

Review Article

The Use of Stem Cell Therapy in the Treatment of Autism Spectrum Disorder

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Abstract

Research on the use of stem cell therapy in regenerative medicine has shown great potential in the treatment of neurological disorders. Specifically, mesenchymal stem cells, adult stem cells from the umbilical cord and embryonic stem cells have been used in both animal models and clinical trials to treat autism spectrum disorder. Autism Spectrum Disorder (ASD) is an incurable neurological disorder characterized by behavioral and neuroanatomical abnormalities, commonly co-occurring with other neurological disorders including anxiety, depression and obsessive-compulsive disorder. Stem cell therapies are currently being researched to alleviate the behavioral tendencies typically seen in individuals with ASD.

Keywords: Autism Spectrum Disorder; Stem Cell Therapy; Embryonic Stem Cells; Mesenchymal Stem Cells

Abbreviations

ASCs: Adult Stem Cells; ASD: Autism Spectrum Disorder; BTBR: Black and Tan Brachyuric Mouse Strain; CARS: Childhood Autism Rating Scale; CBMNCs: Cord Blood Mononuclear Cells; DSM-5: The Diagnostic and Statistical Manual of Mental Disorder 5th Edition; ESCs: Embryonic Stem Cells; hASCs: Human Adipose-Derived Stem Cells; hESCs: Human Embryonic Stem Cells; iPSCs: Induced Pluripotent Stem Cells; MSCs: Mesenchymal Stem Cells; UCMSCs: Umbilical Cord-Derived Mesenchymal Stem Cells; VABS-II: Vineland Adaptive Behavior Scales Second Edition; VPA: Valproic Acid

Introduction

Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a term used to describe a spectrum of complex, heterogenous neurodevelopmental disorders characterized by an early onset and core features in two primary domains: social communication and restricted, repetitive sensory-motor behaviors [1-4]. The Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-5) identifies ASD in terms of five categories: social communication and social interaction, restricted, repetitive behaviors and interests, symptoms present in early development, symptoms causing clinical impairments of function and a lack of better explanation by intellectual disability or global developmental delay. Individuals with ASD tend to present currently or by history social reciprocity, non-verbal communication and difficulty developing, maintaining and understanding relationships as well as the possibility of stereotyped repetition of behavior, insistence on sameness, hypersensitivity or hyposensitivity and highly restricted, fixed interests [4]. In addition to the typical symptoms presented, other neurological and immune disorders are commonly presented in individuals with ASD such as Attention Deficit/Hyperactivity Disorder (ADHD), depression, anxiety and epilepsy, weakened immune system, immune system dysfunction and neuroinflammation (Table 1) [2,4-8,10].

	Social communication	Restricted repetitive behavior
Criteria	Persistent deficits in social communication and social interaction across multiple contexts, currently or by history	Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following:
Illustrative examples of symptoms	(1) Deficits in social-emotional reciprocity, ranging from abnormal social approach and failure of normal back-and-forth conversation, to reduced sharing of interests, emotions, or affect, to failure to initiate or respond to social interactions (2) Deficits in nonverbal communicative behaviors used for social interaction, ranging from poorly integrated verbal and nonverbal communication, to abnormalities in eye contact and body language or deficits in understanding and use of gestures, to a total lack of facial expressions and nonverbal communication (3) Deficits in developing, maintaining, and understanding relationships, ranging from difficulties adjusting behavior to suit various social contexts, to difficulties in sharing imaginative play or in making friends, to absence of interest in peers Symptoms must be present in the early developmental period. Symptoms may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning These disturbances are not better explained by intellectual disability or global developmental delay	(1) Stereotyped or repetitive motor movements, use of objects, or speech. (2) Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (3) Highly restricted, fixated interests that are abnormal in intensity or focus (4) Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment
Specifiers	With or without accompanying intellectual impairment With or without accompanying language impairment Associated with a known medical or genetic condition or environmental factor Associated with another neurodevelopmental, mental, or behavioral disorder With catatonia	

Table 1: Criteria considered in the diagnosis of autism spectrum disorder.

Previous research has also indicated the presence of neuroanatomical abnormalities in the majority of individuals with ASD that differentiate them from neurotypical individuals. These include prenatal overgrowth of the frontal cortex, region-specific changes in volume, alterations of white or gray matter and long-range connectivity between regions [7,9]. ASD development begins in the early embryonic stages with disruption of brain development, neuronal organization and cell reproduction and differentiation which in turn leads to neural migration, abnormal neuron maturation, reduced neural network functioning, synaptogenesis complications, laminar disorganization and neuroinflammation (Fig. 1) [2,10].

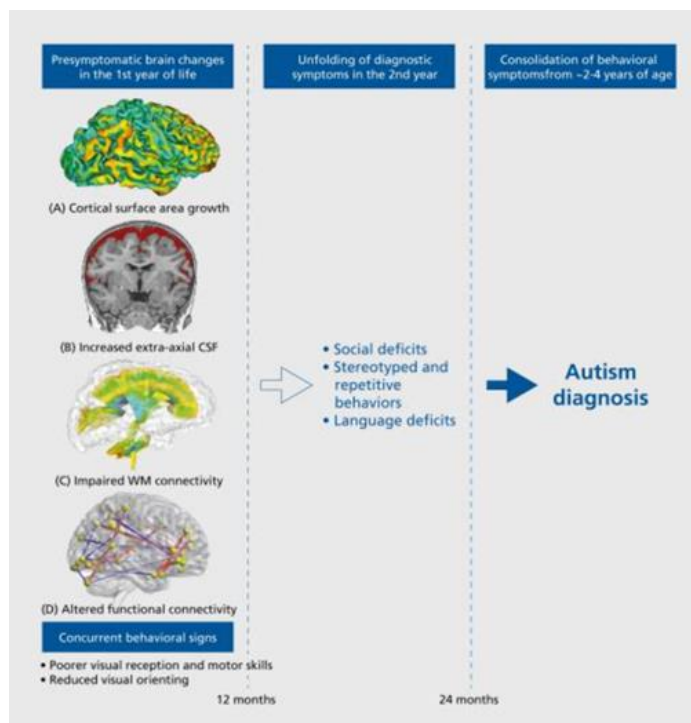


Figure 1: Observable brain features of autism spectrum disorder present in infancy prior to the emergence of typical behavioral symptoms.

ASD is typically diagnosed during early childhood through behavioral analysis [6]. Affecting nearly 1-5% of the global population, autism spectrum disorder is a prevalent disorder, yet its etiology and pathogenesis still remain fairly unknown [2,5,6]. At present time, there is no known cure and no United States Food and Drug Administration approved medication to directly treat ASD [8]. Alternative treatment options include therapies to help control symptoms including behavioral and educational interventions, music and art therapies, nutritional therapy and pharmacological treatments targeting symptoms of common co-occurring disorders such as anxiety and depression [7]. In recent years, researchers have been discussing the possibility of utilizing stem cell therapies to improve the behavioral manifestations of neuroanatomical abnormalities associated with ASD, ultimately improving quality of life.

Stem Cells

Cell therapy is the method of using specialized human cells known as stem cells to replace and repair damaged tissue or cells within the body [5]. Stem cells are a type of human cell that arise from a single cell and are characterized by their ability to self-renew and differentiate into different cell types to be used for varying purposes throughout the body. They are present in all phases of human life including embryonic, fetal, childhood and adulthood. Stem cells originate during the embryonic phase as the human body develops from a zygote and are derived into the three germ layers: endoderm, mesoderm and exoderm. Each of these germ layers give rise to specific organs. Some progenitor cells, or descendants of stem cells that aid in the differentiation and development of the germ layers into organs, remain undifferentiated and are retained as tissue stem cells found within the bone marrow, blood, muscle, liver, brain, adipose tissue, skin and GI tract. These tissue stem cells may remain dormant for a prolonged period of time within the tissue and proliferate when needed during times of injury when repair is necessary. Tissue stem cells located within the bone marrow, lungs, GI tract and liver are typically associated with regular proliferation for normal turnover or injury. Tissue stem cells located within the pancreas, heart, or nervous system are associated with proliferation only when needed to replace specific injured cells [11]. Due to their ability to renew and differentiate continuously, human stem cells have been widely studied and utilized in regenerative medicine.

Stem Cell Classifications

Human stem cells can be classified into five distinct categories based on potency, or differentiation potential: totipotent/omnipotent, pluripotent, multipotent, oligopotent and unipotent.

Totipotent (Omnipotent) Stem Cells

Totipotent or omnipotent stem cells are those that comprise most undifferentiated cells during the time of embryonic development. They are derived from the fertilized oocyte and cells from the initial cell divisions. These stem cells differentiate into both embryonic and extraembryonic tissue, specifically forming the embryo and placenta [18].

Pluripotent Stem Cells

Pluripotent cells are stem cells that are derived from the inner cell mass of an embryo and can differentiate the ectoderm, mesoderm, or endoderm, but cannot differentiate into extraembryonic tissue [18].

Multipotent Stem Cells

Multipotent stem cells are those found in most tissues and are derived from bone marrow, adipose tissues, bones and blood of the umbilical or peripheral blood. They can differentiate from a single embryonic germ layer into mesoderm-derived tissue including bone, adipose connective tissue, cartilage and muscle. There are three main cell types that multipotent stem cells differentiate into: mesenchymal stem cells, which give rise to muscle, cartilage, bone and fat, hematopoietic stem cells which give rise to blood cells and neural stem cells which give rise to neurons and glial cells [11].

Oligopotent Stem Cells

Oligopotent stem cells are those that can differentiate to form two or more lineages within a specific tissue type [11,18].

Unipotent Stem Cells

Unipotent stem cells are the least potent of the stem cells that self-renew and differentiate into only one specific type of cell

[11,18]. Human stem cells are also classified into three distinct categories based on origin: Embryonic Stem Cells (ESCs), Adult Stem Cells (ASCs) and induced Pluripotent Stem Cells (iPSCs).

Embryonic Stem Cells

ESCs are a type of pluripotent stem cell derived from the inner cell mass of the blastocyst that give rise to all types of embryonic lineages and adult cells and can be maintained in an undifferentiated state for a prolonged period of time [15]. Under the proper conditions, these stem cells have the ability to proliferate indefinitely [16].

Adult Stem Cells

ASCs are stem cells specifically derived from adult tissue such as the mesenchymal stem cells of placental tissue. ASCs are particularly of interest in regenerative medicine due to their anti-inflammatory properties. They have been utilized in clinical trials through transplantation to restore damaged organs and promote repair through the secretion of molecular mediators with immunomodulatory, angiogenic, anti-apoptotic and chemoattractant properties [11].

Induced Pluripotent Stem Cells

Induced pluripotent stem cells are human stem cells that are produced from adult somatic cells but can be reprogrammed to resemble ESCs. iPSCs are also frequently used in regenerative medicine due to their ability to mimic ESCs and differentiate into cells derived from all three embryonic germ layers within the body (Fig. 2) [11].

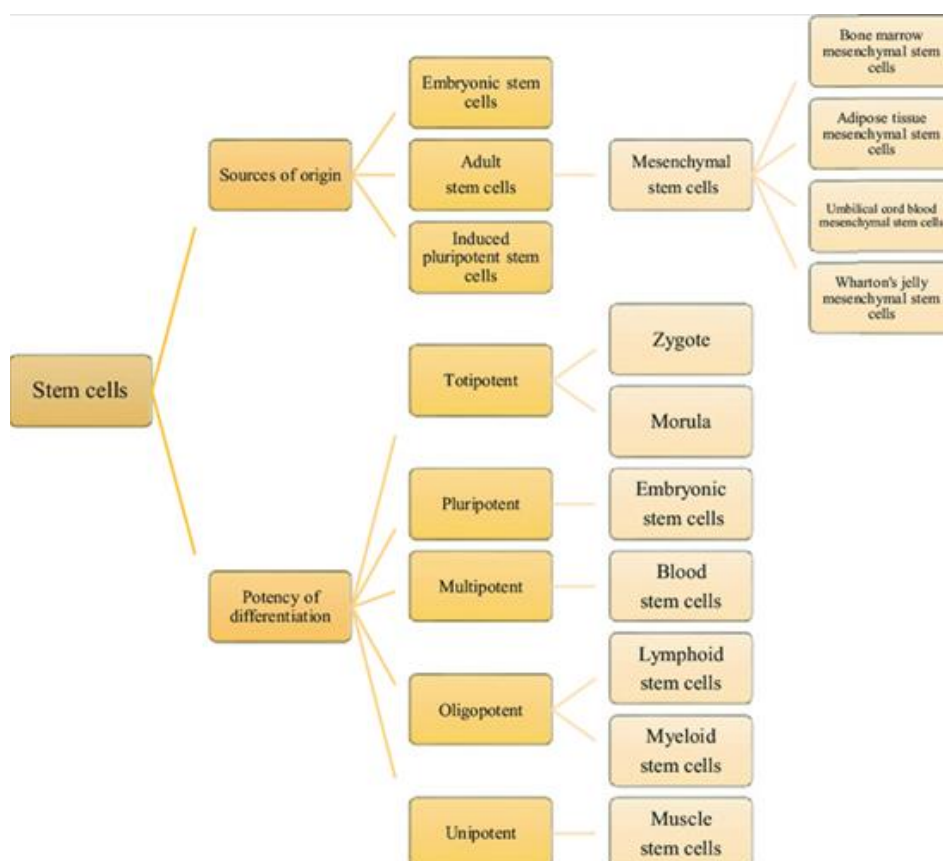


Figure 2: Representation of the classifications of human stem cells based on potency and origin.

Discussion

There is great anticipation of success in evolving stem cell therapies for neurodevelopmental conditions with complex pathophysiology such as autism spectrum disorder [5]. Due to its incurable status and the lack of USFDA approved pharmacological medication available, multiple stem-cell therapies are currently being researched for the treatment of ASD both clinical and animal trials (Table 2).

Type of stem cells	Source	Mechanism of action
Fetal stem cells	Fetus, fetal blood, placenta, amniotic membrane, amniotic fluid, umbilical cord	Secretion of neurotrophic factors Immunomodulatory capacities Suppression of proinflammatory processes
Mesenchymal stem cells	Bone marrow, umbilical cord	Paracrine secretion of several anti-inflammatory and survival-promoting molecules (ie, VEGF, HGF, BDNF, NGF) Neuroprotective effects Hypoimmunogenic and immunosuppressive properties
Neural stem cells	Brain (subventricular zone of lateral ventricles and subgranular zone of hippocampus)	Secretion of neurotrophic factors Maintenance of homeostasis Neuroprotective effects Differentiation into neural-type cells
Adipo-derived stem cells	Adipose tissue	Secretion of trophic factors Immunosuppressive and hypoimmunogenic effects
Umbilical cord- and amniotic fluid-derived stem cells	Umbilical cord, placenta, amniotic fluid	In vitro growth capacity Low immunogenicity and immunomodulation properties
Hematopoietic stem cells	Blood, bone marrow, umbilical cord	Paracrine activity
Induced pluripotent stem cells	Any cell type	Differentiation capacity

Note: Homing and mobility capacities are common for all the stem cell types.

Abbreviations: VEGF, vascular endothelial growth factor; HGF, hepatocyte growth factor; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor.

Table 2: Representation of the types of stem cells currently being researched for the treatment of autism spectrum disorder.

Current Research in Animal Models and Clinical Trials

Animal models are currently playing a significant role in researching the potential of stem cell therapy for the treatment of the phenotypical manifestations of ASD. ASD is a disorder of the human brain shown predominantly through changes in typical human behavior. As a result, animal models fail to perfectly mimic the ASD as it appears in humans [10]. However, the use of animal models remains successful in providing an important basis of information on ASD, offering new data on the phenotypes of the disorder that cannot be obtained through clinical trials. One of the most commonly used animal models for ASD research is the Black and Tan Brachyuric (BTBR) inbred mouse strain, which spontaneously develop brain and behavioral abnormalities similar to that seen in individuals with ASD. In addition, mice of this strain exhibit decreased Brain-Derived Neurotrophic Factor (BDNF) signaling, have reduced neurogenesis of the hippocampus, exhibited cognitive rigidity and displayed repeated behaviors [19].

A study conducted by Segal-Gavish and his team utilized the BTBR mouse model to research the potential of Mesenchymal Stem Cells (MSCs) in ASD therapy through the increase in neural cell proliferation [19]. Mesenchymal stem cells were the primary focus of this study due to their paracrine effect in regenerating injured tissue [19]. Two different groups of BTBR bred mice from The Jackson Laboratory were used and randomly assigned to the placebo treatment condition or the MSC treatment condition. A concentration of 50,000 cells/ μ L in 0.9% saline was injected intracerebroventricularly into the MSC treatment condition mice, while the placebo treatment mice received injections of saline. Following a three-week recovery time, a series of social and behavioral tests were performed to examine any noticeable changes including the open field test, running/jammed wheel assay, water T-maze assay, three chamber social assay and reciprocal dyadic social interaction test. Scores of each mouse were Z-standardized so that higher scores indicated more severe behaviors mimicking ASD in humans. The results of this study concluded that the MSC cell therapy successfully reduced repetitive behaviors such as digging and self-grooming, decreased cognitive rigidity and improved overall social behavior (Fig. 3) [19].

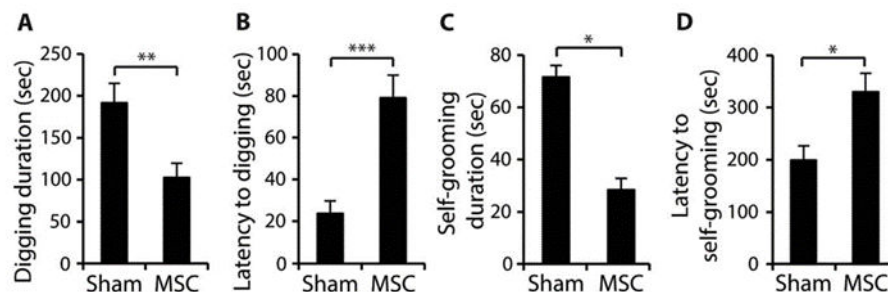


Figure 3: Representation of the improvement of repetitive behaviors in BTBR mice after receiving MSC intracerebroventricular transplantation.

A similar study conducted by Ha and colleagues investigated the effects of human-Adipose Derived Mesenchymal Stem Cells (hASCs) on mice induced as a model of autism through valproic acid treatment. Mice treated with VPA prenatally have been shown to display symptoms typical to that of a human diagnosed with ASD such as low social interaction, increased anxiety, frequent repetitive behaviors, developmental delays and neuroanatomical changes by reducing phosphatase and tensin homolog protein in DNA [29]. In this experiment, VPA-treated mice pups were injected with 2µl of hASCs intraventricularly in the third brain ventricle [29]. Following transplantation recovery three weeks post-injection, the mice were subjected to a series of behavioral tests including a self-grooming test to monitor repetitive behaviors, a three-chamber apparatus test to monitor social deficits and interaction and an open-field test to monitor anxiety. Results showed significant improvement in typical ASD symptoms including a decrease in repetitive behaviors and anxiety as well as an increase in sociability [29]. The VPA-treated mice also experienced a restoration in the phosphatase and tensin homolog expression, marking the first evidence of therapeutic effects on phenotypes of ASD [29].

In addition to animal model studies, promising research on the use of stem cells to treat ASD has been conducted in human clinical trials. A study conducted by Dr. Greta Shroff focused primarily on the use of ESCs to increase blood perfusion to the brain on three pediatric patients previously diagnosed with ASD to improve behavioral abnormalities associated with ASD including fine motor movements, communication and social skills [8]. The ESC treatment during this study was divided into multiple phases. During phase 1, patients received 0.25 mL of ESCs intramuscularly once a day to prime the body, 1 mL of ESCs intravenously twice a week to reinforce the stem cells in one particular area and 1-5 mL ESCs once a week supplementally to introduce the stem cells into the central nervous system. In addition, a nasal spray was utilized to aid in the absorption of the ESCs into the brain. Four additional phases, T2, T3 and T4 were conducted after a 6-8-month recovery time following T1. During these phases, the same treatments were given in attempts to provide additional ESCs to aid in regeneration [8].

The first patient case of this study was a three-year-old boy presenting with behavioral abnormalities such as little to no eye contact, low attention span, little to no social interaction, low functional independence, repeated flapping movement of hands and inability to speak clearly or precisely. In addition to his behavioral presentation of ASD, the patient also presented with hypoperfusion on the frontal and temporal regions of his brain. The patient was treated with the three sessions of ESC therapy. Following the first round of ESC treatment, the patient showed improvements in behaviors such as eye contact, speak, social interaction and hand flapping. Following the second treatment four months later, the patient showed additional improvements in eye contact, speech, social interactions and functional independence. As shown in Fig. 6, a brain SPECT scan revealed minimal hypoperfusion of the left cerebellum and cerebrum of the brain. Following the third and final ESC therapy treatment session, the patient showed improvement in nearly all areas of concern, primarily in eye contact, attention, repeated behaviors, independence and social interaction/awareness (Fig. 4) [8].

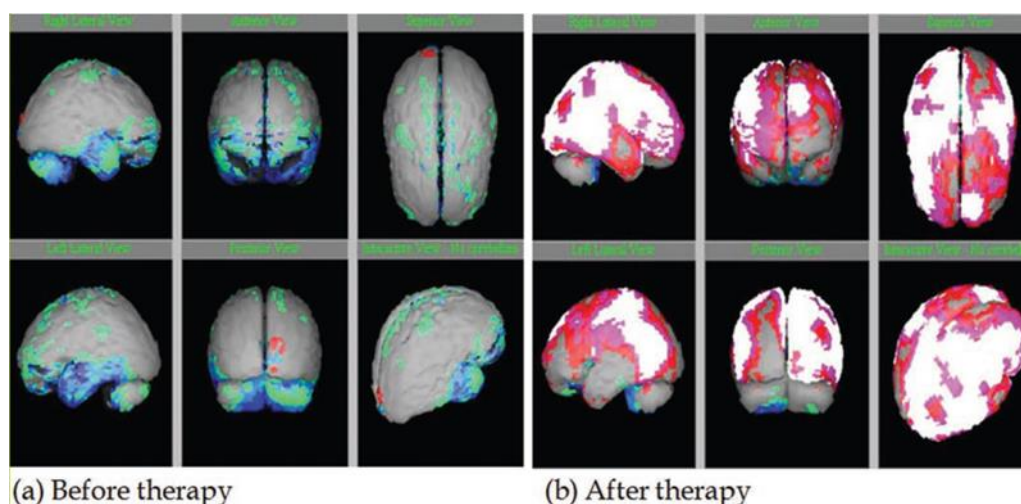


Figure 4: Representation of a brain SPECT scan of a three-year-old patient diagnosed with ASD following two sessions of human embryonic stem cell therapy; green, light blue, dark blue and black coloration indicates hypoperfused regions; grey represents normal regions; red, pink and white represent above normal regions.

The second patient of this study was a ten-year-old boy presenting with impaired speech and walking abilities, low IQ, low concentration, cognitive impairments, impaired sensory perception and obsessive-compulsive disorder. A SPECT scan of his brain revealed severe hypoperfusion in the left cerebellar region (Fig. 5) [8]. After receiving four sessions of ESC therapy, the patient showed improvement in cognitive abilities, communication, coordinated movement, immune system capabilities and a significant decrease in perfusion of the cerebellar region [8].

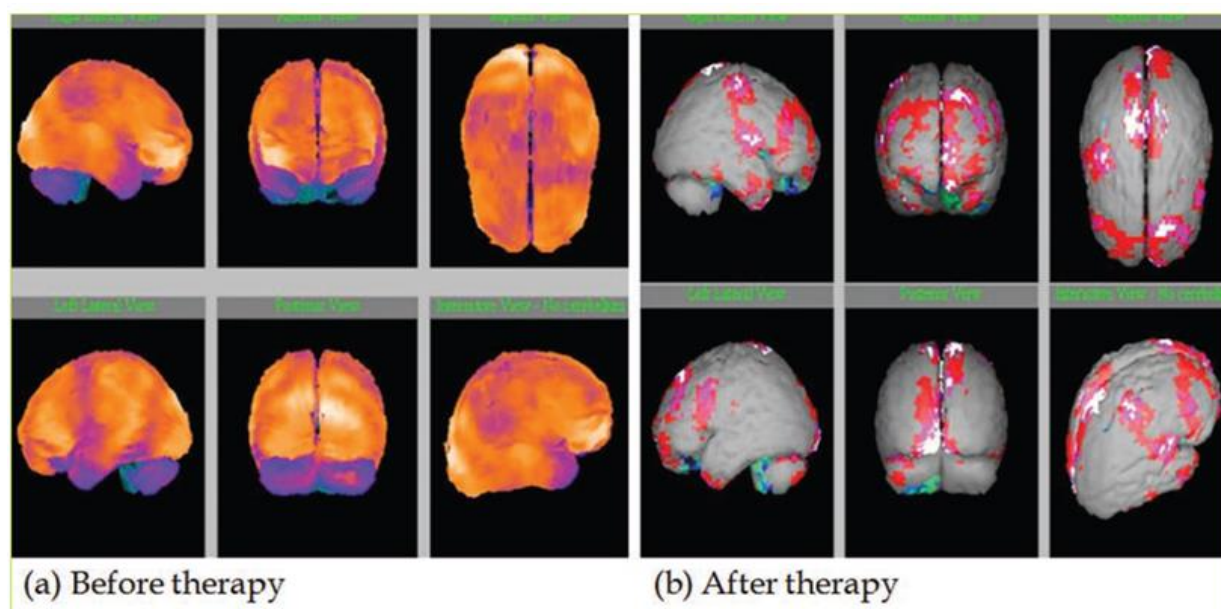


Figure 5: Representation of a brain SPECT scan of a ten-year-old patient diagnosed with ASD following four sessions of human embryonic stem cell therapy; green, light blue, dark blue and black coloration indicates hypoperfused regions; grey represents normal regions; red, pink and white represent above normal regions.

The third patient of this study was a four-year-old boy presenting with impaired fine motor skills and communication, repeated hand flapping behaviors, aggression and developmental delays in speech. In addition, this patient also presented with moderate hypoperfusion of the frontal and temporal lobes of the brain as well as in the cerebellar region. After undergoing four sessions of the same ESC treatment as the previous two patients, this patient showed significant improvements in social skills including eye contact and speech and motor skills (Fig. 6) [8].

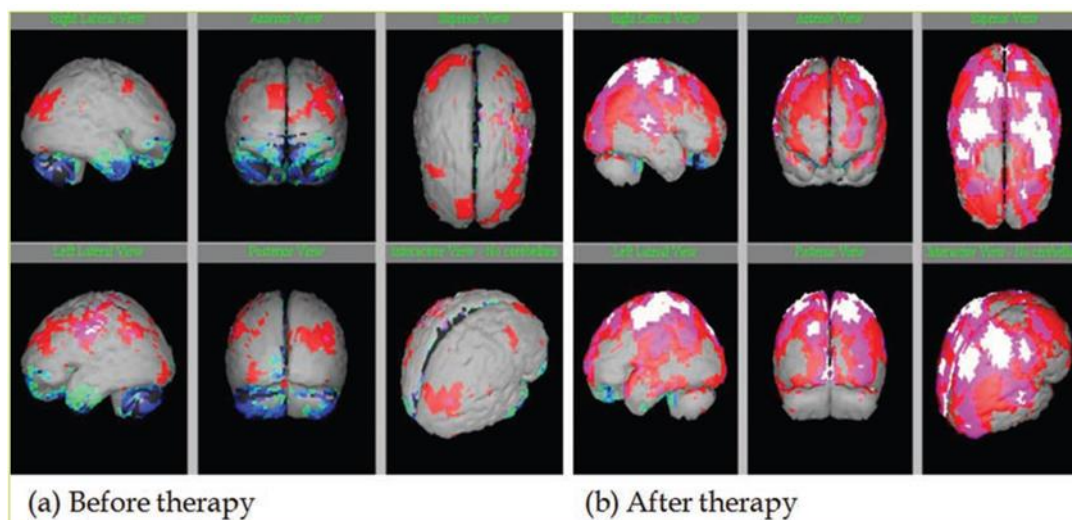


Figure 6: Representation of a brain SPECT scan of a four-year-old patient diagnosed with ASD following four sessions of human embryonic stem cell therapy; green, light blue, dark blue and black coloration indicates hypoperfused regions; grey represents normal regions; red, pink and white represent above normal regions.

Another study conducted by Dawson and colleagues investigated the effects of umbilical cord blood-derived stem cell therapy on ASD symptoms in children. It was hypothesized that these stem-cell therapies would aid ASD symptoms through the alleviation of inflammatory processes within the brain [26]. In this study, 25 children between ages two and six with confirmed diagnoses of ASD and a qualified autologous umbilical cord blood unit were enrolled for participation. Initial baseline evaluations through a series of behavioral and functional tests were conducted prior to intervention, 6 months after and again 12 months after. During this experiment, participants were given one dose of either a portion or entirety of a target 1.5×10^7 TNCC/kg autologous umbilical cord blood infusion intravenously over the span of two to 30 minutes, followed by infusion of intravenous fluids for 30 minutes to one hour [26]. Following the infusion, significant improvements in behavior were observed through parent-reported measures, clinical assessments and objective eye gaze tracking measurements.

Parent-reported measures focused primarily on socialization, communication and adaptive behaviors. Statistically significant improvements were found in these areas within the first 6 months post-infusion and remained stable 12 months post-infusion. In particular, participants with higher nonverbal IQ scores were reported to show positive correlations with improved socialization and adaptive behaviors (26). Clinical measures focused on assessing the severity of core ASD symptoms. Six months post-infusion, 36.4% of participants were scored as “Much Improved” and 13.6% were scored as “Very Much Improved” [26]. Additional clinical measures focused on the ability to match verbal words with visual pictures showed improvement for 57% of participants between baseline and six months post-infusion and 68% of patients between six months and twelve months post-infusion [26]. Finally, a computerized eye-gaze tracking assessment was utilized to observe attention and eye movements regarding various social stimuli surrounded by nonsocial stimuli. Results showed a 20% increase in engagement with social stimuli post-infusion [26].

A similar study conducted by Nguyen Thanh and colleagues examined the use of autologous bone marrow cell transplantation in tandem with educational intervention in children diagnosed with ASD over the span of two years. In this experiment, thirty participants between ages three and seven with Childhood Autism Rating Scale (CARS) scores above 37 were selected to undergo two intrathecal infusions of mononuclear cells. Mononuclear cells were initially collected through an anterior iliac crest puncture, isolated via the Ficoll gradient centrifugation and infused intrathecally in a 5 mL solution mixed with saline [27]. Patients received initial infusion, followed by educational intervention based on the Early Start Denver Model manual for an eight-week span and then received a second infusion six months after initial infusion. Clinical examinations were performed periodically at baseline and then 6 months, 12 months and 18 months post initial transplantation [27].

Following treatment, a significant decrease in ASD symptom severity was observed [27]. The median participant CARS scores

displayed a nearly 4-point decrease and various behavioral symptoms showed improvement (Fig. 7). Social interaction increased from 37% to 97% and eye contact increased from 23% to 93% within 18 months post-treatment, expressive language increased from 47% to 93% within 18 months post-treatment and repetitive behaviors decreased from 53% to 43% [27]. Additionally, improvement in communication, daily life skills and socialization as measured through the Vineland Adaptive Behavior Scales Second Edition (VABS-II) were also observed [27].

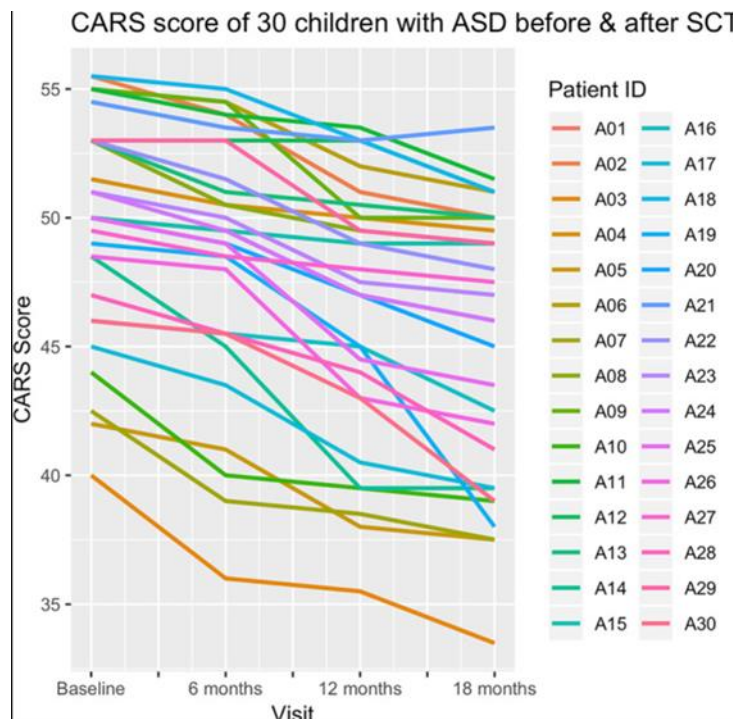


Figure 7: Childhood Autism Rating Scale (CARS) scores for 30 children diagnosed with ASD before and after receiving autologous bone marrow mononuclear cell transplantation.

Lv and colleagues conducted another study on the treatment of children with ASD using combined stem cell therapy transplantation of both human Cord Blood Mononuclear Cells (CBMNCs) and umbilical cord-derived mesenchymal stem cells (UCMSCs) [28]. Thirty-seven participants between the ages of three to twelve who were diagnosed with ASD in accordance with the DSM-5 and had a CARS score of at or above 30 were recruited for this experiment. Participants were divided randomly into three different groups: a control group receiving rehabilitative therapy treatment, a CBMNC group receiving only CBMNC transplantation along with rehabilitative therapy and a final combination group receiving a combination of CBMNC transplantation, UCMSC transplantation and rehabilitative therapy [28]. Participants within the CBMNC and combination groups received four stem cell transplantations intravenously or intrathecally approximately five to seven days apart. The CBMNC group received the initial transplantation intravenously and the rest intrathecally and the combination group received two CBMNC transplantations intravenously, two CBMNC transplantations intrathecally and two UCMSC transplantations intrathecally [28].

Twenty-four weeks post-transplantation, improvements in visual, emotional and intellectual responses, use of body, nonverbal communication, activity level, adaptation to fear or nervousness, hyperactivity, stereotypical behavior patterns, social withdrawal and inappropriate speech were all shown in both the CBMNC and combination groups through results from CARS, Clinical Global Impression Scale and Aberrant Behavior Checklist [28].

Conclusion

Research efforts in both animal model and clinical trials within the past few years have indicated the possibility of great success in the use of stem cell therapy to treat diseases and disorders previously deemed incurable. Based on the results of current experiments focusing on autism spectrum disorder, the use of mesenchymal stem cells, mononuclear stem cells in umbilical cord

blood and embryonic stem cells show great promise in the potential of treating behavioral abnormalities in individuals with ASD. However, due to the limited understanding of the etiology and pathogenesis of the disorder, more research must be done before any definite conclusions can be drawn about stem cell therapy as a viable treatment option for those with ASD. Additionally, there is still much to consider with the use of stem cell therapy in regenerative medicine as a whole.

Ethical and Safety Concerns with Stem-Cell Use in Regenerative Medicine

While the use of stem cell therapies has shown great promise in regenerative medicine, it has also raised both ethical and safety concerns, specifically regarding the use of human embryonic stem cells and mesenchymal stem cells.

Embryonic stem cells are the most common pluripotent stem cells currently being utilized in regenerative medicine, offering useful insight into early human embryology and the treatment of many diseases through cell replacement. However, human embryonic stem cell research particularly raises ethical, political and religious concerns, as these specific stem cells are collected from the cells of embryos of terminated pregnancies that would have otherwise had the potential of becoming viable human beings. In the extraction process, cells are collected from the inner-cell mass of the blastocyst of early-stage embryos, destroying the viability of the embryo. This raises the question of whether it is moral or not to use these methods of destroying a human embryo for the possibility of treating disease.

In addition to the ethical debate regarding hESCs, there are also safety challenges to consider. While their potency enables them to be used for as a variety of different cell types for therapies of many conditions, it also makes hESCs challenging to control after implantation [24]. Research has shown the implantation of undifferentiated hESCs may result in the development of tumors within each of the embryonic germ layers, which can only be controlled through maturation prior to implantation.

Mesenchymal stem cells have also been a topic of safety concern regarding the use of stem cells in regenerative medicine, as they have been found to undergo unintended cell differentiation post implantation, suppress the body's anti-tumor immune response and enhance blood vessel production, leading to increased complications, tumor growth and metastasis.

Future Recommendations

As previously discussed, one of the most prominent methods of researching stem cell therapy for the use of treatment in autism spectrum disorder is through animal models. While these models have shown success in improving ASD-related behaviors, animal models do not directly reflect the behavioral and anatomical abnormalities ASD as presented in humans, offering little insight into how animal models can be generalized to the human population. Future recommendations include further research both in animal models and human clinical trials.

Future studies may also want to expand clinical trial patients to include adolescents and adults previously diagnosed with ASD. As seen through the research previously discussed, most of the clinical trials conducted on humans pertain only to children. While ASD has been thought to have a higher success rate in therapies following early interventions, it would be beneficial to include adult patients in these trials. Doing so would be a step towards confirming the extent that stem cell therapy can improve ASD symptoms and potentially helping improve the life of all individuals living with ASD.

Conflict of Interest

The authors have no conflict of interest to declare.

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