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Mini Review

Stem Cell Therapy Innovative Management Modalities in Children with Cerebral Palsy, Autistic Spectrum Disorders

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Abstract

The application of stem cells as a therapeutic tool for some of the common neurodevelopmental disorders (cerebral palsy, autism, intellectual disability and muscular dystrophy)

Various factors influencing the outcome of stem cell therapy such as different types of cells, different routes of administration and dosage and frequency of transplantation and the role of stem cells is coming up nowadays as a novel therapy and as a future therapy of such incurable diseases.

Stem cells from umbilical cord blood are safe and promising for various brain injuries and disorders. A six-month pilot study predicated on parental observations and completed questionnaires concerning the responses of cerebral palsy stricken children to treatment with umbilical cord stem cells was launched during 2004. As part of this Mexican study, eight children (3–12 years of age) diagnosed with cerebral palsy underwent transplants with 1.5 million stem/progenitor cells (CD34+ and CD133+) that had been purified and expanded from the American Association of Blood Banks (AABB)-certified human umbilical cord blood. According to parent tendered observational reports, none of the children had graft versus host reactions. Eight out of eight children showed some improvement in mobility and/or cognitive function. Six children (75%) were rated as improving in muscle tone, hip movement, leg movement, rolling to the side, balancing while sitting and balancing while standing by the end of the six month follow up.

Use of novel monitoring tools such as MRI MSK and PET-CT scan brain to track the changes occurring at cellular level after stem cell therapy.

We also highlight the importance of a multidisciplinary approach of combining rehabilitation with stem cell therapy

Therapeutic strategies and clinical expectations of patients and medical professionals have not yet been met. Currently, available treatments such as physiotherapy, occupational therapy, behavioral therapy, psychological intervention, speech therapy and pharmacological intervention only focus on alleviating the symptoms of these disabilities and do not address the underlying neuropath physiology. However, the advent of stem cell therapy has opened new avenues for treatment of pediatric neurological disorders.

Keywords: Autism; Stem cell therapy; Cerebral palsy; Physiotherapy; Neuromuscular dystrophy

Introduction

Neurological disorders accompanied by nervous and musculoskeletal dysfunction, resulting in movement impairment and muscle tone abnormalities [1]. Clinical symptoms in such patients include motor weakness, muscle tone changes, delayed milestones, headaches, seizure, and coordination loss. The growing concern about neurological disorder treatment is due to disability of brain and spinal cord neurons to regenerate instinctively [2].

The action of stem cells in tissue repair is a need for further studies. The role of these cells in the secretion of hormones and growth factors in the niche, induction of cell division and differentiation in local cells and differentiation of stem cells in damaged tissue is the samples of effects of tissue repair by stem cells [3]. Moderate and severe neural defect is almost not repaired by human body, so the use of stem cells with high dif-

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ferentiation potency like umbilical cord blood cells and Mesenchymal stem cells (MSCs) can be effective in these injuries [4]. These defects in infants' effect on their lifestyle through their life. So early treatment is important for reduce development of neural defects. Treatments like moderate hypothermia that is done in newborn with hypoxic-ischemic but about one-third newborn die or not impairment. So, research for new treatment methods with more efficacy is necessary [5].

The distinguishable phenotypic features of stems cells are an integral component of the understanding the biology and potential for cell-based therapies in CP [6-9]. Indeed, to determine their safety, efficacy, and putative mechanisms of beneficial action, stem cell identity is paramount. It is necessary to determine the source of stem cells and thus mechanisms of action associated with cell therapy. Notably, diverse types of stem cells have been identified for potential use in CP Here we focus on those cells most proposed for CP. While autologous cells may superficially seem appealing, allogenic cells are likely better for preterm neonates because of limited quantities, stem cells arising in the context of the etiology of CP (e.g., fetal inflammatory response syndrome), and immune immaturity [10]. Both autologous and allogenic stem cells can be challenging to reliably produce for clinical trials [11-13].

Cerebral Palsy (CP)

CP is characterized as a neurological disorder among children [14]. It is defined as a spectrum of disorders accompanied with movement and postural development. It causes restriction in activity. Perception, hearing, vision, speech and psychic disabilities are cardinal symptoms of cerebral palsy [15]. Also, it results from injuries causing motor control disturbances happening in newborns, infants up to 1 year after birth, or within the pregnancy [16].

Etiological factors associated with CP include chorioamnionitis and preterm birth, maternal and/or neonatal infections, intrauterine growth restriction, neonatal encephalopathy, infantile traumatic brain injury, and genetic mutations [17-19]. Congenital abnormalities in children with CP are more common than appreciated previously [20]. Importantly, many children with CP have either multiple overlapping etiologies [21] or fail to have a specific cause identified; both factors impact clinical trial design and outcomes [22].

Hypoxia is explained as the cardinal reason for CP [23]. CP as a non-progressive disability characterized by an incidence of 2 per 1000 among live birth [24]. Two categories of CP treatment are notable: treatment of injured site of brain, that are responsible for muscle coordination, and controlling the muscle coordination dysfunction resulting from cerebral palsy. CP encompasses variety sites of developing brain involved with several types of injuries including migration failure within brain development from origin to suitable functional sites, failure to myelin deposition
of oligodendrocytes, causing weak impulses, death of cells located in grey matter and, synapses with poorly function in brain cells [25].

CP risk factors are as below: low birth weight, multiple pregnancy, prematurity [26]. The most frequent single form of CP is periventricular leukomalacia [27]. A clinical study carried out by Wang X et al. in pediatric CP patients provided the safety feasibility, and effectiveness of autologous Bone marrow mesenchymal stromal cells transplantation using the Gross Motor Function Measure (GMFM) about motor function development [28]. Research in China evaluating the safety of neural progenitor cell transplantation in 45 children suffering from severe CP have depicted effectiveness of NPC transplantation as a therapeutic method [29].

Autism Spectrum Disorders (ASDs)

ASD affects more than 1% of the general population (1:59 subjects) [30] and are characterized by two core symptoms: the first one is impaired social communication, and the second situation is restricted, repetitive types of behavior, interests, or activities. However, the biggest problem in autism is triggered by associated symptoms such as irritability, anxiety, aggression, compulsions, mood lability, gastrointestinal issues, depression, and sleep disorders [31]. On the basis of the core and associated symptoms, autism is diagnosed through observational and psychometric tests; therefore, the clinical diagnosis is made based on the presence or absence of core behaviors. The Diagnostic and Statistical Manual of Mental Disorders is conventionally used as a gold standard for autism diagnosis [32]. However, the neurometabolic differences of autism lead us to look for biologic markers that respond to a correct, precise, and concise diagnosis [33]. These biologic markers should be detected early during pregnancy, because the pathogenesis of ASD is not set at one point in time and does not reside in one process, but rather is a cascade of pre- and postnatal pathogenic processes in the vast majority of ASD toddlers

Stem Cells

Stem cells are able to renew themselves and have the ability to differentiate into distinctive mature cell types, leading to new tissue formation, repair, and regeneration [34-37]. Mononucleocytes (MNCs) originated from bone marrow consist of various cell types including hematopoietic stem cells, tissue-specific progenitor cells, stromal cells, and specialized blood cells within different developmental stages. Data of researches show that stem cells can migrate from site of injection into the injured position [38]. Moreover, increase in angiogenesis, producing signaling factors including Vascular endothelial growth factor (VEGF) and Fibroblast growth factor (FGF) by stem cells result in neovascularization [39]. Other relevant mechanisms are tissue remodeling, apoptosis prevention, inflammation decline, and satellite cells activation [40]. Hematopoietic, endothelial and angiogenic cells are found in Bone marrow (BM), which is a source for many stem cells [40,41]. Stem cells can able to differentiate in brain [42].

Conclusion

Stem cell-based therapy may be an effective strategy to regenerate and repair pediatric neurological disorders. Current therapeutic intervention methods for children with neurological disabilities are limited, although various research on animal models have carried out, resulting in effectiveness of cell therapy.

Cell-based therapies for CP must also undergo similar rigorous standards. Continued identification of mechanisms of genetic, structural, and functional variables that drive impairment and recovery, and the development of biomarkers of CP, will advance scientific support for use of cell-based therapies. Effective interventions during the acute, subacute, and repair phases following injury could possibly mitigate or lessen the long-term disability in person with CP. Increased rigor of both

preclinical and clinical efforts is essential to move the field forward and improve precision diagnosis and treatment for everyone with CP.

Besides, case reports evaluating cell-based therapy have been performed, showing safety and effectiveness of this procedure also in pediatrics with CP intrathecal infusion of autologous Bone-Marrow-Derived Mononuclear Cells (BMMNCs) was efficient and showed recovery of motor, cognitive, and sensory function. Because the performed research about this issue do not seem to be enough, more investigations and experiments are suggested nonetheless this review showed pediatric clinical research approaching challenges of neuronal repair development, and decreasing incidence among children are required.

Conflicts of interest: None.

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