Chapter

Stem Cell Therapy for Learning Disability

Alok Sharma, Nandini Gokulchandran, Hemangi Sane, Sakshi Desai, Pooja Kulkarni and Prerna Badhe

Abstract

Learning disabilities (LDs) are caused by genetic and/or neurological factors that alter brain functioning and affect processes related to learning, which include dyslexia, dysgraphia, and dyscalculia. It hinders the child's academic, social, and overall life skills. Current treatments for LD include medication and rehabilitation, focusing on management of symptoms. Thus, there is a need to explore newer treatments which will work at cellular level. Stem cell therapy is an evolving field of regenerative medicine and has shown great potential as a treatment strategy for various neuro-developmental and neurological disorders. It addresses the core underlying pathology and its benefits are enhanced when combined with standard treatments. This chapter focuses on various aspects of stem cell therapy in LD which includes the basics of stem cell therapy, rationale for use of stem cells, mechanism of action, monitoring tools like PET CT scan, and multidisciplinary rehabilitation. We have also enumerated our clinical experience and results of patients who underwent autologous bone marrow mononuclear cell transplantation combined with extensive rehabilitation. These patients showed a positive outcome, without any major adverse events. Nineteen out of 20 patients showed improvement in reading, writing, mathematical skills, attention, memory, problem-solving, comprehension skills, spelling, vocabulary, and overall increased academic performance.

Keywords: stem cell therapy, learning disability, bone marrow-derived mononuclear stem cells

1. Introduction

Learning disability (LD) is an umbrella term that includes *dyscalculia* or difficulty in calculating numbers, *dysgraphia* or difficulty in writing, and *dyslexia* or reading difficulty [1]. Also known as Specific Learning Disabilities (SLD), it causes the inability to read and comprehend, which is a major obstacle to learning and may have long-term educational, social, and economic implications while interfering with children reaching their full potential [2]. SLD results not from a global intellectual deficit, but from impairments in one or more of the specific processes of speech, language, reading, spelling, writing, or arithmetic. This possibly results from cerebral dysfunction [3]. Neurological differences in brain structure and function affect a person's ability to receive, store, process, retrieve, or communicate information. While the specific nature of these brain-based disorders is still not well understood, considerable progress has been made in mapping some of the characteristic difficulties of

LD to specific brain regions and structures [4]. Hypoxia can lead to hypoperfusion of the brain and the reversal of hypoxia may lead to self-repair and neural proliferation, which is observed in many animal models of cerebral ischemia. Chronic cerebral hypoperfusion to a lesser degree is known to cause neurodegeneration over a period of months to years through neuronal apoptosis without acute infarction [5] and individuals with chronic cerebral hypoperfusion usually have cognitive deficits of varying degrees [6].

Currently, all treatments for LD involve medications and rehabilitative techniques that focus on managing the symptoms. Thus, there is a need to explore other treatments which will work at the cellular level. Stem cell therapy is a new evolving field of regenerative medicine and has shown great potential as a treatment strategy for various disorders such as autism, intellectual disability, and cerebral palsy among many neuro-developmental conditions. It addresses the core underlying pathology of LD. In experimental studies, stem cell therapy has been shown to repair the hypoxia-damaged neural networks and restore the lost neuronal connections [7]. Stem cells, when injected, migrate to the target tissue and differentiate into mature cells. Along with regenerating and restoring the neurons and glial cells, they have a neuroprotective effect [8]. Several vertebrates regenerate tissues and organs, like the salamanders, regenerate lost body parts through the de-differentiation of specialized cells into new precursor cells. These de-differentiated cells then proliferate and later form new specialized cells of the regenerated organ. Stem cells or progenitor cells are the common denominators for nearly all types of regeneration [9]. The goal of stem cell therapy is thus to enable the localization of therapeutic cells to impaired/injured regions of the brain, to stimulate tissue repair and maintenance via a paracrine effect, and potentially even to generate new neurons [10]. Therefore, stem cells, through re-perfusion of the damaged brain regions in SLD can lead to improved neurological functions. This can increase academic performance and chances of employability in the future. Stem cell therapy has shown improved brain function and quality of life in similar neurological impairments such as autism spectrum disorder, cerebral palsy, intellectual disability.

This chapter focuses on the Regenerative capacity of Stem Cell Therapy in learning disability. It has a detailed description of what stem cells are, where they are obtained from, how they are injected into the body, and their mechanism of action. Furthermore, it explains how stem cell therapy results in a positive outcome in children with learning disabilities. We have included neuroimaging techniques such as PET CT brain scan as a monitoring tool to study the effect of stem cell therapy.

2. Unmet medical need

With increasing awareness, the prevalence of learning disability has risen considerably. Most often LD is managed with medications and rehabilitative therapies which include behavioral therapy, alternate methods of learning like remedial education, individualized education plan (IEP), and intervention programs. However, these treatment strategies do not address the underlying neuropathology of LD. Hence, there is a need for a treatment that focuses on cellular repair and further addresses the cognitive deficit.

3. About stem cells

Stem cells provide the building blocks for every organ in the body. They have the unique ability to divide asymmetrically and to differentiate into the various cell

types of the body. They simultaneously replicate to maintain a stem cell lineage. Stem cells are present in almost every human tissue. In embryos, they differentiate into all the tissues and organs of the body and provide a renewal capacity in most organs in fully developed humans. In neurological disorders wherein the neurons are damaged or defective, stem cell therapy repairs and replaces damaged/lost neurons [10]. Cell therapy is based on allogenic (patient receives stem cells from a healthy donor), or autologous transplantation (patient receives their own stem cells) of cells, with the goal of regenerating the damaged tissue or organ of the patient and replenishing specific stem cell populations [11].

3.1 Type of stem cells

Classification of stem cells depend on major characteristics such as (**Figure 1**):

- *Source* of stem cells
- *Potency*—the ability to differentiate into different cell types

3.1.1 Based on the source of stem cells

i. *Embryonic Stem Cells* **(ESCs)—**These are pluripotent, derived from the inner cell mass of the blastocyst, a stage of the pre-implantation embryo, 5–6 days post-fertilization [12]. Our understanding of stem cells began with embryonic stem

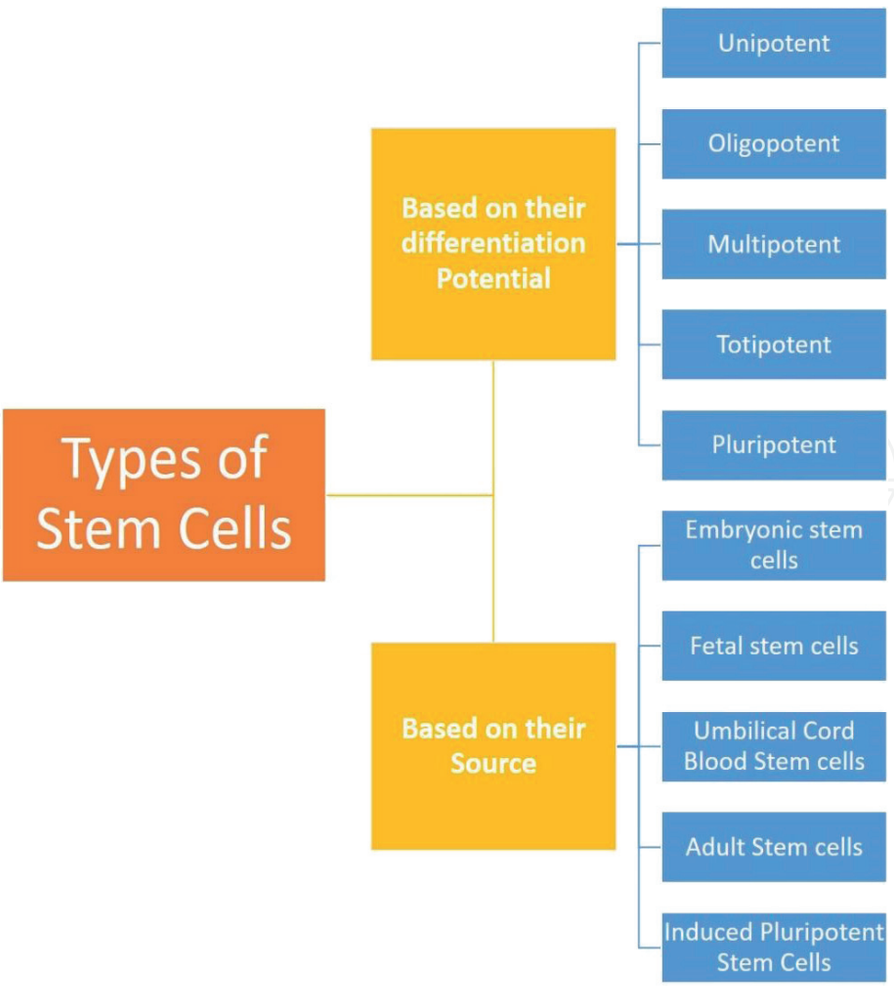

Figure 1.
Types of stem cells based on differentiation potential and source.

cells. They come from a ball of cells called the blastocyst, which forms 5 days after an egg is fertilized and develops into the embryo. In 1998, Professor James Alexander Thomson and his team at the University of Wisconsin-Madison grew the first human embryonic stem cells in a laboratory dish (in vitro). This allowed scientists to learn how the cells function [13]. ES cells have an unmatched capacity for self-renewal and pluripotential. These two factors continue to increase the relative potential of ES cells in cell replacement and regenerative therapies. However, their safety is questionable as they translate into tumors like teratoma and teratocarcinoma *in vivo* which remains the single greatest hurdle to successful ES cell-based therapies. Without rigorous elimination of this possibility, clinical transplantation of Embryonic stem cells will never be safe [14].

ii. *Umbilical Stem Cells*—Human Umbilical cord stem cells have shown the capacity to differentiate into many types of cells in the human body including neurons under appropriate conditions. They have shown the ability to induce the neurorestorative processes of neurogenesis, angiogenesis, and synaptic plasticity that are essential for the recovery of neurological functions [15]. Hematopoietic, endothelial, epithelial, and neural tissues can be derived from umbilical cord blood cells. Thus, transplantation of these stem cells may be a promising therapeutic strategy in neurological disorders.

iii. *Adult Stem Cells*- These are undifferentiated cells derived from adult tissues that divide to replenish dying cells and regenerate damaged tissues. Examples include bone marrow, adipose tissue-derived, neural stem cells among others. These cells have shown to be anti-inflammatory and augment repair in animal models of injury. Mesenchymal Stem Cells which are the most widely present type of cells have the ability of rapid proliferation, differentiation into cell types of endodermal and ectodermal origins, secretions of various trophic factors, and immunomodulatory action, which make them a preferable candidate for cellular therapies [16, 17]. *Bone marrow* is a mixture of various cell types that can be potentially used for regeneration. Bone marrow stem cells can be differentiated into numerous cell types including blood cells and neural cells. These cells act as small biological pumps that secrete cytokines and growth factors with autocrine effects on themselves and paracrine effects on their neighboring resident cells. These actions might stimulate neurogenesis and angiogenesis and may also have a neuroprotective effect [18]. *Adipose*-derived stem cells (ASCs) have become one of the most promising stem cell populations identified so far because they are ubiquitous and can be relatively easily harvested in larger quantities with less donor-site morbidity [19]. Functional experiments indicate that intravenous application of AD-MSCs improves hindlimb motor function through activation of angiogenesis along with upregulation of upstream kinase protein activity, such as ERK1/2 and Akt, in turn promoting cellular survival pathways and tissue-repair mechanisms [20].

iv. *Dental Pulp Stem Cells*—DPSCs are a mesenchymal types of stem cell present inside dental pulp which has osteogenic and chondrogenic potential in vitro and can differentiate into dentin, in vivo [21]. They can proliferate and give rise to identical cells and further differentiate to various cell types such as neuro and adipose cells [22]. In these cells, there is easier surgical access to the collection site, very low morbidity and moreover, can be cryopreserved. DPSCs possess immunoprivilege (able to tolerate the introduction of antigens without eliciting an inflammatory immune response) and anti-inflammatory properties [23]. However, their

oncogenic potential is yet to be determined in long-term studies. Research in this area has been mainly confined to animal models and their extensive clinical application is yet to be tested. These stem cells have other limitations such as difficulty in identifying, purifying, and growing them consistently in labs [24].

v. *Fetal Stem Cells*—These can be obtained from cadaveric fetuses following spontaneous abortion, stillbirth, or surgery due to ectopic pregnancy in obstetrics and gynecology hospitals. In addition, such tissue may be derived from elective abortions. The obtained fetal tissue is ordinarily processed and used for grafts in the form of a cell suspension, which is usually intravenously or intraperitoneally injected or, otherwise, transplanted into predefined implant sites during surgery [25]. However, their ability to differentiate is far from proven and the number of FS cells that can be generated is even less than that of Adult Stem cells which hinders their wide-scale applicability to regenerative medicine [14].

vi. *Induced Pluripotent Stem Cells*—iPSCs are the cells that are reprogrammed from somatic cells using different transcription factors. They possess properties of self-renewal and differentiation to many types of cell lineage. Due to this reason, and the absence of any ethical issues, iPSCs could replace the use of embryonic stem cells in research and clinics. In addition, iPSCs are used in various disease conditions for the production of patient-specific cells which can be transplanted to the site of injury or the site of tissue degeneration. The use of iPSCs may eliminate the chances of immune rejection as patient-specific cells may be used for transplantation in various engraftment processes. These stem cells were generated by using a combination of 4 reprogramming factors, including Oct4 (octamer binding transcription factor-4), Sox2 (sex determining region Y)-box 2, Klf4 (Kruppel like factor-4), and c-Myc, and were demonstrated both self-renewing and differentiating like ESCs. Their use offers a good approach for treatments in regenerative medicine as the cells that will be transplanted to the patient's body will be differentiated from the repaired iPSCs generated from the somatic cells from the patient's own body. However, limitations to the use of iPSCs do exist like safe delivery, post-treatment adverse effects, and standardization of protocols to generate large amounts of pure good quality cells. Generation of iPSCs make use of retroviral or lentiviral systems, so, it needs to be studied whether viral systems get incorporated with the host genome. The genetic material inserted via retroviral vectors may randomly integrate into the genome of the host which can cause genetic aberration and teratoma formation [26]. Given the 4 reprogramming factors of iPSCs, the overexpression of Oct4 may lead to epithelial cell dysplasia [27]. The expression of Sox2 has been reported to cause mucinous colon carcinoma [28]. Klf4 has a role in the formation of breast tumors [29]. c-Myc plays an important role in the formation of around 70% of human cancers [30].

3.1.2 Based on potency

i. *Totipotent stem cells* divide and differentiate into cells of the whole organism. Totipotency has the highest differentiation potential. One example of a totipotent cell is a zygote.

ii. *Pluripotent stem cells* (PSCs) that form cells of all germ layers but not extraembryonic structures, such as the placenta. Embryonic stem cells (ESCs) are an example.

iii. *Multipotent stem cells* have a narrower spectrum of differentiation than PSCs, but they can specialize in discrete cells of specific cell lineages. One example is a hematopoietic stem cell.

iv. *Oligopotent stem cells* can differentiate into several cell types. A myeloid stem cell is an example.

v. *Unipotent stem cells* are characterized by the narrowest differentiation capabilities and special property of dividing repeatedly. Their latter feature makes them a promising candidate for therapeutic e.g. dermatocytes [31].

3.1.3 Routes of administration

i. *Intrathecal injection* has a unique feature that allows stem cells to directly migrate to the lesion site in patients with central nervous system (CNS) diseases and for the treatment of neurological diseases is safe and feasible while having good clinical application prospects [32]. The intrathecal route enhances the possibility of a maximal number of transplanted cells "homing" onto damaged sites [33].

ii. *Intravenous injection* is a simple and minimally invasive approach that is ideal, given broad biodistribution and easy access. However, data show that following intravenous infusion, MSCs are trapped within the pulmonary capillaries, causing pulmonary and hemodynamic alterations, and preventing the intended access to other organs [34].

iii. *Intracranial*—The direct stereotactic implantation of stem cells would offer a highly focused delivery vehicle that could potentially enhance engraftment levels [35]. Initial in vivo investigation into the intracerebral implantation of MSCs has shown migration and engraftment at the site of injury, increased endogenous cellular proliferation, and functional improvement up to 8 days after injury [36, 37]. On the other hand, direct implantation into the CNS can cause tissue damage and exacerbated inflammatory response in the events of repeated transplantation [35].

iv. Intra-arterial—Cell delivery involves endovascular infusion of progenitor cells directly in the artery perfusing the ischemic tissue. This route of cell delivery bypasses the peripheral filtering organs, thereby increasing cell delivery. It is less invasive than intracerebral transplantation, it is repeatable, it would allow for a systemic biological effect, and could lead to a widespread distribution in the affected brain regions [38]. Bioluminescent Imaging has shown that intra-arterial injected neural cells engraft in the hypoxia/ischemia-injured brain and engraftment efficiency for intra-arterial injection was 12× higher compared with intravenous delivery [39]. However, it is an invasive procedure with an increased risk of complications.

3.2 Mechanism of action of stem cells

Stem cells have a unique property of homing and targeting specific damaged areas on administration. The homing mechanism is attributed to the expression of growth factors, chemokine, and extracellular matrix receptors on the surface of cells. On administration, they survive, migrate, proliferate, and differentiate into the required cell types [40]. They not only replace the damaged cells but also carry out the repair process via paracrine mechanisms [41]. Transplanted stem cells

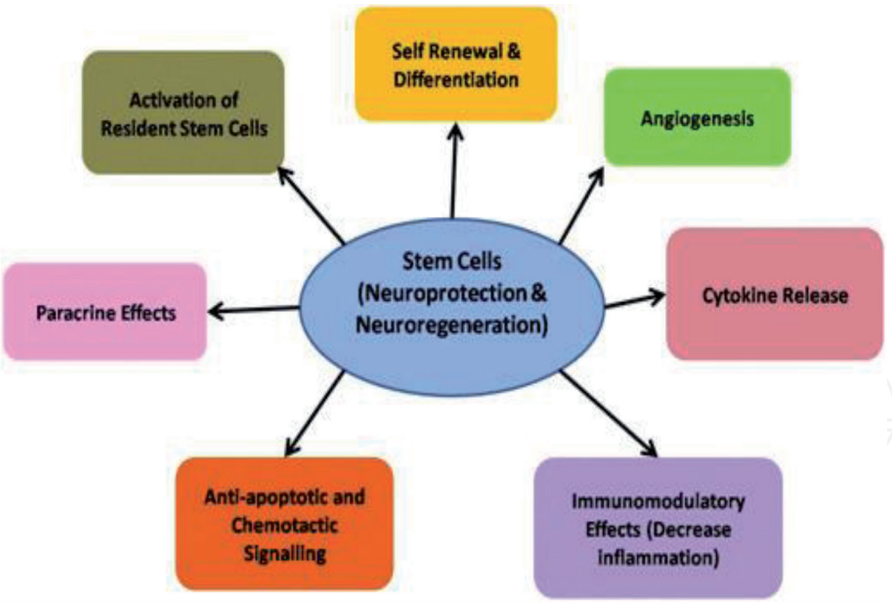

Figure 2.
Mechanism of action of stem cells.

express paracrine signaling factors including cytokines and other growth factors, which are involved in the repair process through neuroprotection, increasing angiogenesis, decreasing inflammation, preventing apoptosis, activation of resident/satellite cells, etc. (**Figure 2**).

3.2.1 Neuroprotection

Stem cells secrete a vast array of neuroprotective growth factors including BDNF, nerve growth factor (NGF), neurotrophin-3 (NT-3), glial cell line-derived neurotrophic factor (GDNF), fibroblast growth factor-2, and insulin-like growth factor type 1. These growth factors activate signaling pathways, enhance the differentiation, survival of neurons and maintain neuronal functions [42].

3.2.2 Increased angiogenesis

Stem cells secrete signaling molecules like vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and basic fibroblast growth factor (FGF2) resulting in improved perfusion, regional blood flow, enhanced angiogenesis, and oxygenation [43].

3.2.3 Immunomodulation

Stem cells impart an immunomodulatory effect as they reduce the levels of pro-inflammatory molecules TNF-α, IL-1β, IL-1α, IL-6 and increase levels of anti-inflammatory molecules such as IL-10 therefore, enhancing endogenous brain repair [44].

3.2.4 Activation of neighboring resident stem cells

The resident stem cells may possess growth factor receptors that can be activated to induce their migration and proliferation and promote both the restoration of dead tissue and the improved function in damaged tissue. Transplanted cells stimulate these endogenous cells to carry out the repair process [45].

4. Published literature

To our knowledge, there are no clinical studies of stem cell therapy in learning disability. However, it has been greatly explored in various pediatric neurological disorders such as autism, cerebral palsy, and intellectual disability [46].

Sharma et al. have established the safety and efficacy of bone marrow-derived mononuclear cells in autism and intellectual disability. In 254 cases of autism spectrum disorder, 95.27% of patients showed an improved score on CARS while 94.48% of cases showed improvement in ISAA. Symptomatic improvements were observed in eye contact, attention and concentration, hyperactivity, sitting tolerance, social interaction, stereotypical behavior, aggressiveness, communication, speech, command following, and self-stimulatory behavior. Eighty six patients who underwent a repeat PET CT scan showed improved brain metabolism after intervention in areas that correlated to the symptomatic changes [47].

In intellectual disability, the outcome of 29 patients of the intervention group was compared to that of 29 patients from only the rehabilitation group and it was found that all patients in the intervention group showed improvement while there was no improvement in 20.69% of patients from only the rehabilitation group. Improvement was noted in cognition, memory, problem-solving, understanding of relationships, social inhibitions, toilet training, command-following, eye contact, aggressive behavior, and attention and concentration. Comparative PET-CT scan study in patients of the intervention group showed improved metabolism in the frontal, parietal cortex, thalamus, mesial temporal structures, and cerebellum. No serious adverse events were recorded [48].

5. Clinical data

We have studied the outcome of autologous bone marrow-derived mononuclear cells in 20 individuals diagnosed with learning disability.

5.1 Demographic data of study population

Demographically, 14 male and 6 female patients were included, where 6 patients were within ages 1–10 years, 13 within 11–20 years, and 1 patient in the 21–30 years age range. Symptomatically, these patients presented with dysfunctions in academic performance, attention and concentration, reading, writing and mathematical skills, spelling, comprehension and recognizing words, problem-solving, and memory issues. Their functional capacity was measured by functional independence measure (FIM) and intelligence and/or social quotient through various tests such as BKT and VSMS measures.

5.2 Procedure

For the procedure of stem cell transplantation, autologous bone marrow mononuclear stem cells (BMMNCs) were selected as they were easily obtainable, safe, and did not involve any ethical issues. Intrathecal route of administration is a minimally invasive, safe, and effective procedure as compared to other routes. Studies have also shown that a mixture of cells exhibits more benefits as compared to a single subfraction of cells [49]. Hence, intrathecal autologous BMMNC transplantation was carried out in our study.

The patients were administered Granulocyte Colony Stimulating Factor (GCSF) before the harvest and transplantation of BMMNCs. On the day of the transplantation, 80–100 ml bone marrow was aspirated using a bone marrow aspiration needle from the right anterior superior iliac spine. This was collected in heparinized tubes and transported to the laboratory. Thereafter, in the culture laboratory, MNCs were separated by the density gradient technique. CD34 counts were performed and transported back to the operation theater in a cool sterile container. With the patient in a left lateral position, using a spinal needle, the thecal sac was punctured at L4-L5 space and the cells were injected through that spinal needle. Following this, Methylprednisolone 500 ml isolyte P was given intravenously, and the patient was observed for any adverse events.

After the stem cell transplantation, all patients underwent specialized rehabilitation such as special education, occupational and physical therapy, psychological counseling, and speech therapy.

6. Result

No major procedure-related adverse events were recorded. One patient reported a slight increase in absence seizures, which was controlled with medications. On an average follow-up of 26 months, 94.7% patients showed an improved clinical status. Reading skills improved in 75% patients, writing skills in 88% patients and mathematical skills improved in 70% affected patients, attention increased in 94% patients, memory skills in 78.5% patients, problem-solving skills improved in 69% patients, and comprehension skills in 72.7% patients. Spelling and vocabulary skills improved in 75% and 60% patients respectively. Overall increased academic performance was reported in 70% patients (**Figure 3**).

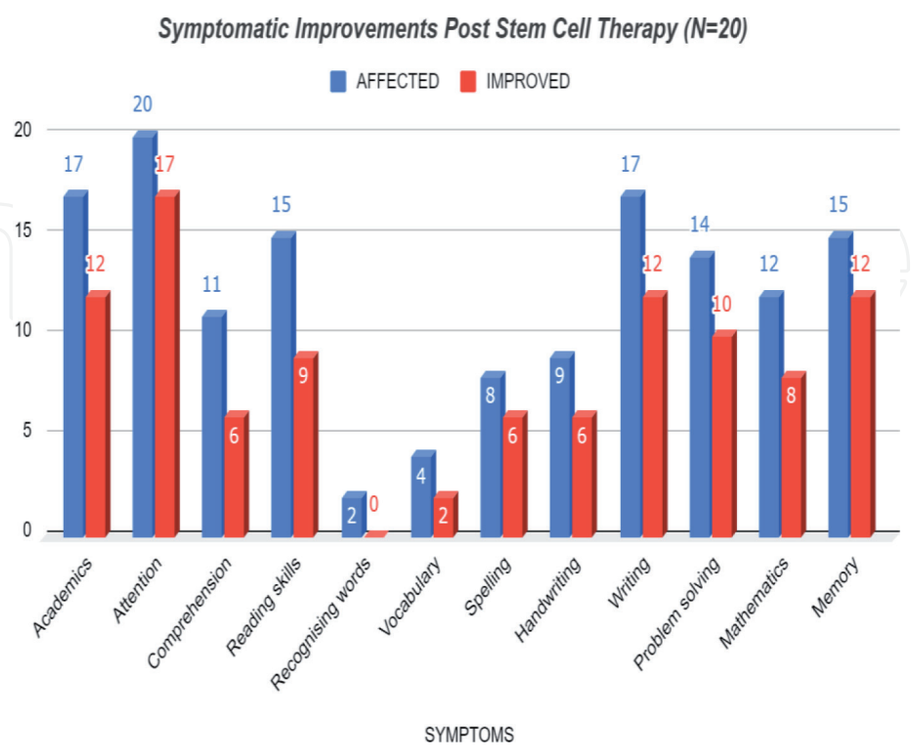

Figure 3.
Improvements were seen in various areas in 20 patients with learning disability post stem cell transplantation.

7. Role of rehabilitation in combination with cellular therapy

Evidence suggests that exercise induces mobility in the injected stem cells, thereby helping in the migration of the cells and helping upregulate neural plasticity [50]. Exercise also improves oxygenation and blood supply to the brain. Hence, the synergistic effect of stem cell therapy and neurorehabilitation brings about maximum functional recovery. Post stem cell therapy, the aim of rehabilitation in individuals with LD is to address the specific deficits that impair their ability to learn through sensory integration therapy, context-specific training, psychological counseling, and vocational training. Occupational therapy interventions use sensory integration methods to enhance sensory processing skills such as understanding, attention, sitting tolerance, and memory skills along with higher cognitive skills like judgment and problem-solving skills. Focusing on fine motor hand functions, handwriting grip, and writing skills are facilitated. Making use of visual schedules and timers to enhance time organization. Some studies showed direct instruction and modeling of letter formation, combined with memory retrieval, self-evaluation, fluency, and/or orthographic coding activities, led to improvements in students' legibility and writing fluency in the studies [51–53], and improvements in correct word sequences [54]. Speech therapists may collaborate with instructors to incorporate instruction that involves multiple modalities to facilitate connections between letters and sounds, as well as between written and oral language that incorporates visual and auditory cues. Students with LD benefit from explicit and systematic instruction that is closely related to their area of instructional need [55]. Special education differs from general education for students with LD when it is more explicit, intensive, and supportive [49]. Some ways of facilitating improved academic performance and life skills are through controlling task difficulty, teaching students in small, interactive groups, modeling and teaching strategies for generating questions and thinking aloud while reading, writing, or working on a scientific or mathematical problem, direct and explicit instructional practices, higher-order processing skills and problem-solving along with learning when, where, and how to apply strategies, ongoing progress monitoring of specific skills, teaching the building blocks of reading and writing like phonemic awareness, writing speed, the process of writing and the organizational and mechanical aspects of writing [56–60]. These strategies enhance the specific skills of reading, writing, arithmetic and inculcate generalization of strategies in life. Alternatively, Art therapy can be used in people with SLD who have difficulties in expressing themselves. It is a form of psychotherapy using art media as its primary mode of communication. Making artwork can facilitate expression and communication for people who find it difficult to express their thoughts and feelings verbally, and it is an accessible approach for children and adults with learning disabilities [61].

8. Radiological imaging

Brain tissue requires glucose for functional activity. The PET-CT scan records brain metabolism by using fluorodeoxyglucose (FDG) uptake. The active neural tissue absorbs glucose in direct proportion to its function. In turn, FDG uptake measures glucose metabolism and detects neuronal activity, which is the level of brain function. It is a promising technology to detect cellular effects of neurorestoration [62, 63]. In our study, a PET-CT scan was performed for all patients prior to cell transplantation to determine the dysfunctions in the brain. In the patients who underwent a repeat stem cell transplantation, PET images were compared to study the changes in brain metabolism after cell therapy. The images prior to stem cell therapy revealed hypo-metabolism in bilateral cerebellar hemispheres, medial temporal lobe, anterior

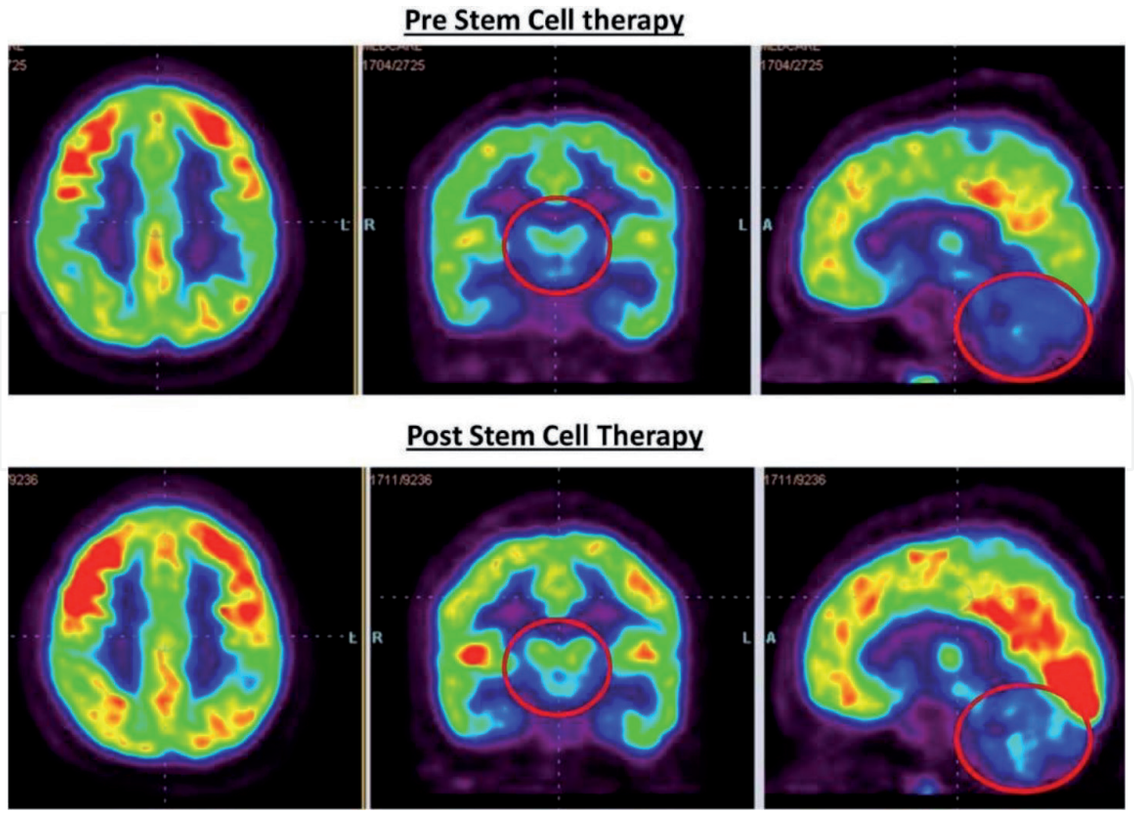

Figure 4.
Improvements were seen in reduced hypometabolism in areas of cerebellum and basal ganglia 12 months post stem cell therapy (the blue hypometabolic areas turn green post cellular therapy).

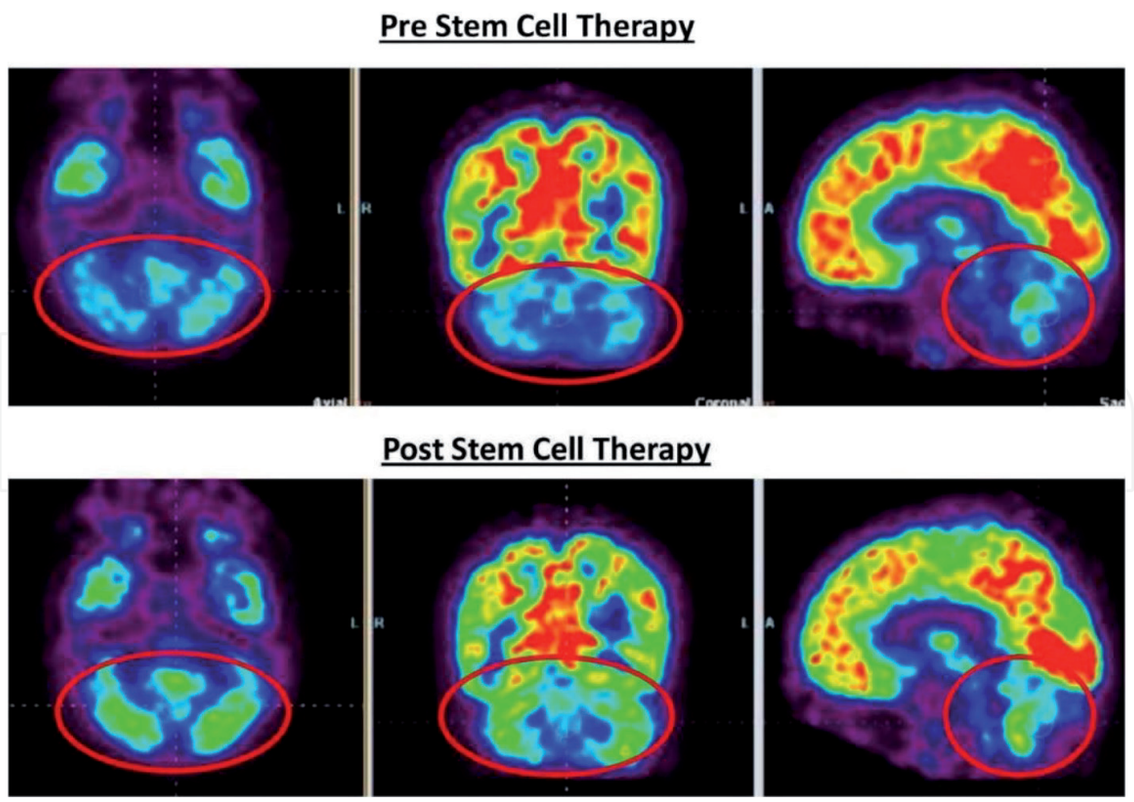

Figure 5.
Improvements were seen in reduced hypometabolism in areas of the cerebellum, temporal and parietal lobes 8 months post stem cell therapy.

and posterior cingulate gyri, and bilateral thalami with basal ganglia involvement, whereas hyper-metabolism was seen in the prefrontal cortex in many cases. These areas showed improved metabolism after cell therapy (**Figures 4** and **5**).

9. Conclusion

Stem cell therapy in combination with standard treatment and rehabilitation is a novel therapeutic option for learning disability. Its safety and efficacy have already been established in other incurable pediatric conditions such as autism, cerebral palsy, intellectual disability. Likewise, the results of our study conducted on patients with a learning disability have demonstrated a positive outcome and is an excellent foundation upon which future research can be advanced. Future studies should focus on analyzing the benefits of different cell types, the number of cells, and the route of administration for optimal use of cell therapy in learning disability.

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