Review Article

Utilizing Sertoli Cell Transplantation as a Therapeutic Technique for the Management of Neurodegenerative Diseases

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ABSTRACT

Neurodegenerative diseases (NDs), such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD), are defined by aberrant protein accumulation, brain atrophy, and gradual decline of neuronal function. Despite the considerable endeavors devoted to discovering treatments for NDs in recent decades, the demand for efficient therapeutic agents persists. Sertoli cells (SCs) play a crucial role in providing a supportive structure and environment for the development of germ cells. SCs, whether transplanted as xenogeneic or allogeneic cells, present a viable choice for enhancing graft persistence via the release of immunomodulatory and trophic factors, including neurturin (NTN), platelet-derived growth factor, Fas (CD95) ligand (FasL), glial-derived neurotrophic factor, interleukin 1 (IL1), brain-derived neurotrophic factor, interleukin 6 (IL6), transforming growth factors, and vascular growth factor, that protect replaced cells and tissues from the immune system. However, there is currently no cohesive evidence regarding the neuroprotective influence of the transplantation of SCs on NDs. Therefore, this review focuses on assessing stem cells' neuroprotective impact on neurodegenerative diseases in pre-clinical settings and presenting cohesive information. A comprehensive search was conducted between 2000 and 2022. In the identification stage, after a comprehensive search across databases, including Web of Science, Scopus, and PubMed/Medline, 103 papers were obtained. The search conducted in the present study yielded a total of nine relevant papers on the therapeutic effect of the transplantation of SCs on NDs. It was found that the transplantation of SCs exhibits a promising impact on enhancing the symptoms of neurological diseases in rats. The findings highlight the need for multiple standardized pre-clinical trials to find reliable information to confirm the utilization of the transplantation of SCs and the reduction of the symptoms of neurodegenerative diseases.

Keywords: Neurodegenerative diseases, Huntington's disease, Parkinson's disease, Cerebellar Ataxia, Sertoli cells (SCs)

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1. Context

Neurodegenerative disorders (NDs) exhibit a gradual decline in neuronal function, improper protein accumulation, and cerebral shrinkage. These disorders comprise Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD), which present distinct etiologies and affect various brain regions. Given their severe impacts on the elderly population, NDs have become a major source of morbidity and disability, attracting increasing attention. HD, AD, PD, and ALS are all characterized by neuronal destruction (1), which often manifests as memory impairment, cognitive decline, and motor dysfunction, among other symptoms. Currently, NDs are incurable, and available medications offer only symptomatic relief or slow disease progression (2). Consequently, there is an urgent need for ND treatment. According to prognostications by the World Health Organization (WHO), in the next two decades, neurodegenerative diseases (NDs), specifically those that impede motor functions, are expected to surpass cancer as the second major cause of death, following cardiovascular diseases (3). The pathogenesis and therapeutic options for NDs are well documented in the existing literature. However, the permeability of the therapeutic elements to the blood-brain barrier (BBB) is the fundamental impediment to the development of a successful treatment plan. Except for molecules that are small enough, the BBB stops all molecules from passing through, which becomes a significant issue in the treatment of brain illnesses. For instance, central nervous system (CNS)-active medications are difficult to transport across the BBB, necessitating the development of therapeutic alternatives (3). Efforts to discover therapeutic interventions for ND have been extensive in the past few decades; however, efficacious therapeutic agents are still in demand. This inadequacy could be attributed to multiple factors. Firstly, despite the identification of diverse cellular and molecular pathways linked to the pathophysiology of these disorders, the cause of neuronal death is still unknown, and no particular molecular pathway has been established to decelerate disease progression. Secondly, the absence of reliable biomarkers poses a challenge for the early detection of these disorders. Thirdly, as neurodegeneration advances, it generally gives rise to secondary outcomes like chronic inflammation, necessitating therapeutic modifications (4). Currently, the focus of cell treatment for ND is primarily centered on the replenishment or protection of cells that have been lost during the progression of the disease (5). There are Sertoli cells (SCs) within the seminiferous tubules of the testis, which produce an immune-privileged environment for the development of spermatogonia. The SCs possess unique characteristics as a non-dividing cell population that maintains functionality throughout the reproductive lifespan of the animal while also exhibiting cyclical alterations in morphology and expression of genes. By forming multiple junctional compounds and membrane specializations, SCs serve to construct a scaffold and milieu for the development of germ cells. Moreover, SCs are capable of secreting various trophic and immunomodulatory factors, including neurturin (NTN), platelet-derived growth factor (PDGF), Fas (CD95) ligand (FasL), glial-derived neurotrophic factor (GDNF), interleukin 1 (IL-1), brain-derived neurotrophic factor (BDNF), interleukin 6 (IL-6), transforming growth factors (TGF), and vascular growth factor (VEGF) (6, 7). In NDs, the decline of growth factors, such as GDNF, NTN, and BDNF, has been indicated to have deleterious effects on CNS activity, resulting in an increase in cellular death and damage.

2. Evidence Acquisition

The SCs have shown evidence of local immune protection (6). The transplantation of xenogeneic or allogenic SCs presents a viable option for increasing graft longevity via the secretion of trophic and immunomodulatory factors, which safeguard replacement cells and tissues from infection (8-11). Approximately 110,000 individuals residing within the confines of the United States of America (USA) are currently awaiting the opportunity to receive a transplant. Unfortunately, approximately 8000 individuals pass away before being granted the opportunity to undergo the procedure at the optimal moment (www.donatelife.net). Despite the potential risks associated with chronic rejection and adverse reactions linked to prolonged systemic immunosuppressive therapy, transplantation is still a viable and rational treatment choice (12-15). However, the employment of cell allotransplants in people enduring life-threatening maladies is restricted due to the limitations imposed on tissue procurement and the demand for recipient immunosuppression (16, 17). Presently, there is a lack of immunosuppressive medications that can avert the rejection of xenotransplants of organs, tissues, or cells. The employment of stem cells, which possess immunity against the host's immune system, along with their capability to protect co-transplanted alternative materials, poses a unique and innovative approach to the induction of acquired tolerance towards xenografts of cellular and tissue substitutes (8-11). The present review focuses on furnishing physicians and other neurological specialists with a suitable instrument for advancing neurological processes in patients. It will be achieved by assembling consistent data on the use of SCs to mitigate the deleterious impacts of neurological disorders in animal research. The researchers adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, albeit with certain alterations.

2.1. Search Strategy

In the present study, a systematic review of published papers was conducted to screen for related articles concerning the efficiency of stem cell transplantation in neurodegenerative diseases in pre-clinical studies. Furthermore, various databases, including Scopus, PubMed, and Web of Science (WOS), were thoroughly searched for relevant full-text studies published between

2000 and 2022. Three separate occasions were searched to ensure that all relevant articles could be documented. The following keywords were used to obtain related studies: (1) Sertoli cell; (2) neurodegenerative disease; (3) Huntington; (4) Alzheimer; (5) Amyotrophic lateral sclerosis; (6) Cerebellar ataxia; (7) Parkinson; (8) Transplant; (9) Cell transplantation injection (10). First, studies were searched and retrieved. After removing duplicates, the articles were removed based on their titles and abstracts. Finally, studies that met the inclusion criteria were involved in the present investigation.

2.2. Inclusion and Exclusion Criteria

The current study includes primary research encompassing randomized controlled trials and experimental studies that provide conclusive information on the utilization of the transplantation of SCs as neuroprotective cells for NDs. The selection criteria for articles included studies written in English, containing abstracts, published within the last twenty-two years (2000 to 2022), investigations that used Sertoli cells, and cohort studies. The exclusion criteria were letters, editorials, reviews, posters, conference papers, and other papers that did not have the inclusion criteria mentioned above.

2.3. Data Extraction

The extraction form included 1) author and year, 2) country, 3) study design, 4) type of neurodegenerative disease, 5) aim of the study, 6) method of delivery, 7) subjects, and 8) outcome.

2.4. Bias Assessment

Two authors individually assessed the accuracy of the encompassed information, employing exclusion and inclusion standards to diminish bias and heighten the quality of the research. The inconsistencies between the initial two reviewers were effectively resolved with the assistance of the third author**.**

3. Results

3.1. Literature Search

A total of 103 papers (Scopus = 37, PubMed = 28, WOS = 36) were selected. After removing the duplicates, this number reached 30, which entered the screening stage, whereby the titles and abstracts of the papers were examined for testing their eligibility. After this stage, 22 papers ultimately remained. After the investigation of the full texts of the papers, 13 papers were eliminated due to irrelevant results, and finally, nine papers remained, which were included in the main study. A visual representation of the screening process can be found in figure 1.

3.2. Data Extraction

Following full-text screening, nine studies were selected for data extraction. Furthermore, table 1 represents the characteristics of the included studies. All nine investigations are animal studies. Among these investigations, 3, 2, 2, and 1 studies used HD, PD, ataxia, and AD as models, respectively. The remaining studies used amyotrophic lateral sclerosis. Three studies implanted SCs in the striatum, and two implanted them in the cerebellar hemisphere. The remaining studies implanted SCs in the hippocampus or spinal ventral horn.

3.3. Huntington's disease

Huntington's disease (HD) is characterized as a degenerative, progressive, and hereditary neurological disorder that manifests in various symptoms, such as lack of coordination, psychiatric manifestations, low muscle tonicity, motor impairment, cognitive decline, and chorea. Typically, the manifestation of indications occurs during the middle stages of an individual's life, after matrimony and the establishment of a family. Nevertheless, the disease's manifestation is not exclusive to this age group, as it can manifest itself at any point in the developmental trajectory from early childhood to advanced age. The altered form of the protein Huntington is responsible for the development of HD caused by a repetitive cytosine-adenine-guanine (CAG) nucleotide sequence. A polyglutamine strand is produced due to extensive protein repetition in CAG, which is ultimately attached to the N-terminus. The N-terminus undergoes a defective transformation, leading to the formation of a toxic substance with a destructive function. In addition, the abnormal protein structures generated by genetic mutations or metabolic damage cause an excessive accumulation of insoluble aggregates, which is linked not only to HD but also to various disorders (2). In 2003, Rodriguez et al. evaluated the outcomes associated with the transplantation of SCs in a rat model of HD that had been induced with 3-nitropropionic acid (3-NP). Systemic application of 3-NP, which inhibits the mitochondrial citric acid cycle, causes a progressive impairment in locomotion similar to the symptoms observed in HD. The rats were then inadvertently stratified into two distinct groups and subsequently underwent bilateral striatal transplantation of SCs at a rate of 2 µl per site. The healing process was assessed by evaluating locomotor activity at 4 and 12 weeks following transplantation. The researchers discovered that locomotor hyperactivity, induced by 3-NP in rats, dramatically decreased after the transplantation of SCs in comparison to the control group. Furthermore, some of the behaviors returned to baseline levels. In addition, the researchers noted that SCs could persist in the striatum without the need for systemic immunosuppression and that some of them produced tubule-like structures. The administration of the 3-NP dosage regimen was not observed to inflict harm on the striatum. However, upon analysis of ventricular size, it was observed that control rats that were administered 3-NP exhibited larger ventricles in comparison to those that did not receive 3-NP. Therefore, this finding is concrete evidence of the striatal atrophy induced by 3-NP (18). In 2016, Luca et al. conducted an assessment of the therapeutic benefits of microencapsulated pre-pubertal porcine SCs in an animal model of HD. The SCs were subsequently introduced into R6/2 mice by solitary intraperitoneal administration at a rate of 1×10^6 SC/gram of body weight. The inflammatory pattern, lifetime, and motor function in the striatum were all

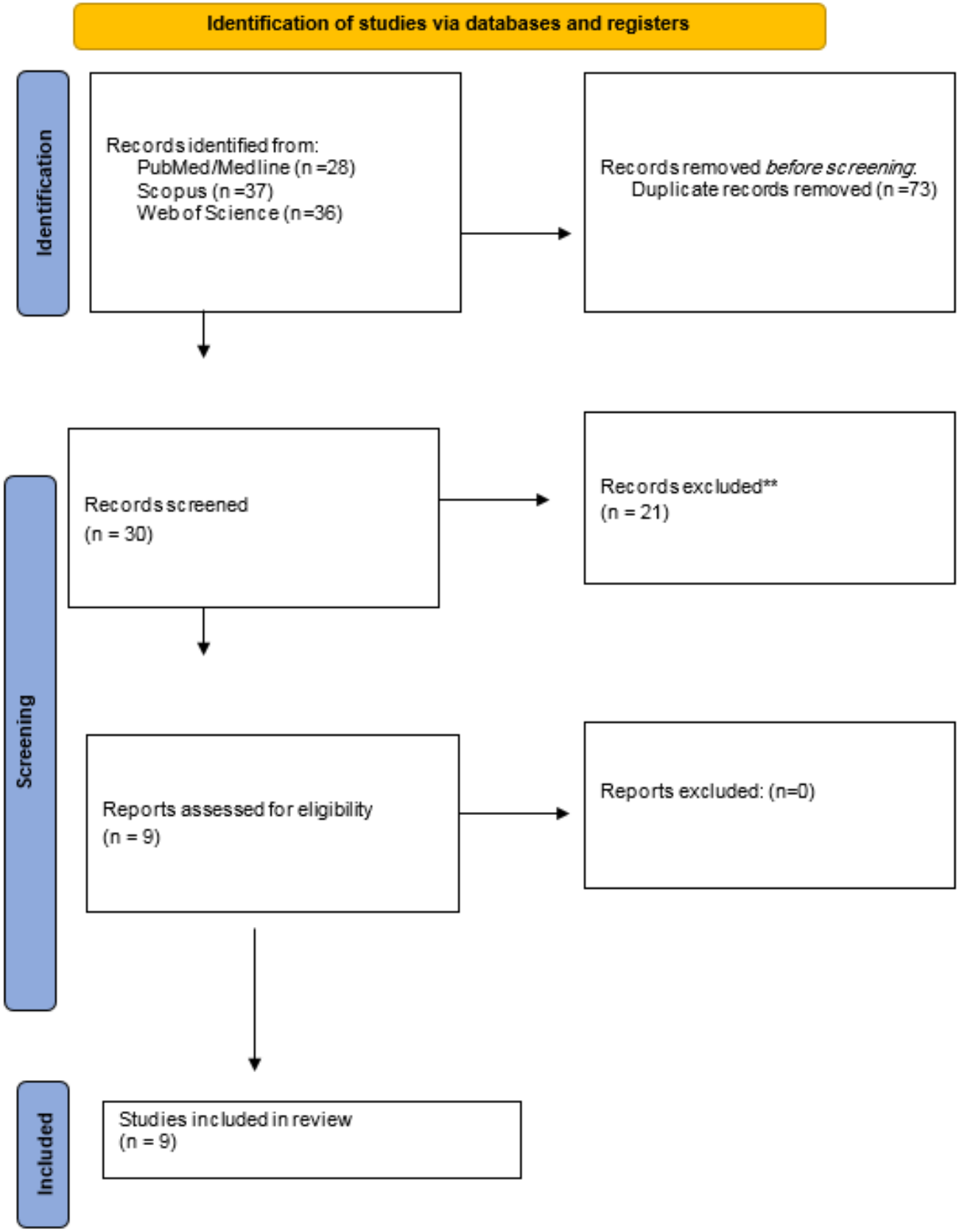

Figure 1. PRISMA 2020 flow diagram for systematic reviews

Table 1. Transplantation of SCs on models of NDs

Author, Year	Study Design	Type of neurodegenerative disease	The aim of study	Delivery Method	Subjects	Outcome
Rodriguez et al. [18] (2003)	Animal study	HD	Assessing the SCs Transplantation in a model of HD.	SCs were surgically inserted into the striatum of laboratory rats	Sixteen male Sprague-Dawley rats aged 16 weeks old	The transplantation of stem cells has the potential to augment locomotor abnormalities.
Luca et al. [3] (2016)	Animal study	HD	Assessing the emerging immunoregulatory and antiinflammatory properties of SC in HD.	Intraperitoneal injection of microencapsulated prepubertal porcine SC	Ten R6/2 transgenic mice aged 6 weeks	SCs transplant increased performance and elevated the lifespan of HD mice.
Ahmadi et al. [4] (2018)	Animal study	HD	Assessing the effect of SCs on oxidative stress, in a model of HD.	Bilateral striatal implantation of SC in a rat model of HD	Thirty male Sprague Dawley rats weighing between 200 and 220 grams	• The CM-SC markedly elevated neurite outgrowth and cell survival while safegaurding PC12 cells against oxidative stress. • Transplanted SCs decreased gliosis and production of inflammatory cytokine, and increased motor and muscle function. • It elevated dendritic diameter and striatal mass.
Aliaghaei, et al. [6] (2019)	Animal study	AD	Assessing neuro-restorative/protective effects of SCs transplantation in model of AD.	SCs were implanted into the hippocampus of rats.	Male albino Wistar rats, ranging from 20 to 30 days of age	• Implanted SCs demonstrated viability and exhibited a significant decrease in apoptotic activity, as well as a reduction in the migration of astrocytes • SCs transplantation increased memory, long-term synaptic, and learning of hippocampus.
Hemedinger, et al. [30] (2005)	Animal study	Amyotrophic lateral sclerosis	Assessing the effect of SC on spinal cord parenchyma' motor neurons	Transplantation of SCs was conducted on the spinal ventral horn of transgenic mice at the (L4-L5) level.	Seventy murine specimens, who have undergone transgenesis, display the anomalous (G93A) human Cu-Zn superoxide dismutase	• ChAT-positive motor neurons increased • SCs implants increased neuroprotection to susceptible motor neurons.
Saeidikhoo et al. [32] (2020)	Animal study	Ataxia	Assessing the neuroprotective impact of SCs on cerebellar ataxia symptoms.	Bilateral implantation of SCs was performed on each cerebellar hemisphere	Albino Wistar rat ages 20–30 days old	• SC-CM increased cell viability while decreasing the level ROS. • There was a remarkable raise in neuromuscular response. • SCs increased behavioral traits, cell survival, and motor function.
Mohammadi, et al. [33] (2018)	Animal study	Ataxia	Assessing the distribution of purkinje cell in a rat model of ataxia after SC transplantation.	Injection of 5 µL of SCs in cerebellar hemisphere	Wistar/Sprague-Dawley rats (220–240 g)	• The number of purkinje cells significantly elevated after SC transplantation.
Jhao et al [41] (2019)	Animal study	PD	Assessing impact of SCs with VM tissue co-grafting on hemiparkinsonian rats.	Intrastriatal implantation of either rat or pig ventral mesencephalic tissue (referred to as rVM or pVM, respectively) with or without a simultaneous co-graft of Schwann cells (termed rVM+SCs or pVM+SCs)	Male Sprague–Dawley rats aged eight weeks old (280–300 g)	• Compared to the VM alone groups, the rVM+SCs and pVM+SCs groups exhibited markedly better rotating behavior induced by dugs. • PET demonstrated a markedly raise in [18F] DOPA and [18F] FE-PE2I specific uptake ratios in transplanted striatum of the rVM+SCs and pVM+SCs groups in comparison to the rVM and pVM groups. • The co-graft of SC and VM tissue increased the survival of dopaminergic cells. • In comparison to groups without SCs, the groups that underwent co-grafting exhibited a decreased quantity of T-lymphocytes and a diminished presence of activated microglia.
Shamekh, et al. [42] (2005)	Animal study	PD	Assessing the potential of SCs in regulation of the immune system.	The cell suspension of SCs and VM was injected e into two sites in the striatum.	One hundred and five C57BL/J6 male mice (20-25g)	• SC+VM inhibited astrocytic infiltration of the graft area.

evaluated. The findings indicated that pro-inflammatory factors, such as the expression of cyclooxygenase-2 (COX2), inducible nitric oxide synthase (iNOS), and activation of nuclear factor kappa B (NF-κB), were reduced. In addition, polymerase chain reaction (PCR) analysis showed decreased IL-10, IL-1b, and TNFα levels. The study demonstrated that apoptosis was decreased in HD mice given SCs compared to other groups. Moreover, the lifespan and motor coordination of HD mice given SCs increased compared to those of the other groups. The findings indicated the beneficial impact of SCs on motor coordination, and the data markedly illustrated the anti-inflammatory and neuroprotective impact of SCs. These impacts expanded the lifespan and increased the motor performance of mice. Overall, it was indicated that disease progression was reduced throughout the study (3). In 2018, Ahmadi et al. conducted a study on the efficiency of SCs in an animal model of HD. Firstly, they reported that SCs secrete GDNF and VEGF. Secondly, PC12 cells were subjected to hydrogen peroxide (H_2O_2) exposure while in the company of SC-conditioned media (SC-CM), and the ensuing neurogenesis and cell activity were evaluated. In the *in vivo* stage of the study, bilateral transplantation of striatal SCs was performed in rats. According to the *in vitro* results, it was observed that neurite ramifications and cell survival markedly increased due to the protective effects of SC-CM on PC12 cells against oxidative stress. Furthermore, grafted SCs exhibited a decrease in gliosis and inflammatory markers, leading to an improvement in muscle movement and motor collaboration. In HD rats, SCs demonstrated the ability to preserve striatum volume and prevent further atrophy and neuron expansion. Overall, these findings establish that SCs have favorable effects and play a supportive role in HD (4).

3.4. Alzheimer's Disease

Alzheimer's disease (AD) represents the major general manifestation of dementia, defined by the presence of neurofibrillary tangles, amyloid plaques, as well as synaptic and neuron loss in the brain, culminating in progressive cognitive decline and dementia. The principal constituents of these pathological features are the amyloid-A peptide and tau protein (19). The accumulation of amyloid beta (Aβ) within the cortical regions of the precuneus and default mode network (cortical areas) at an early stage is followed by a symptomatic mental decline, the accumulation of tau protein, cortical hypometabolism, and decreased hippocampal mass. Cognitive dysfunction is frequently correlated with a reduction in synaptic and neuronal activity in the entorhinal cortex (20). The neurofilament light chain (NFL) present in plasma and cerebrospinal fluid (CSF) has been purported to reflect the extent of general neurodegeneration in various types of neurodegenerative dementias (5, 21). The persistent stimulation of microglia, the local macrophages of the brain, and other immune cells have been observed to present both amyloid and tau pathology, leading to the progression of the disease (22). Moreover, the acceleration of AD development can be attributed to the malfunctioning of M1 and M2 microglia due to excessive stimulation (7). Nonetheless, the specific causes of AD remain unknown.

In 2019, Aliaghaei et al. evaluated the therapeutic impact of the transplantation of SCs in rats that had been damaged by the injection of newly prepared Aβ1-42 amyloid-beta toxicity. Seven days after the toxin injection, bilateral transplantation of SCs in each hippocampus was performed. The findings of their study demonstrated that the transplantation of SCs had a revitalizing effect on the neural network of the hippocampus, which in turn resulted in the recovery of learning and dependent memory in the rat model of AD. The renewal of synaptic transmissions and enduring synaptic plasticity were instrumental in enabling the subsequent transplantation of stem cells into the impaired hippocampal region, thereby decreasing gliosis, emigration of astrocytes, and cell death and ultimately preventing further hippocampal damage (6).

3.5. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a complex condition that is defined by the continuous deficit of motor neurons, eventually leading to paralysis and death (23). Motor neuron degeneration is in the large pyramidal neurons located in the primary motor cortex, the anterior horns of the spinal cord, and the brainstem (24-26). Currently, ALS drugs exhibit only a negligible impact on the progression of the disease. The mechanism that triggers motor neuron degeneration remains unknown (23). Several genes have been introduced to have a role in the production of ALS in an autosomal dominant manner when altered, although it is unclear whether mutations of superoxide dismutase type 1 (SOD1) promote the degeneration of motor neurons (27). The majority of individuals suffering from ALS are sporadic (i.e., sALS). Only 5-20% of these patients have a family history of the disease (i.e., fALS). The sALS and fALS are highly similar, sharing multiple neuropathological traits (28). Various cell types that regulate neuroinflammation are remarkably involved in the disease's development (29). It is mainly hypothesized that the disease originates within motor neurons.

Hemedinger et al. evaluated the impact of the transplantation of SCs into the parenchymal of the spinal cord in rats induced with ALS. Sertoli-enriched cells

extracted from the testes were unilaterally administered into the ventral horn of the rats at L4-L5 levels. Subsequently, the graft site underwent rigorous evaluation both histologically and morphometrically. There was a significant increase in the number of persisting choline acetyltransferase (ChAT)-positive motor neurons in the ipsilateral region of the insertion. The proximity of the injection site was found to affect the increase in density of motor neurons on the ipsilateral side. However, there was no discernible variation in the density of motor neurons in areas situated either cranially or caudally relative to the point of insertion. In the context of the SOD1 transgenic model, the introduction of an SCs-reinforced amalgamation exhibited significant neuroprotective characteristics (30).

3.6. Cerebellar Ataxia

Disturbances affecting the peripheral nerve pathology and different distinct sensory or motor portions of the CNS have the potential to give rise to ataxia, along with other pathophysiological symptoms, such as dyssynergia, nystagmus, postural sway, dysarthria, and dysmetria, are correlated with cerebellar injury (31). These symptoms can elicit a high-amplitude tremor, which is concomitant with movement. Several findings demonstrated that abnormalities in Purkinje cells are associated with disturbances in the production of action potential and ataxia pathophysiology (32). In 2020, Saeidikhoo et al. conducted a study on the potential neuroprotective influence of SCs in the context of cerebellar ataxia. In order to evaluate the neuroprotective effects of SCs, PC12 cells were exposed to SC-CM in the presence of H_2O_2 *in vitro*. After the transplantation of SCs, motor and neuromuscular assessments were conducted. The results obtained from the *in vivo* experimentation demonstrate a significant augmentation in neuromuscular reactivity, in contrast to the declining condition of the ataxic group. The findings suggested that SCs can reduce necroptosis, thereby extending cell longevity and resulting in increased behavioral traits and motor function. In addition, the *in vitro* results indicated that SC-CM increased the viability of cells while remarkably reducing the level of reactive oxygen species (ROS) (32). In 2018, Mohammadi et al. assessed the influence of the transplantation of SCs on the spatial organization of Purkinje cells in the cerebellum in an animal model of ataxia. The researchers divided rats into ataxic rats with the transplantation of SCs (3-AP-SC) or without this transplantation (3-AP). The immunohistochemistry (IHC) indicated a random organization at greater distances within Purkinje cells in the 3-AP and 3-Ap-SC groups. Consequently, the transplantation of 3-AP and SCs resulted in irregularly oriented Purkinje cells, and the spatial configurations of the cells were maintained after the induction of ataxia in rats. The IHC analysis demonstrated a marked increase in the number of Purkinje cells following the transplantation of SCs. Finally, the transplantation of SCs enhanced the spatial organization of Purkinje cells in an animal model of ataxia (33).

3.7. Parkinson's Disease

Parkinson's disease (PD) is a commonly occurring neurodegenerative disorder that is defined by the selective degradation of dopaminergic neurons in the pars compacta region of the substantia nigra. The symptoms of PD include postural instability, bradykinesia, rigidity, and resting tremors (34, 35). Although stimulation of the deep brain and other therapies (pharmacological or surgical) may alleviate these symptoms to a certain level (36), they do not impede the progression of the disease. Additionally, the effectiveness of agents may diminish over time, and prolonged therapy can lead to some complications, including dyskinesia, paresthesia, and depression (37-40). In 2019, Jhao et al. investigated the impact of SCs on allotransplantation and xenotransplantation of ventral mesencephalic (VM) tissue in a PD model. The rats were implanted with intrastriatal rVM (VM tissue from rat) or pVM (VM tissue from pigs), employing co-grafting of SCs or without co-grafting of SCs (1.25105 cells; rVM+SCs or pVM+SCs). The efficacy of dopaminergic function and graft survival were assessed. Compared to the VM-alone groups, the rVM+SCs and pVM+SCs groups demonstrated considerably increased rotating behavior induced by drugs. Positron emission tomography (PET) showed a remarkable enhancement in [^{18}F] DOPA and [^{18}F] FE-PE2I specific uptake ratios (SURs) in the transplanted striatum of the rVM+SCs and pVM+SCs groups relative to the rVM and pVM groups. The co-transplantation of SC and VM tissue notably improved the sustenance of dopaminergic cells. The co-grafted groups exhibited reduced numbers of T-cells and enabled microglia relative to the control group. In an animal model of PD, the results indicate that the concurrent transplantation of SCs confers advantages over both xenotransplantation and allotransplantation of the VM tissue. The incorporation of SCs facilitated the enduring and efficacious amelioration of grafted dopaminergic neurons (41). In 2005, Shamekh et al. investigated the potential for immune modulation by SCs and the feasibility of xenografting them alone or in combination with allografted or xenografted brain tissue. The SCs utilized in this study were derived from rats. The rVM was obtained from rat embryos aged 12-14 days, with the viability of cells and concentration found

to be comparable to SCs. Before transplantation, the cells earmarked for the VM+SCs co-transplant groups were pooled and introduced into two striatum locations. Although all the transplants demonstrated indications of active microglia in the nucleus of the graft, the incorporation of rat SCs into the mouse striatum, regardless of whether it was accomplished with mouse- or rat-extracted VM, was found to inhibit the infiltration of astrocytes at the graft site. Across all experimental conditions, tyrosine hydroxylase-positive neurons survived despite the grafts being notably limited in size at their most optimal. The SCs were detected at 1 and 2 weeks following the transplantation; however, only a few SCs were found after two months. Additional study is necessary to thoroughly assess the immunological capacities of SCs in a xenogeneic context (42).

4. Conclusion

The present research revealed that the transplantation of SCs can mitigate the detrimental effects of NDs. The immunologically privileged nature of testicular SCs creates an attractive option for the advancement of innovative therapeutics. Co-transplanting SCs with neurons yields immunological protection, thereby enhancing the survival of the co-transplanted cells and producing a conducive environment for their activity in treating NDs. Moreover, SCs produce therapeutic agents, such as GDNF, BDNF, and VEGF neurotrophin. These results signify that SCs could serve as a viable alternative therapy for ameliorating the negative impact of NDs, and further exploration is needed. Nevertheless, such claims remain inconclusive due to the inadequate number of studies conducted in this field.

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Authors' Contribution

Study concept and design: G. H. M.
Acquisition of data: M.A., H. A., G. H. M.
Analysis and interpretation of data: H. A., G. H. M.
Drafting of the manuscript: M.A., H. A., G. H. M.
Critical revision of the manuscript: G. H. M.

Ethics

We hereby declare all ethical standards have been respected in preparation of the submitted article.

Conflict of Interest

The authors declare that they have no conflict of interest.

Data Availability

The data that support the findings of this study are available on request from the corresponding author.

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