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CASE REPORT

The use of stem cells in the treatment of cerebral palsy

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Abstract

Cerebral Palsy (CP) is one of the most common reasons for physical disability in children. There are numerous factors that affect the development of this disease which occur predominantly in the perinatal period. The aim of this report is to highlight new possibilities for treating cerebral palsy with stem cells, based on a literature review with the focus on a clinical case from a Child Neurology Department in Lublin, eastern Poland. To date, treatment methods have not had good results. A future alternative is the administration of stem cells. The clinical case presented is evidence that further research is needed to improve this new treatment method. Among all the symptoms of CP, the most important is reduction in muscle tone in the children, and stem cell administration reduces the spasticity. Intensive rehabilitation and support from psychologists and neurologists are still the primary means of improving the performance of patients with CP.

Key words

rehabilitation, cerebral palsy, mesenchymal stem cells

INTRODUCTION

Cerebral Palsy (CP) is one of the most common reasons for physical disability in children with the frequency of 2 per 1,000 live births. There are numerous factors that affect the development of this disease, predominantly they occur in the perinatal period and are associated with maternal infections, preterm births, intrauterine growth restriction, or use of specific medications [1].

Epidemiological studies have shown that infections of the genito-urinary tract (GUI) during pregnancy, especially chorioamnionitis, play a significant role in pathogenesis of CP. It is believed that clinical chorioamnionitis increases the risk of CP in term (relative risk = 4.7) and preterm infants (relative risk = 1.9), due to inflammatory response to intrauterine infection that causes periventricular leukomalacia [2]. It is essential to remember the coexistence of GUI and preterm births as the risk factors of cerebral palsy, since pregnant women with maternal infections tend to have preterm labour (before 32 week's gestational age) [3].

It has been proven that CP appears more frequently in children born prematurely, and the risk is inversely proportional to the decreasing gestational age. The most common subtype of cerebral palsy in this particular group is spastic diplegia [4]. In addition, pre-term births have a strong connection with intrauterine growth restriction (IUGR), as infants born before 37 weeks' gestation tend to weigh less and grow slower than infants born after 37 weeks [5].

Studies have shown that the use of paracetamol and aspirin during the second trimester may increase the risk of two spastic types of CP – unilateral spastic CP due to paracetamol use, bilateral spastic CP due to aspirin use. However, more research is required to collect prospective data about the negative effect of some medications on the brain development of a child [6].

The aim of this paper is to highlight new possibilities for treating cerebral palsy with stem cells, with a focus on a clinical case from a local clinic.

Previous treatment methods of Cerebral Palsy. So far, the treatment of cerebral palsy has been mainly based on the nature of the problem to be addressed in this report, and needed a Multi-specialist Patient Management Team headed by a team leader who coordinated all the activities of the specialists. The team also included a surgeon, physiotherapist, occupational therapist, speech therapist and psychologist [1]. Nowadays, as soon as a doctor makes a diagnosis, sick children are referred to a physiotherapist [7]. This is based on a thorough history-taking from the parent, analysis of neuroimaging findings, including a neonatal MRI performed before 5 months of age, and a Hammersmith infant neurological examination and specialized neurological scales, including Pechtel's qualitative assessment of general movements [8].

The physiotherapist assesses motor skills, improves mobility and assists with positioning to improve children's daily functioning. The two main types of intervention are training in task-specific skills to improve motor coordination and performance, and the other, physical training [7]. Physiotherapy implemented soon after diagnosis provides much better benefits for young patients, which include a detailed assessment of motor skills, which helps to identify possible intervention targets. In addition, it increases mobility and provides an opportunity to position patients for improved daily functioning. Physiotherapists focus on task-specific skills training, which improves motor coordination and performance. Additional physical training strengthens the weakened limbs and improves their muscle strength. In the

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case of unilateral upper limb involvement, physiotherapists use the activity method in the treatment, which involves intensive training of the limb to improve hand function. In the case of lower limb therapy, strengthening is mainly used, which is the most effective option to-date for improving gait [9]. An additional equally effective method for improving locomotion is ground gait training or treadmill gait training, as it allows the safe repetition of steps under controlled conditions while increasing intensity [10].

Group physiotherapy uses movement initiated by the affected child and task-specific practice and environmental adaptations. These interventions include Learning Games Curriculum, CIMT and GAME [8]. Water therapy is proving to be an extremely important element in adapting children with cerebral palsy to become more independent in the future. Studies confirm changes in muscles that have the effect of increasing mobility and positioning of patients. In addition, aquatic therapy allows for the development of motor skills, thus increasing large motor functions. Recent studies show that therapy conducted in water has significantly better effects compared to therapy on land, with better thermal and mechanical conditions contributing to this. The mechanical conditions result in reduced gravity and stress on the joints, so that postural control and muscle strength are optimised [9].

An important aspect in the treatment of patients is also to highlight the positive effect of animals on the reversal of disease symptoms.[1] Recent studies have shown improvements in posture, postural control or function of each body part. Better control of the body, especially of the head, shoulders and trunk, was observed in patients. In addition, a reduction in anterior-posterior displacement of the head and spine could be observed, which improved overall body stability. Ionatamishvii et al. showed a significant reduction in involuntary movements in the head, trunk and limbs, as well as a decrease in muscle tension. To-date, however, the optimal frequency of hippotherapy in children has not been established, so it is worth further investigation into this relationship [11, 12].

Stem cell administration in different diseases. Recently, there has been a growing number of promising and advanced scientific research on stem cell therapy [13]. Stem cells are a type of pluripotent and unspecialized cells that have been used for many years to treat certain neurological diseases. Their wide application results from the possibility of self-differentiation and high proliferative capacity [14, 15]. Stem cells have the ability to directionally differentiate and become specialized cells such as motor neurons, hepatocytes or renal cells [16]. Moreover, through their migratory, self-renewal and differentiation capacity stem cells contribute to the regeneration of damaged and diseased tissues [13]. They also restore connections between damaged nerve cells by replacing damaged cells, influence the inflammatory response, and have an immunomodulatory effect due to the mechanisms of reduced release of cytotoxins, excitotoxins and oxygen free radicals [13].

It is also worth mentioning the trophic mechanisms of stem cells. They enable extended cell viability by influencing angiogenesis or anti-apoptosis. One of their primary functions in the treatment of CP is their paracrine and immunomodulatory effects that affect the micro-environment of the central nervous system [16]. After the administration of stem cells they eventually differentiate into neurons and glial cells, such as astrocytes. These functions of stem cells are used not only in cerebral palsy therapy, but also in neurological diseases such as Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, spinal cord injuries or Huntington's disease, where they show both high efficiency and a high safety profile [17, 18]. Studies on the effect of stem cells in the treatment of cerebral palsy have shown significant effectiveness. Positive results mainly concern the improvement of gross motor function, although there are also studies confirming their beneficial effect on cognitive function and fine motor skills [13].

Among the many symptoms included in CP, the greatest improvement after stem cell administration is noticeable in the reduction of muscle spasticity [16]. According to available research, therapy using stem cells has a high safety profile, which encourages the use of this form of treatment. Only administration directly into the central nervous system is associated with a higher risk of side-effects. However, the incidence of serious adverse reactions is relatively low across all routes of administration [18]. Among the several possible sources of stem cell collection, the most common currently is the human umbilical cord blood/umbilical cord, while a slightly less common solution is the collection of stem cells from the bone marrow. These are non-arousing methods that do not involve complicated procedures and do not raise ethical controversies. The most common routes of stem cell administration are lumbar puncture and intravenous. The disadvantage of intravenous administration is limited by the blood-brain barrier, which means that only a small part of the administered cells reaches the brain parenchyma [18].

CASE REPORT

A clinical case of autologous cord blood stem cell administration in cerebral palsy. A girl diagnosed with cerebral palsy, age of 2 was given autologous cord blood stem-cell therapy. She was born at term through a natural birth with an unremarkable perinatal history. She weighed 3,600 g and measured 57 cm, and scored 9 points on the APGAR scale. During the first months of life, her parents observed a developmental delay in their daughter as she did not reach developmental milestones. Increased tension in the lower limbs with exaggerated tendon reflexes was observed. Emotional and cognitive development also remained delayed. MRI scan of the head showed periventricular leukomalacia and small diffuse hypoxic-ischaemic foci.

At the age of 2, she could barely sit unassisted and roll from prone to supine and from supine to prone position. She could not assume a quadruped position or crawl. Neurological examination revealed increased muscle tone in the lower limbs, decreased muscle strength, exaggerated tendon reflexes, contractures in the Achilles tendons and positive Babinski sign. Bilateral convergent strabismus was observed, speech development was also delayed: she could only speak single words and perform the simplest tasks. Based on the whole clinical picture, the child was qualified for stem-cell therapy with autologous cord blood.

Cord blood was obtained from the patient's umbilical cord at the day of her birth. It was collected by qualified personnel into a blood collection bag filled with CPD (citrate phosphate dextrose). The specimen was then submitted to

1 There is no explanation about how animals help in the therapy

sedimentation in a 6% hydroxyethyl starch solution, followed by centrifugation, and, eventually, refrigeration. Before cord blood collection, the mother was examined for bacterial and viral infections such as hepatitis B (HBsAg, anti-HBc, HBV DNA) and C (anti-HCV, HCV RNA), HIV infection (anti-HIV-1 & 2, HIV RNA), syphilis and cytomegaly (anti-CMV IgM). All tests proved negative. The cord blood sample was stored at the Polish Stem Cells Bank (PBSC) and met the standards of Association for the Advancement of Blood & Biotherapies (AABB) and Polish Ministry of Health for blood collection and storing. As a medical experiment, blood cord administration required the approval of the Bioethical Committee of the Medical University of Lublin in eastern Poland. Inclusion criterion for therapy was the diagnosis of Cerebral Palsy, whereas the exclusion criterion was a finding of drug-resistant epilepsy.

The patient was given 2 cord blood injections over a period of 5 months, at a dose of 1×10^6 total nucleated cell (TNC)/kg body weight each. The second injection, however, came from an unrelated person. Both before and during the stem-cell therapy, the girl was submitted to the same kind of intensive rehabilitation, consisting of neurodevelopmental treatment (NDT-BOBATH), hippotherapy, craniosacral therapy, early childhood stimulation (ECS) and speech therapy. Some progress was observed after the first cord blood injection. The girl started to crawl, and muscle strength had increased significantly since the previous examination (performed before cord blood administration), and contractures in the Achilles tendons slightly decreased. However, the muscle tone in the lower limbs remained abnormally high, tendon reflexes were still exaggerated, and the Babinski sign was positive. The patient improved her speech and cognitive skills: she began to form two-word sentences, point at different parts of the body andwas able to focus better on the performed task.

It was not until the second stem cell injection that a truly astonishing improvement was observed. Five months after the second cord blood administration, at the age of 3, the patient was able to stand up from a sitting position, retain a standing position, walk with leg orthoses, and maintain correct body balance. Further increase in muscle strength and a decrease in muscle tone was observed. The girl improved eye-hand coordination (capably putting together building blocks and puzzles). Her social skills also improved significantly: she cooperated willingly with therapists during therapy sessions and began to interact easily with other children. She also underwent potty training. Improvement was identified by physiotherapy assessment and neurological examination. Prior to the application of the stem cells, the child had been receiving physiotherapy on a regular basis, but progress was not as pronounced as with the simultaneous application of the stem cells and physiotherapy.

The administration of stem cells triggered a remarkable progress in our patient's neurological development. Not only did it normalize her neuromotor status (muscle tone, muscle strength, tendon contraction reduction), but also enhanced her gross and fine motor skills, as well as speech and social development. According to the experience of the Department of Child Neurology of Medical University of Lublin, children with CP treated with CB in the clinic exhibit a clear out-performance, compared to patients treated conventionally. The efficacy of CB in the treatment of CP in animal models has also been repeatedly proven and in numerous ongoing clinical trials [18, 19, 20].

DISCUSSION

Umbilical cord blood stem cells have been used for over 20 years as a cell source for haematopoietic stem cell transplantation. They are currently used in clinical trials for the treatment of autoimmune diseases or cerebral palsy. Their long-term positive effects include improvement of large motor skills, as demonstrated by the presented clinical case, derived from their homologous paracrine signalling which stimulated recovery in the injured brain [19, 20].

Allogeneic umbilical cord blood stem cell transplants are mainly performed, as most children do not have their own cells banked before treatment. Studies have shown that allogeneic stem cells may be more beneficial than autologous cells for CP patients, because the allogeneic treatment group demonstrated significantly decreased levels of pro-inflammatory, factors and greater improvement in motor and social behaviour, compared to the autologous treatment group [20]. During the treatment period, no serious adverse effects were observed among patients in the short- or long-term after stem cell administration, such as death or GVHD. Only fever and vomiting were most commonly observed [21].

Intrathecal infusion and the age in the initiation of treatment ≤10 years old might be associated with the occurrence of adverse events. A dose-response relationship cannot be shown and there is a lack of a unified worldwide standard for the optimal cell number [20]. In one study, dose was important and better results were obtained by children receiving higher doses and lower doses better results than placebo but despite traditional forms of treatment min physiotherapy children achieved very significant functional improvement [19]. children receiving cell doses ≥2 × 107/kg had a response is important? [19, 20].

Among all the symptoms of CP, motor symptoms are predominant, resulting, among other things, from the reduction in the children's muscle tone. Stem cell administration improves the large motor symptoms of patients to the greatest extent by reducing spasticity [20]. Nevertheless, intensive rehabilitation and support from psychologists and neurologists are still the primary means for improving the performance of patients in CP.

To-date, numerous studies on the efficacy of stem cell administration have confirmed a positive effect on improving motor function. A significant difference could be observed after transplantation of autologous BMMNCs in lying down, rolling over and sitting, as well as running, walking or jumping. After transplantation of bone marrow-derived stem cells, a mitigating effect on motor function was demonstrated. Ongoing studies on transplantation of mononuclear cells from peripheral blood show improvement in gross motor function, with no change in grade of severity [18].

None of the studies performed showed a significant an effect of cell transplantation on small motor function, as on large motor function. Only neuronal progenitor cells from the foetal brain were proven to improve hand movements, including pinching small objects or eye-hand coordination. Almost all studies have confirmed that there are changes in muscle tone after stem cell transplantation; however, this is a slight decrease of approximately 3.4 – 2.0. It is noteworthy that no study has confirmed changes in muscle tone after cell therapy with cells from hUCB/UC or peripheral blood [18].

Numerous clinical studies demonstrate the efficacy of stem cell administration in the treatment of CP, but this requires

the establishment of precise criteria for qualifying patients for this therapy, determining the appropriate dose and route of administration. Most studies have had a short follow-up period of patients after treatment, and further measurements would need to be made to assess the long-term effects and safety after stem cell application [18].

CONCLUSIONS

Cerebral palsy is still a very difficult disease to diagnose and treat. Currently, there are no widely available reimbursable drugs on the pharmaceutical market to help treat young patients. Stem cell therapy, however, holds great hope for changing this situation. Published studies show significant improvements in large as well as small motor skills. Physiotherapy and rehabilitation of young patients remains an essential therapeutic component. More research into the effectiveness of the innovative therapeutic method is needed, but the clinical case presented offers great hope for a better future for patients with cerebral palsy.

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