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Case Report

Clinical Case of Successful Therapy for the Patient with Autism by use of Fetal Stem Cells

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Abstract

More than 60 million persons all over the world are living with the diagnosis of "Autism", in accordance with the UNO. According to the WHO, almost every hundredth child is a sufferer of ASD. Such figures emphasize globalization of the problem, and its impact not only on the child's family but also on the economies of entire countries.

Autism diagnosis is difficult and based on the general symptoms in kids. Today, the neuroimaging techniques (methods of functional Magnetic Resonance Imaging (MRI) and MRI tractography), Electroencephalography (EEG), evoked cognitive potentials and dynamic monitoring of the results help with an objective evaluation of stem cell therapy.

Treatment options in modern pharmacology and rehabilitation psychotherapy for ASD kids are limited. Therapy methods do not ensure a full integration into social life and personality awareness. To alleviate likely problems in society, different therapeutic approaches exist that might reduce the manifestation of the various autism symptoms. FSC therapy is one such innovative method that has recently become enough popular.

We inform about the clinical case of successful treatment using fetal stem cells for a child with autism followed by the period of 1-year follow-up showing significant clinical results. Over one year, the positive changes that had been proved by the ATEC questionnaire, the EEG results, and MRI-tractography were noted for the patient's family. As emphasized in the clinical case report, fetal stem cell therapy is a promising and efficient treatment for children with autism. All that was sufficiently confirmed by the results acquired because we saw an overall improvement in this patient.

More Information

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Introduction

Autism Spectrum Disorders (ASD) belong to the developmental problems of the CNS. Those neurology diseases are usually associated with the impairments of a child's social interaction, verbal and non-verbal communication, obsessive-compulsive behavior, and difficulty in association with the world around them. Likely problems commonly begin in children during the first 3 years of life. ASD reveals a broad spectrum of cognitive, emotional, and neurobehavioral abnormalities, dysfunction of social interaction and communication, limited interest, and repetitive or stereotyped verbal/non-verbal behavior [1].

The prevalence rate for patients with ASD was quickly growing all over the world and nowadays it is composed of 0.6% (95% with a confidence interval (CI): 0,4% - 1%). Analysis of the subgroups defined its spreading among the ASD patients of Asia, America, Europe, Africa and Australia which made up 0,4% (95% CI: 0,1-1), 1% (95% CI: 0,8-1,1), 0,5% (95% CI: 0,2-1), 1% (95% CI: 0,3-3,1), and 1,7% (95% CI: 0,5-6,1) respectively [2].

ASD is a significant burden for public health worldwide. Despite the growing number of cases, and financial and social consequences of this state, such interventions' effectiveness might be restricted and so those emphasize the importance of the biological approach, targeted at studying various etiological aspects of ASD both on the cellular and molecular levels.

In the world of practice, stem cell-based ASD therapy is rapidly gaining popularity [3]. Stem cells (SCs) can be split depending on their origin: Embryonic Stem Cells (ESCs) (including induced pluripotent SCs), FSCs, and adult organism SCs (derived from umbilical or cord blood, placenta, bone marrow, immobilized blood, adipose tissue, etc.) [4].

FSCs used in our treatment differ from ESCs and adult SCs. FSCs have greater proliferative and differentiation potential compared to adult SCs [5,6]; however, at the same time, they lost their ability for spontaneous transformation and uncontrolled cell differentiation which might be a factor for tumorigenicity, as in the cases with ESCs [7]. The high proliferative activity and plasticity of FSCs allow their native clinical application without preliminary cultivation. Cultivation is the reproduction and division of cells outside their natural environment. Each division leads to exhaustion of the cells (as in the case of Mesenchymal Stem Cells (MSCs) obtained from adult organism SCs by cultivating them) and is likely to accumulate the "errors".

FSCs and progenitor cells do not cause rejection by the recipient, as observed in the cases of adult SC use (graft-versus-host reaction). Such characteristics refer to the FSCs as being immunologically immature because their Human Leucocyte Antigen (HLA) complex has not been yet developed enough [8].

Unlike umbilical cord blood, bone marrow, or SC preparations derived from immobilized blood, FSC preparations contain stem cells with a low expression of the markers of pluripotency [4].

Regeneration of the damaged cells and restoration/improvement of the functions within the organs are stipulated by the different mechanisms of FSCs action potential:

1. Differentiation of the cells into the appropriate types of specialized cells.

2. Restoration of the damaged or dying cells by way of the cells merge.

3. Secretion of the paracrine factors such as the growth factors, cytokines and hormones (vascular endothelial growth factor (VEGF), Platelet-Derived Growth Factor (PDGF), Angiopoietin-1 (ANG1), Interleukin-11 (IL-11), Prostaglandin E2 (PGE2), gene-6, stimulated TNF-6, Stromal-Derived Factor (SDF-1), hepatocytes growth factor (HGF), insulin-like growth factor-1 (IGF-1)).

4. Transfer of the mitochondria by tunneling effect on the nanotubes or microvesicles.

5. Transfer of the exosomes or the microvesicles containing RNA and the other molecules.

The unique value of our treatment is the administration of the neuronal SCs, extracted solely from the fetal brain [9,10]. The progenitors of the neural cells can contribute to neurogenesis, regeneration of the nervous system, intercellular communication, and development of the synaptic links, as well as modulation of the neuronal networks [11,12]. These cells decrease local inflammation of the nervous tissue [13], improve cerebral microcirculation [14-16], promote neuroprotection [17], and affect the microglia abundance, playing the main role in resolving injury and inflammation within the central nervous system [18]. The neural cells contribute to remyelination by means of releasing the angiogenic and axonal growth factors. A combination of the appropriate neuron-glia links, as well as the other repair processes shall definitely improve the functional recovery [19].

Clinical case description

A 12-year-old child, who has been under the supervision of a pediatric psychiatrist at the Clinical Hospital "Psychiatry" beginning from the age of 3 years was admitted to the Cell Therapy Center "EmCell" because of diagnoses: F.70, F.84.8, R.94, in accordance with a generally accepted classification, and the diseases encoded according to the ICD 10. Following the established diagnosis, the patient was provided psychological-pedagogical correction, including speech therapy classes. In addition, within the last 2 years and until the visit to the clinic, the child was prescribed drug therapy using memantine 10 mg/day. During the primary visit, the parents were concerned about the child's incomplete understanding of the spoken language, the patient was not able to follow the simple instructions and needed detailed guidance and examples to perform all complex tasks. There were issues with visual selection for certain associations, as well as choosing the analogue with the pictures, etc. The child had difficulties with the verbal explanation (was not able to fit opposite meanings or pick up the divergent sense by the pictures). The patient's age-inappropriate development of socio-dialogic language was remarkable too. The parents were also concerned about understanding the logical-grammatical constructions and the patient's ability to establish a cause-and-effect relationship. The child showed an incomplete understanding of the social and emotional context according to various situations. The parents reported the child's poor attention span and concentration, difficulty with organizing the educational process, as well as the patient's impulsiveness. It was difficult for the child to concentrate on the tasks owing to the constant distraction of attention towards the other objects around.

Our patient is the first and the only child in the family. Maternal pregnancy emerged against the background of moderate anemia in the mother. Labor was in the due terms. Complications – unremarkable. Birth weight – 3720 g, height – 54 cm, head circumference – 35.5 cm, chest circumference – 35 cm. Apgar score – 7/7 scores. Breastfeeding was until 1 year and 3 months. During the first year of life, the child developed normally: for the first 6 months, the patient smiled, "cooed" and reacted to the external stimuli. The child sat at 6 months of age and started walking at 11 months. The child started saying the first words at the age of 10 months, and skills to build up the phrases appeared after the age of 14 months. Beginning from the age of 2 years, the patient began playing and stereotypical behavior was noticeable. From the age of 2 years and 6 months, speech development stopped and the child's behavioral disorders progressed. The patient went to the inclusive preschool and from the age of 7 years – attended the school, where the child partially lagged behind the peers in psychological development. After the family's evacuation outside Ukraine, because of the full-scale invasion of Russia, the patient's previously acquired skills regressed.

The results of the examination

ASD diagnosis was confirmed in accordance with the diagnostic criteria of the 10th revision International Classification of Diseases (ICD-10): the presence of the disorders with speech development (receptive and expressive speech delay) in the early age child (up to 3 years), as well as patient's deficits of social and functional interaction. The results of evaluation after the interviews and autistic behavior evaluation questionnaires according to the ADI-R+ADOS, and ATEC scales [20] were applicable to identify the therapeutic effects after ASD treatment. At the beginning of the study, we applied the ATEC scale for assessment of the results as follows: language/communicative skills — 5 scores, social adaptation — 20 scores, sensory/cognitive abilities — 16 scores, health/physical development/behavior — 19 scores. The child met the criteria for a moderate degree of autism (60 scores). During the Electroencephalogram (EEG) investigation, the higher peak frequency of the dominant α-rhythm power spectrum (10 Hz) was verified to be compared with the age norm in children. At hyperventilation for (2-3 min.), the formation of the transient focus of paroxysmal activity in the posterior-frontal areas of the cerebral cortex was determined as the flashes, paroxysmal "sharp" waves with a frequency of 5-6 beats/sec. and maximum amplitude up to 100 - 150 µV, without generalization events. No evidence of the "absence" discharge or the signs of decreased threshold of the epileptic readiness in the brain was identified.

According to the results of the brain MRI and the MR Tractography readings (magnetic resonance tomography *TOSHIBA Vantage Titan 1.5 Tesla*) with 3D reconstruction to evaluate the conduction pathways in the brain, MR signs of damage to the cingulate, the arcuate and the upper longitudinal pathways on the left were demonstrable (Figure 1).

Diagnosis: Children's autism with qualitative disorders of social reciprocity and communication, disorders of activity and attention span, emotional-volitional disturbances, grade II receptive-expressive speech disorders, as well as evidence of neuropsychological deficits in the form of semantic dyslexia, acoustic and optical dysgraphia. The diagnosis was confirmed in the LLC "Clinical Hospital – Psychiatry", in Kyiv, Ukraine.

Treatment: The patient underwent a two-day course of treatment by Fetal Stem Cells (FSCs). In our treatment, the source of cryopreserved stem cell suspension was used for therapy which included the FSCs extracted from the dead fetus of 7 weeks - 8 weeks gestation, acquired resulting from the legal abortion, in conformity with family planning or social reasons. The donors of the abortive material were practically healthy women who were tested "negative" for hemic infections prior to pregnancy interruption. The bio-ethical principles are strictly followed for all stages of our clinical study and treatment has been performed according to the legislation of Ukraine, which regulates stem cell therapy on the territory of Ukraine. The therapy program included intravenous administration of fetal hematopoietic and pre-mesenchymal stem cells, as well as fetal neuronal stem cells for subcutaneous and intranasal administration. The child also received the preparation of the exosomes harvested from the FSCs and used for the inhalation procedure (Picture 1). Both at the time of our treatment and within the whole period of observation, no single side effect or complication after stem cell therapy had been reported.

Examination over 1 year

At the time of the child's examination of over 1 year, improvement of the spoken language perception had been worthy to remark (the patient could perform simple requests and complex instructions; there was no need for additional explanations or hints for the patient), the child's improved ability to explain verbally was also present. A partial discrepancy between the age and development of the socio-dialogic language was preserved. Difficulty with understanding the logical grammar constructions and establishing the cause-and-effect relationship was not the case. The patient showed an understanding of the social and emotional context of the situations and demonstrated improvement in concentration and attention span. The child had moderate problems with the educational process organization. The patient's persistent impulsiveness disappeared, though it was still sporadically noticed.

According to the parents: "The teachers noted improvements of the child's behavior and learning during the school classes, the patient had better communication with both teachers and the age mates."

The analyzed results by the ATEC scale showed the following results: language/communicative skills — 2 scores, social adaptation — 8 scores, sensory/cognitive sphere— 7 scores, health/physical development/behavior — 9 scores, which were corresponding to a mild deviation towards developmental delay in a non-autistic child (28 scores).

According to the EEG data, slight changes in the brain bio-

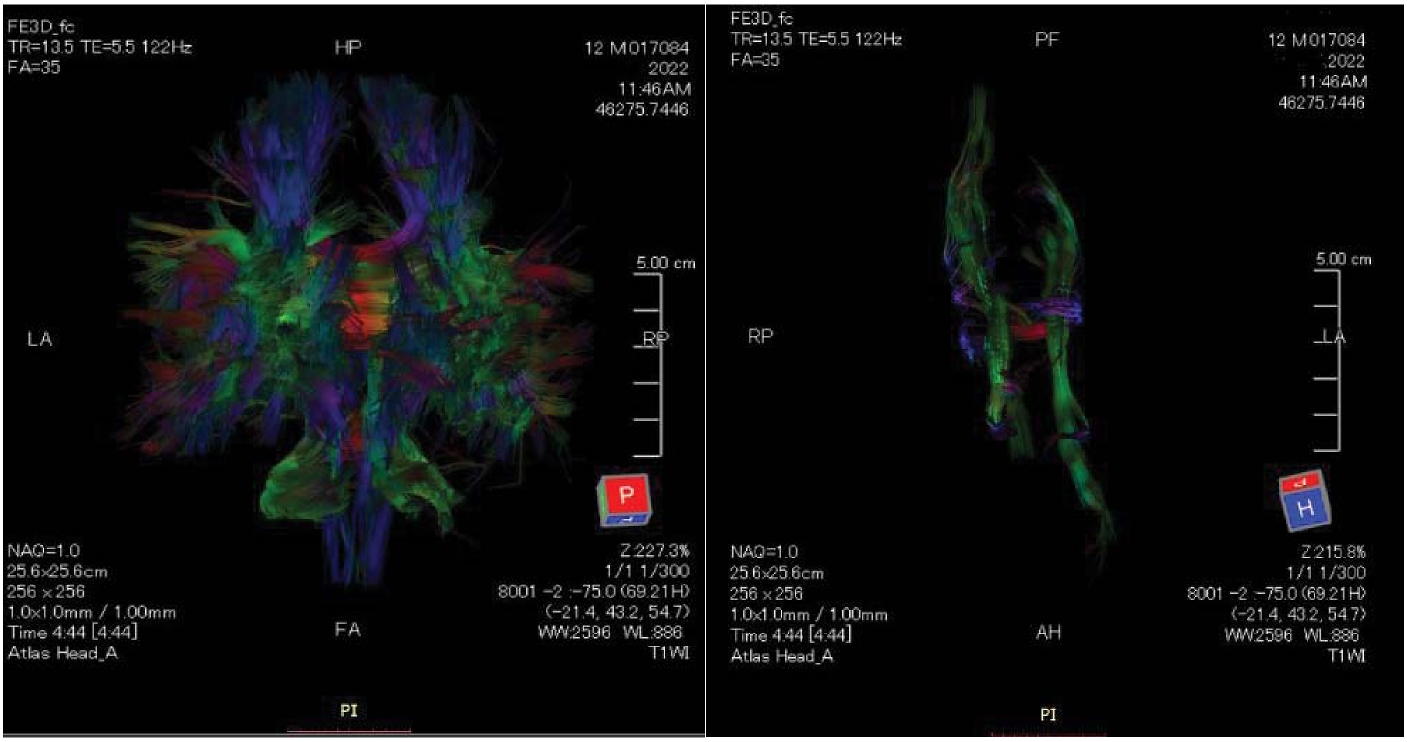

Figure 1: MR signs of damage to the lumbar, arcuate, and upper longitudinal pathways on the left.

potentials were represented by a mild periodic bioelectrical background activity slow down. The frequency of the main rhythm remained according to the patient's age. Reactivity to afferent stimuli is normal. Epileptic activity and regional delays are not demonstrable. The positive dynamic in the patient was identified if compared with the previous study.

Over 1 year, when the repeated brain MRI study and MR tractography (magnetic resonance tomograph *TOSHIBA Vantage Titan 1.5 Tesla*) were conducted providing the reading for 3D reconstruction, certain positive dynamics were shown, when compared the results after the previous brain MR study and we observed a partial renewal of the retrosplenial component over the left cingulate pathway, as well as the partial restoration of the temporal part of the left arcuate pathway (Figure 2).

Discussion

The above-mentioned case of ASD child treatment by administration of the FSCs, including the fetal progenitors of the neural cells is worthy of special consideration from the viewpoint of the obtained data about the subjective positive changes which were also proved by the objective evidence. Subjective results consist of the feedback from the parents, as well as from the child's teachers who are in direct contact with the child and conduct the educational work.

The improvement of the patient's conductive pathways proved by the results of the dynamic MRI tractography is the most interesting out of the objective evidence results.

The restored conductive pathways are considered to be the functional substrate for expressive and receptive speech development, and complex social and behavioral functions in children [21-23]. Thus, the data of the scientific literature support a likely hypothesis that abnormalities of the white matter referred to cingulum bundle play a clue role in the neurobiology of ASD. The cerebral structural conductive pathways and advantages of the micro- and macro-structural organization of the brain white matter are commonly estimated by use of the diffusion-weighted MRI study (DW-MRI). There are several DW-MRI analytical approaches, including voxel analysis, diffusion tractography, and connectomics. A large number of DW-MRI investigations using such diagnostic methods provide for the atypical microstructural organization of the white matter in various brain regions and white matter tracts in children with ASD [24].

Impressive was the speed of developing positive changes in the child's social adaptation and cognitive ability after stem cell therapy [1], having been confirmed by the results of the ATEC questionnaire. Over 1 year, we can observe significant changes in the child's psychological and behavioral status. Within a year, progress with the child's development and communication skills (due to the increased level of socialization and cognitive sphere) as well as the patient's higher parameters of overall health made it possible to change the child's evaluation from the group of the ASD with a moderate degree of severity to the rank of non-autistic children who are showing a mild deviation towards the direction of developmental delay.

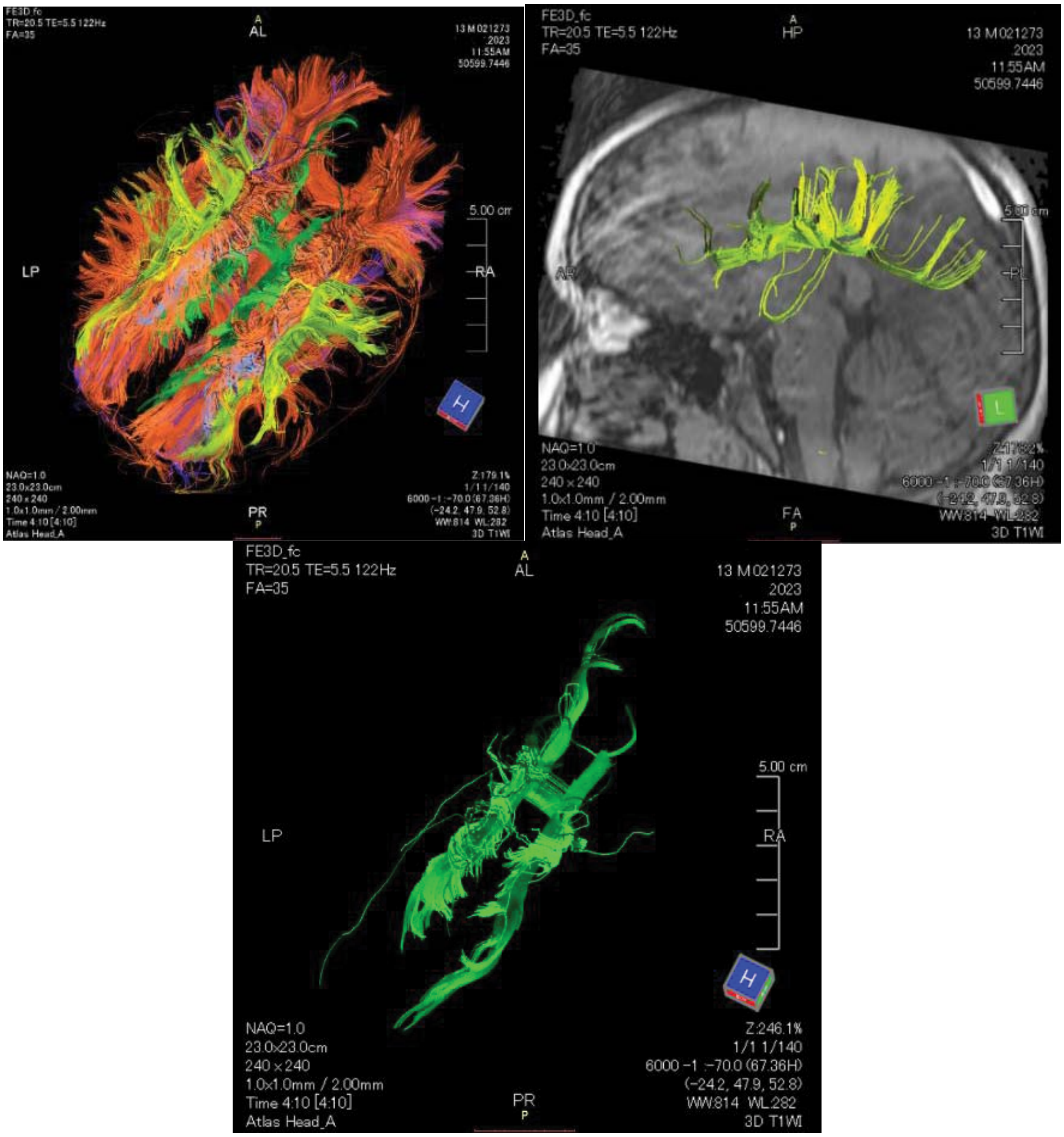

Figure 2: Partial restoration of the retrosplenial component over the left cingulate pathway; partial restoration of the temporal part of the left arcuate pathway.

There was no fever, graft-versus-host reaction, or other undesirable adverse reactions both at the time of our treatment and within the whole period of observation. The arousal of the epileptic background activity was not demonstrable; on the contrary, FSC treatment improved the brain action potential in the child.

Conclusion

This case of treatment for a child with ASD demonstrated the high effectiveness of FSC therapy, which had become proof of the patient's significant clinical improvements. The child had the advantage after therapy as soon as over 1 year, which had been identified by the ATEC scale, the results of EEG, and the MRI-tractography readings.

The data obtained require future follow-up to monitor the stability of all acquired therapeutic effects, as well as performing a large-scale investigation for ASD patients shall be pursued. Treatment by administration of FSCs is thought to be the promising and safe therapy method for autistic children care.

Ethical considerations

All bio-ethical principles are strictly followed within all clinical studies and our stem cell treatment is performed according to the legislation of Ukraine which regulates stem cell therapy on the territory of Ukraine.

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