Stem cell research in cerebral palsy: Option of treatment in future

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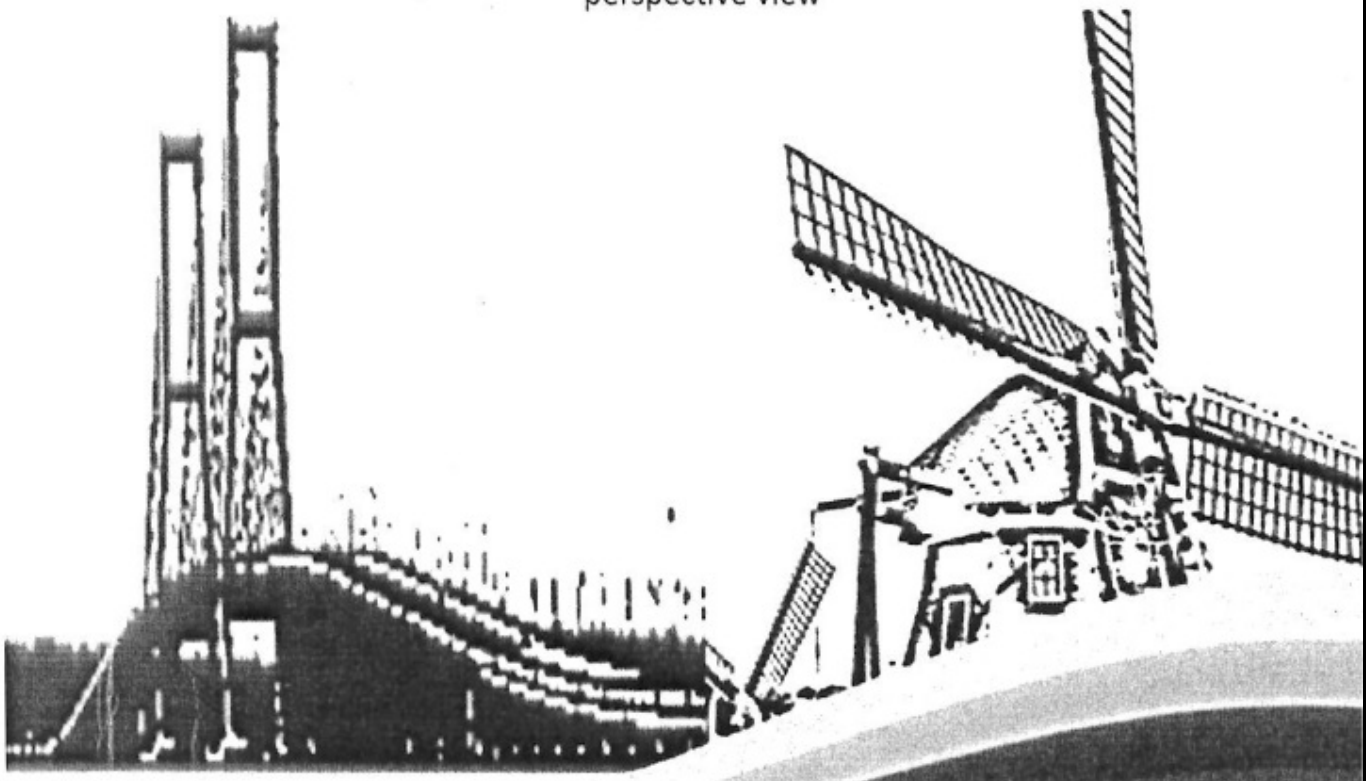

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Stem Cell Research In Cerebral Palsy
Option of Treatment in Future?

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Childhood cerebral palsy is a non-progressive brain disease that results from various cerebral insults that can occur before birth and 1 month after birth. Patient primarily present with motor developmental delay or motor dysfunction and possible mental retardation, epilepsy, behavioural disorders and sensory and perceptual disturbances. Conventional therapies for treating cerebral palsy include physical therapy, motor function training, language training, surgery and intramuscular injections of botulinum toxin. However these methods hav not improved cerebral injuries in patients with moderate-to-severe cerebral palsy (An, 2006).

Stem cell transplantation is a novel and promising treatment for cerebral palsy. However, this procedure is still in the initial stages of investigation (Caroll, 2011). Several preclinical experiments on animal models of cerebral palsy have been carried out to demonstrate the potential of cell transplantation to minimize damage and promote recovery. However, limited clinical trials have been initiated to study the effect cell therapy in humans.

Human umbilical cord blood cells (hUCBCs) have been explored to a great extent in cerebral palsy. hUCBCs have been administered in rat models of neonatal hypoxia/ ischemia. It alleviate spastic paresis in neonatal rat models resulting in normal walking (Meier, 2006). It is also observed that these cells exhibit a neuroprotective effect in the striatum, and decrease the number of activated microglial cells in the cerebral cortex of treated animals, further resulting in better functional recovery (Pimentel-Coelho, 2010). They protect the mature neurons in the neocortex from injury, bring about near-normalization of brain damage in the subventricular zone (SVZ) leading to significant improvement in behavioral functions. The long lasting effect of these cells is due to the paracrine effects of hUCBCs which stimulate recovery in the injured brain and protect against further brain damage (Bae, 2012). On transplantation, hUCBCs have shown to ameliorate neurological and motor deficits in CP model by reducing the levels of pro-inflammatory cytokines (Interleukin-1α (IL-1α) Interleukin-1β (IL-1β), and Tumor necrosis factor α (TNFα (Rosenkranz, 2013). Human umbilical cord blood (hUCB) cells have also shown to reduce sensorimotor deficits after hypoxic ischemic brain injury in neonatal rats. The dimensions of cortical maps and receptive fields, which are significantly altered after injury, are largely restored. Additionally, the lesion induced hyperexcitability is no longer observed in treated animals compared to control animals. The results demonstrate that hUCB

cells reinstall the way central neurons process information by normalizing inhibitory and excitatory processes (Geissler, 2013).

Various preclinical studies have shown that transplantation of stem cells in the CP models lead to survival, homing and differentiation of these cells into neurons, oligodendrocytes, astrocytes etc.

A Chinese study, wherein neural stem cells derived from human fetal brain (hNSCs) were transplanted into cerebral ventricle of HI injury neonatal rat, too demonstrated the survival, migration and differentiation capacity of these cells in rat brain (Qu, 2005). Similarly, Zheng et al showed that Multipotent astrocytic stem cells (MASCs) from mice transplanted into a rat model of hypoxia-ischemia (HI) survive, migrate and differentiate into neurons and astrocytes (Zheng, 2006). Park et al reported clonal neural stem cells (NSCs) when transplanted into brains of postnatal hypoxic-ischemic (HI) injury mice, home preferentially to and integrate extensively within the ischemic areas. They differentiate into neurons and oligodendrocytes, the cell types damaged due to HI (Park, 2006). Yasuhara et al, investigated the efficacy of intrahippocampal transplantation of bone marrow derived multipotent progenitor cells (MPCs) in HI injury. They found that transplanted MPCs ameliorated motor deficits associated with HI injury (Yasuhara, 2006). Webber et al in their study highlighted the protective effects of oligodendrocyte precursor cell transplantation in neonatal inflammation-induced

rat model of periventricular leukomalacia (Webber, 2009). Chen et al, transplanted magnetically labeled mesenchymal stem cells in a model of perinatal brain injury. They found that these cells migrate to lesion sites and proliferate. They are neuroprotective and indirectly contribute to brain repair (Chen, 2010). Study by Titomanlio et al, implanted neurosphere-derived precursors in neonatal mouse model of cerebral palsy induced by excitotoxicity. They observed that cells migrated to the lesion site, remained undifferentiated at day 10, and differentiated into oligodendrocyte and neurons at day 42. Although grafted cells finally die there few weeks later, this procedure triggered a reduction in lesion size and an improvement in memory performance compared with untreated animals (Titomanlio, 2011). All the above preclinical studies have been carried out in animal models of acute hypoxic injury, hence showing significant results. But, similar results are difficult to replicate in human cases since the intervention always cannot be carried out immediately post injury. Thus, more studies should be carried out in chronic injury models. Based on this observation, it can also be concluded that earlier the intervention better is the outcome.

Below are few of the published studies carried out in human cases of cerebral palsy.

Papadopoulos et al, administered autologous umbilical cord blood cells in 2 children diagnosed with spastic diplegic CP. They found that this therapy was safe, feasible and led to functional

improvements in children which was seen by the change in GMFCS (Papadopoulos, 2011).

Luan et al, carried out a study on 45 patients diagnosed with severe CP. They underwent transplantation of neural progenitor cell (NPC) derived from aborted fetal tissue. After 1 year, the developmental level in gross motor, fine motor, and cognition of the treatment group was significantly higher compared to the control group. These results suggested that NPC transplantation is a safe and effective therapeutic method for treating children with severe CP (Luan, 2012).

Li et al, transplanted autologous bone marrow mesenchymal cells in an 11 year old CP case with visual impairment. On six month follow up, he could walk better and his vision had improved significantly. These findings were supported by the electrophysiological examinations (Li, 2012).

Purandare et al, reported a case of cerebral palsy who was administered with autologous bone marrow mononuclear cells. On follow up, they recorded a significant improvement in motor, sensory, cognitive, and speech. Bowel and bladder control was also achieved. On the GMFCSE& R level, the patient was promoted from grade III to I. Hence, concluding that intrathecal infusion of autologous BMMNCs is feasible, effective, and safe in CP patients. (Purandare, 2012).

Chen et al, injected neural stem cell-like (NSC-like) cells derived from autologous marrow mesenchymal stem cells in 30 cases of cerebral palsy. The control group only received rehabilitation treatment. On follow up, they observed an increase in the GMFM scores and language quotients compared to the control group. No adverse events were recorded indicating that NSC-like cells are safe and effective for the treatment of motor deficits related to cerebral palsy (Chen, 2013).

Minet al, carried out a double blind, randomized, controlled trial in which the researcger administered allogeneic umbilical cord blood cells potentiatedwith recombinant human erythropoietin (rhEPO) in CP patients. Compared with the EPO and control the pUCB group had signifanctly higher scores on the GMPM and BSID II Mental and motor scales at 6 months. They observed improvementin motor and cognitive dysfunction in children with CP, accompanied by structural andmetabolic changes in the brain. (Min, 2013).

Wang et al, reported a case of a 5-year old girl with CP who underwent umbilical cord mesenchymal stem cells (MSCs) transplantation. She was treated with multiple times of intravenous and intrathecal administration of MSCs derived from her young sister and was followed up for 28 months. The gross motor dysfunction was improved. Immunity was enhanced, physical strength improved along with speech and comprehension (Wang 2013).

Jensen et al, recently published a study wherein a 2 ½ year old boy received autologousumbilical cord blood mononuclear cells intravenously. At 2-months follow-up the boy's motorcontrol improved, spastic paresis was largely reduced, and eyesight was recovered, as did the EEG. He smiled when played with, was able to sit and to speak simple words. At 40 months, independent eating, walking in gait trainer, crawling, and moving from prone position to freesitting were possible, and there was significantly improved receptive and expressive speech competence (four-word sentences, 200 words). This suggested that autologous cord bloodtransplantation could be a treatment alternative for cerebral palsy (Jensen, 2013).

Stem cell therapy for cerebral palsy still remains in its infant stage. Although cellular therapy for cerebral palsy has moved from the preclinical studies to bedside therapy; evidence remains inconclusive regarding multitude of variables. These variables are pertaining to cerebral palsyand cellular therapy. Pre-clinical models of effects of cellular therapy in cerebral palsy are farfrom the ideal state and show benefits only in acute injury. Majority of the human application of stem cells in cerebral palsy is for individuals who already have established pathology, hence at a chronic stage. Animal models of chronic injury are therefore required to study the efficacy and mechanism of action of stem cells. The individuals suffering from cerebral palsy are from

various age groups, and present with varied kinds and severitie of clinical manifestations;there is only a limited evidence abou which of these groups will benefit the most from cellular therapy

Stem cell therapy has been extensively studied but stil needs to be standardized before itbecomes a definitive treatmen modality. Autologous BMMNCs are safe and feasible option bu their effectiveness needs more clinical trials. Other types of sten cells need to establishsafety and efficacy. Though not a cure, sten cell therapy has emerged as a novel therapeuticoption to improv the quality of life.

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