FSCT effect, the following advantages are registered: neuronal cell replacement, blood vessel regeneration, astrocyte and microglial cells replacement, blockade of splenic release of inflammatory cells and protection of intrinsic cells. One of the principal advantages appropriate to stem cell transplantation in children with perinatally induced developmental delay is that stem cells could replace the cells of damaged CNS. Most scientists working with adult stem cells show only a minimal survival of the cells transplanted with few if any, of such stem cells displaying markers/functionality of nervous tissue [26-28].

It does not mean that replacement alone would be sufficient to justify all improvements in developmental delay children under study. While embryonic or iPS cells may have somewhat greater potential for likely replacement and transformation, the number of cells involving into this process is quite limited in vivo. Even though, some replacement by transplanted cells may be potentially promoted, stem cells often do not develop normal processes and cannot induce functions within the neural circuitry [29]. Thus, cell replacement as an explanation for any advantage on the models is unlikely to be the case.

**Conclusion**

Use of fetal stem cells in a combined treatment of children with developmental delay after perinatal damage of nervous system is proved to be safe and effective method. The following significant clinical advantages of FSCT have been reported:

Syndrome of early post-infusion improvement. Effects to overall physical and emotional state were observed in 78.57% of children under study.

Our study has shown that FSCT, irrespective of DD severity in children with perinatal CNS affection, favorably impact the course of development among infants as well as promote advantages in immunology markers. Procedure of FSCT is simple and non-invasive, not causing any sort of complication or development of allergy reaction.

For advanced fetal stem cells effects we can additionally recommend a complex treatment with inclusion of medicines and application of the other supplementary methods for the patients.

Still, the way fetal stem cells exert influence on developmental delay children with perinatal affection of nervous system is understood incompletely and further full-scale studies are required. Likely profound research is demanded in the future altogether with the larger randomized, placebo-controlled trials to identify the potential of fetal stem cells in much detail along with all related improvements in children with developmental delay resulting from perinatal damage of CNS of the newborns.

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**Competing Interests**

This work is intended to be an original; all authors of the article are members of Cell Therapy Center EmCell, Kyiv, Ukraine. The authors have approved the article on this study and do agree to its submission to the journal. There are no matters pertaining to the conflict of interests among the authors contributing the above article to publication.

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