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Transplantation of human glial cells into murine brains: A systematic review of efficacy and safety in neurodegenerative disorders

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Cell Therapy; Neural Pathways; Therapeutic Effects; Glial Cells; Non-Communicable Diseases

Abstract

Background: Neurodegenerative diseases impact millions of individuals globally. Over the years, brain research has predominantly focused on neurons, but attention is now shifting to glial cells, the brain's support cells, which play a vital role in neurodegenerative disorders. Therefore, glial cell transplantation represents a groundbreaking treatment approach for various neurodegenerative disorders, with the potential to restore neuronal function. We evaluated the evidence on the therapeutic effectiveness of human glial cell transplantation in neurodegenerative disorders.

Methods: The literature review was performed in PubMed, Scopus, and Web of Science from 2000 to 2024. The authors independently reviewed the screened articles. The study outcomes on cell differentiation, long survival restoration of neuron function, and adverse outcomes were analyzed.

Results: Study results highlight promising findings, including astrocytes improving motor function and slowing disease progression in neurodegenerative animal models through neurotrophic factor secretion and reduced inflammation. Similarly, microglia transplantation has demonstrated effectiveness in reducing α-synuclein toxicity in Parkinson's disease (PD), removing amyloid-β plaques in Alzheimer's disease (AD) models, and enhancing neuronal survival. Additionally, in demyelinating pathologies like multiple sclerosis (MS), oligodendrocyte transplantation promotes remyelination, restoring axonal conduction and enhancing functional outcomes.

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Cografting astrocytes with neuro progenitor cells significantly improved dopamine neuron engraftment and survival for at least 6 months post-transplantation. **Conclusion:** The transplantation of human glial cells offers promising therapeutic potential for neurodegenerative disorders, improving neuronal survival, restoring damaged circuits, and reducing disease progression.

Introduction

The burden of non-communicable diseases (NCDs) is rising in developing nations like India, which are going through an epidemiological transition. This change is mostly attributable to improvements in healthcare services, especially in the areas of promotion and prevention. Among these NCDs, neurological conditions account for a significant amount of the worldwide illness burden.[1] Neurodegeneration is recognized as the central pathophysiological process underlying the majority of brain-related disorders. As neurons are crucial for enabling communication, they are necessary for the human brain to function properly.[2] While most neurons originate in the brain, they are found throughout the entire body. Neural stem cells (NSCs) produce a significant number of neurons during childhood, but as people age, the amount they produce drastically decreases.[3] The progressive loss of neurons, their structure, and/or their functions known as neurodegeneration is a major health concern and a significant contributor to the pathophysiology of several brain diseases, even though neurons are not immortal.[4] In addition to the breakdown of synapses and neural networks, neurodegeneration is linked to an accumulation of physiochemically altered protein variations in the brain.[5] All diseases that have neurodegeneration as a defining characteristic are referred to as neurodegenerative disorders.[6]

Neurodegenerative disorders affect millions of people globally, ranging from congenital leukodystrophies, which cause white matter disruption in childhood, to those that become more prevalent as people age, like amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Alzheimer's disease (AD). Many neurodegenerative diseases eventually result in dementia, which is expected to impact 150 million people globally by 2050. Along with incalculable effects on patients and their families, this will result in an estimated $10 trillion in economic cost.[7] Age is the primary contributing factor in neurodegenerative diseases, but recent research shows that an interaction of environmental factors and genetic predisposition can significantly increase the risk. Furthermore, the disorders are largely determined by the expression of particular genes linked to them in an individual and the extent of neurodegeneration.[8] Modern science has worked endlessly to create surgical or medical remedies; however, the outcomes remain unchanged.

Current neurodegenerative disease treatments in clinical trials show promise during the initial stages of the disease and concentrate on maintaining surviving neurons or preventing protein aggregation. However, the development of effective remedies is still essential for the treatment of cases in which a substantial loss of cells has already taken place, especially as there are now no reliable methods for identifying individuals who are not yet with symptoms.[9] Particularly in the human brain, where neurons are post-mitotic cells, cell transplant therapy is a viable means of restoring function in regions where cells die. After injury, neurons do not recover strongly, with the exception of a few specialized areas.[10] Transplanting glial cells into the central nervous system (CNS) of patients with neurodegenerative disorders presents a groundbreaking approach to treating diseases that were previously considered incurable.[9]

As a result, significant efforts have been dedicated to advancing cell transplant therapy for this particular brain condition and bringing it into clinical practice. The goal of transplanting different stem cells into the penumbral region is to lessen inflammation and rebuild the destroyed neural network. Intravenous or arterial infusion and stereotaxic surgery, which targets the brain directly, have been used to carry out these procedures. Neurodegenerative disease research has generally focused on the transplantation of stem cell-derived neurons. Researchers have now turned their attention to glia, another type of CNS cell. Many essential functions are carried out by these brain support cells. Studies have shown that glia are essential to the pathophysiology of a number of brain disorders.[11]

Since acetylcholinesterase (AChE) inhibitor-based AD medications are mainly palliative, targeting only memory impairments without stopping or reversing the progression of the disease, there is an urgent need for more efficient therapeutic approaches. Symptomatic alleviation is the main goal of current treatments like deep brain stimulation and dopamine replacement therapy in PD. However, severe side effects including

hallucinations and drug-induced dyskinesias frequently restrict their therapeutic efficacy.[12] Cell-based therapeutic approaches hold significant promise in meeting this need by potentially targeting the underlying pathological mechanisms and promoting neural repair or regeneration.[13] To evaluate the safety and effectiveness of transplanting human glial cells as a treatment for neurodegenerative diseases, we aim to develop new approaches that do more than just relieve symptoms. These approaches will target the underlying disease mechanisms to promote neural repair and regeneration.

Materials and Methods

Following the standards of the Preferred Reporting Items for Systematic Reviews (PRISMA), a literature review was conducted (Figure 1). Scopus, PubMed, and Google Scholar were systematically searched for all articles including relevant information on dyslexia published from 2000 to 2024. Relevant articles were obtained using linked search terms (by 'OR', 'AND' modifiers) and their combination: 'glial cell',' transplantation', 'astrocytes', 'oligodendrocytes', 'neurodegenerative disorder', 'Parkinsons disease', 'Alzheimers disease', 'amyotrophic lateral sclerosis', 'remyelination', 'cell replacement therapy'. The studies with potential evidence on functional outcomes such as cell differentiation, long survival restoration of neuron function, and adverse outcomes were analyzed. Reviews, unpublished articles, and non-English studies were excluded.

Assessment of risk of bias: The Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was employed to perform the risk assessment.[14] The following bias domains were considered in the analysis as shown in figures 2 and 3: "risk of bias due to confounding (D1), bias due to selection of participants (D2), bias in classification of interventions (D3), bias due to deviation from intended interventions (D4), and bias due to missing data (D5), risk of bias arising from measurement of outcome (D6), and risk of bias in selection of reported results (D7).

Results

Specification of glial cells in transplantation: The rationale for transplanting glial cells as a potential treatment for brain diseases is grounded in the non-cell autonomous concept of neurodegeneration. Glial cells can be targeted to improve or repair the functions of neurons and white matter impairment, offering a promising treatment option for several chronic neurodegenerative diseases, such as ALS, PD, and AD. Each disease may have a distinct etiology, including inherited forms with different genetic bases and sporadic ones. However, regardless of the origin of the disease, targeting glial cells can be a common strategy in this case.[13]

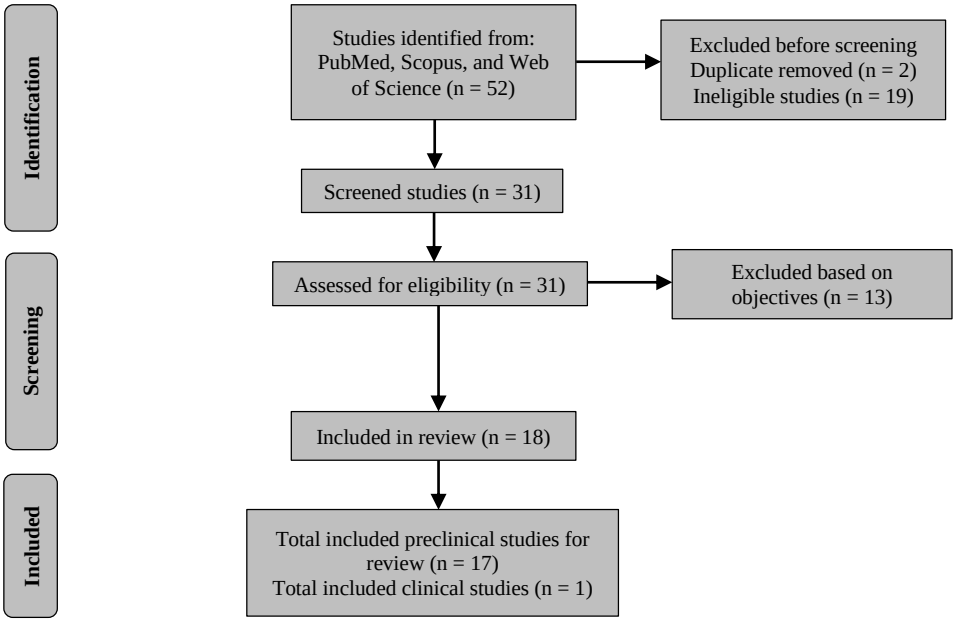

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart

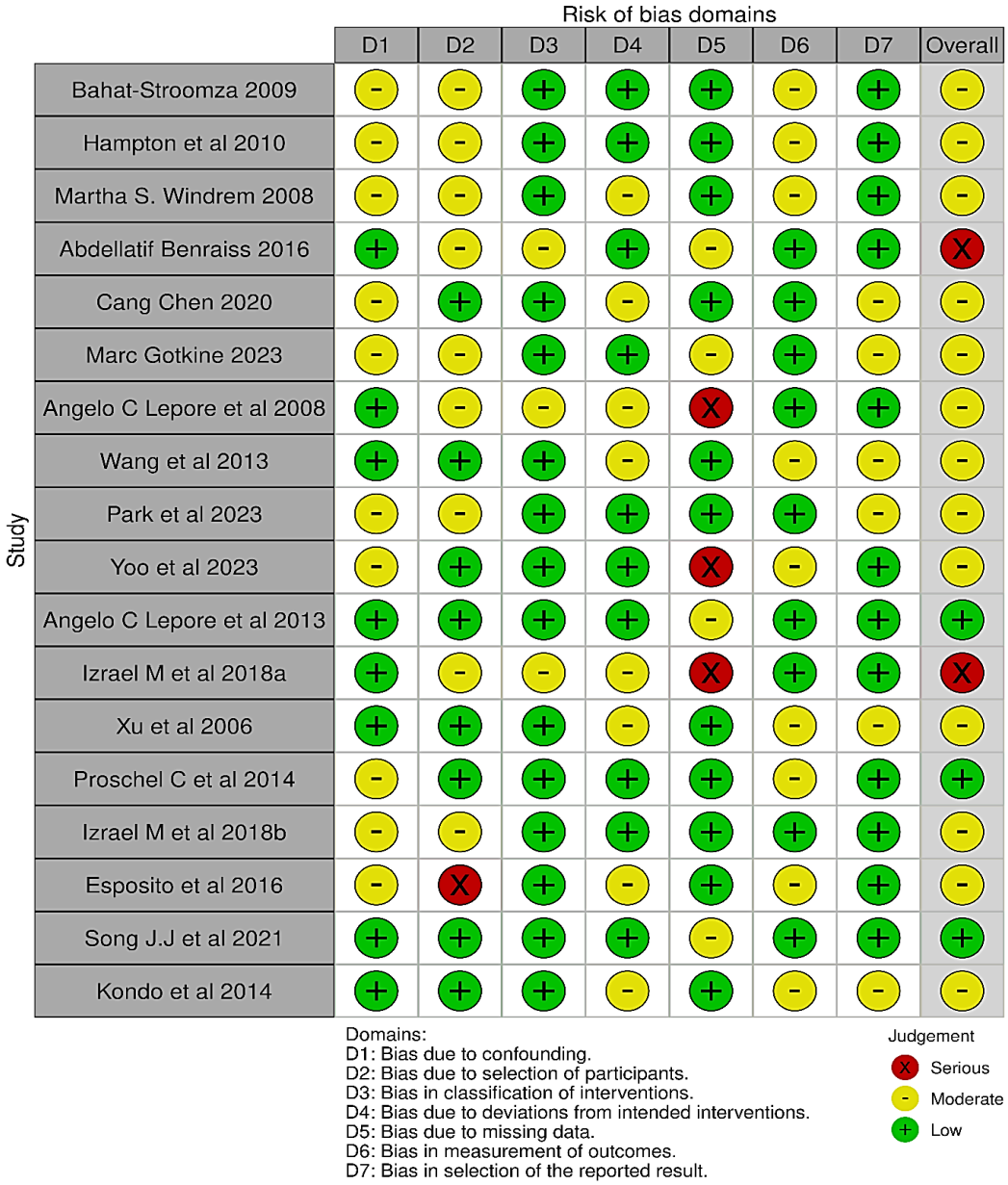

Figure 2. Risk of bias assessment (Traffic light plot)

Microglia, oligodendrocytes, and astrocytes are different types of glial cells.

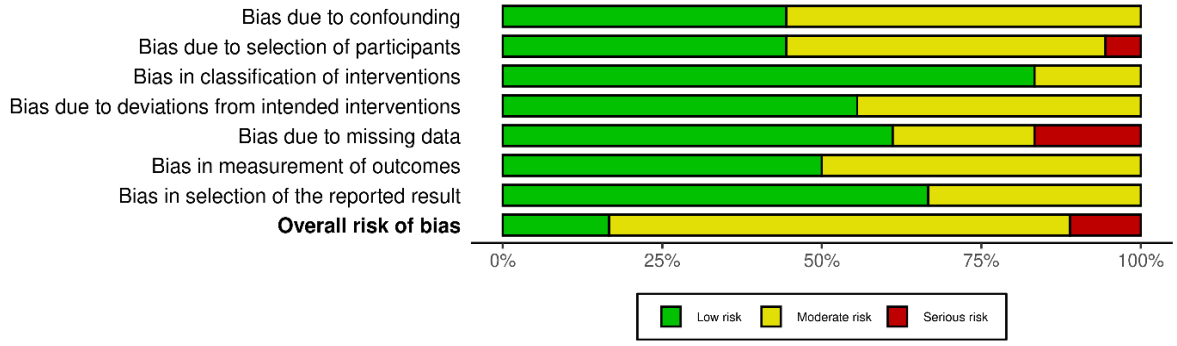

Figure 3. Distribution of risk of bias judgment

Microglia, which make up 5–10% of the glial cells in the brain, are involved in phagocytosis, synapse formation, and immunosurveillance.

The progression of numerous CNS-related injuries and diseases linked to neurodegenerative states is slowed down by the intricate associations that microglia have with neurons and other glial cells, including astrocytes and oligodendrocytes.[13-15]

About 30% of the cells in the CNS are astrocytes, the most prevalent kind of glial cell in the brain. They create complex networks that communicate with oligodendrocytes, microglia, and neurons. Astrocytes are essential parts of the neurovascular unit and the tripartite synapse. Its functions are especially significant in the human brain, where they play a key role in neuroinflammatory responses and help maintain metabolic homeostasis.[15,16]

Finally, oligodendrocytes, which account for 20–75% of glial cells, are primarily responsible for myelination, with the highest concentration in white matter. These cells are involved in conditions like multiple sclerosis (MS) and white matter stroke. Another common glia population, especially in white matter, is oligodendrocytes. Their main role is to produce myelin, leading axons to become myelinated and giving them trophic support. They also help action potentials propagate. The loss of oligodendrocyte cells is a common feature of MS and white matter damage in stroke. By substituting injured or dysfunctional oligodendrocytes with healthy oligodendrocytes, axons may also be saved by aiding in remyelination processes.[17] The overview of the transplantation of glial cells and its mechanism of neuroprotection are illustrated in figures 4 and 5.

Sources of glial cells for transplantation: Glial cells for transplantation can be derived from a variety of sources. Glial progenitor cells are another option for producing glial cells, in addition to NSCs, induced pluripotent stem cells (iPSCs), and embryonic stem cells (ESCs). Intermediate cells known as 'glial progenitor cells' can differentiate into particular glial cell types. They can be generated from pluripotent stem cells or taken from fetal or embryonic brain tissue using specific differentiation techniques. ESCs and iPSCs are currently the main sources for glial cell transplantation. To obtain the best phenotype for transplantation, these cells are selected and, subsequently, differentiated into glial progenitor cells in both cases. Once transplanted, they are expected to integrate into the recipient's CNS and perform their normal functions, including immune surveillance and phagocytosis.[18] Multipotent neural progenitor cells (NPCs) and NSCs, such as radial glia in the cerebral cortex, give rise to astrocytes during CNS development.

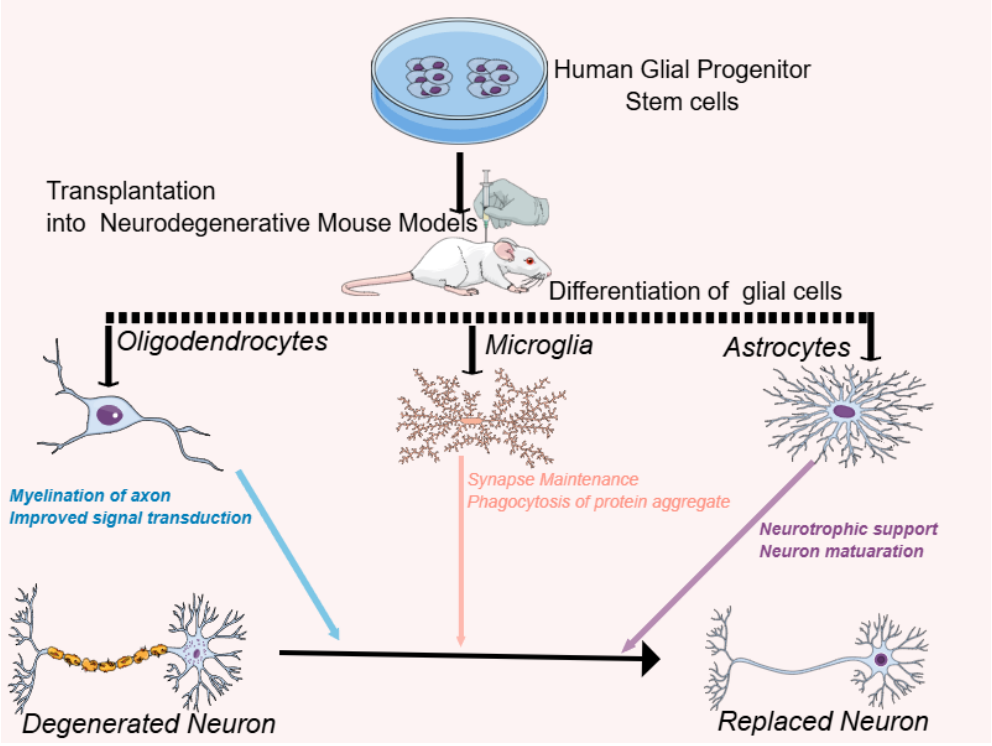

Figure 4. Overview of Glial cell transplantation and neuroprotection

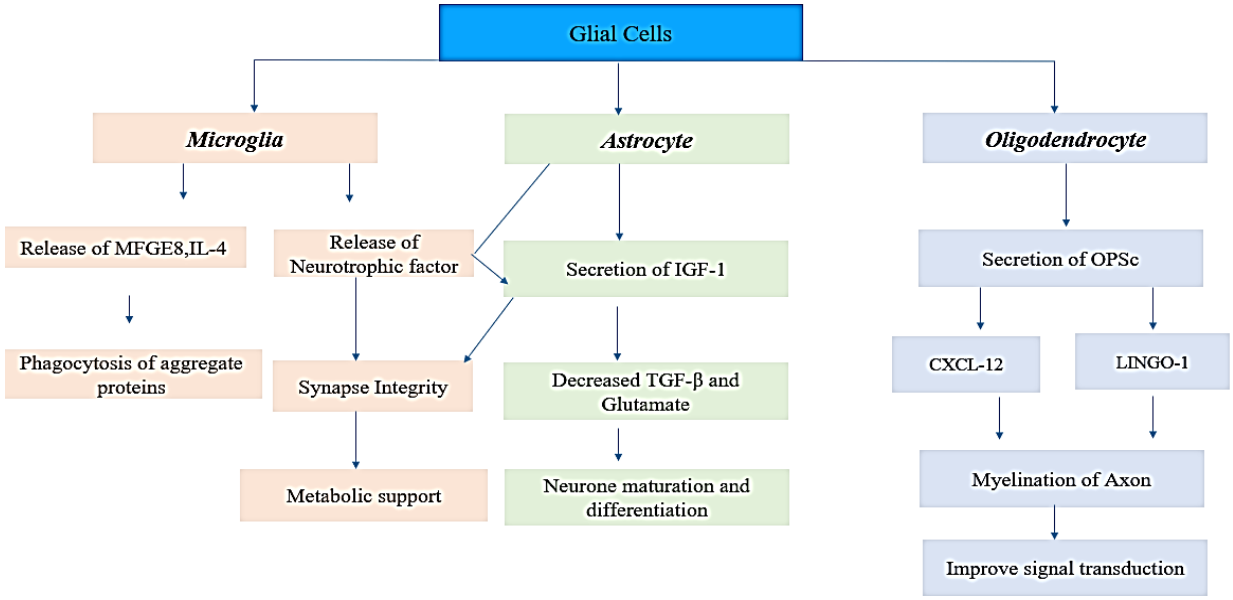

Figure 5. Mechanism of Glial cell-mediated neuroprotection

NSCs first produce neurons, which are followed by the development of glia progenitor cells (GPCs), which can develop into oligodendrocytes and astrocytes. When injected into neonatal and adult mice, GPCs generated from the fetal human brain integrate widely as astrocytes and enhance outcomes in models of neurodegenerative disorders.

Evidence on safety and efficacy of glial cell transplantation

Microglia: Neurodegenerative disorders like spongiform encephalopathies are associated with prion diseases. These disorders are caused by the prion protein PrPSc, which is a higher-order aggregate of the membrane protein PrPC that is abundant in β sheets.

The seeds produced by PrPSc aggregates stimulate more prion protein misfolding and aggregation.[19] Microglia in cooperation with astrocytes release MFGE8 in order to remove PrPSc. This protein identifies apoptotic cells that contain PrPSc, making it easier for microglia to phagocytose them.[20]

Microglia are essential to eliminate amyloid β (Aβ) aggregates, which are hallmark features of AD. They enhance the phagocytosis of these aggregates, a process influenced by apolipoprotein E (ApoE) levels.[21] However, chronic stimulation by Aβ can result in sustained activation of microglia, leading to prolonged inflammation. This inflammatory response is mediated through various microglial receptors, including CD36, toll-like receptors, and inflammasomes, which activate pro-inflammatory cytokines and, thereby, contribute to neuroinflammation.[22] Due to their dual role in neuroprotection and neuroinflammation, microglia are considered promising therapeutic targets in AD.[23]

PD is characterized by Lewy bodies, which develop when microglia act on misfolded α-synuclein. Initially, α-synuclein aggregates and is phagocytosed by microglia, which lessens its harmful effects. By releasing anti-inflammatory cytokines and brain-derived neurotrophic factors, they promote neuronal survival in the early stages of the disease.[24]

Microglia protect motor neurons against misfolded proteins, including mutant SOD1 aggregates, early in the development of ALS. They release neurotrophic factors including insulin-like growth factor I (IGF-I) and encourage neuronal regeneration.[25]

Microglia transplantation in models of neurodegenerative disorders has shown promising results in a number of preclinical investigations. Proinflammatory M1 phenotypes versus anti-inflammatory M2 microglial transplanting into spinal cord damage were compared by Kobashi et al.[11] Comparing the M2 microglia transplantation group to the control and M1 groups, a significant improvement in motor function was observed. Furthermore, the transcription of a number of neuroprotective molecules, including IGF-1 aids in tissue regeneration.[11]

Table 1 shows the summary of the studies included on human glial cell transplantation.

Table 1. Summary of included studies on human glial cell transplantation

Study	Disease model	Glial cell type	Cell source	Delivery route	Sample size	Intervention details	Outcomes assessed	Adverse effects
Kondo et al.[12]	ALS	Astrocytes	hiPSC-derived	Spinal cord	30 mice	hiPSC-derived glial-rich NPCs	↑ lifespan, ↑ survival signals	NESTIN+ cells, no tumors
Chen et al.[26]	Parkinson's	Microglia/ macrophage	HSCs + GDNF vector	Intracerebral	n = 10 mice/group	Ex vivo lentiviral-transduced HSCs	↑ locomotor activity, ↓ neuron loss	None reported
Ban et al.[27]	Alzheimer's	Microglia	Genetically modified	Intracerebral	12 mice	Microglia expressing NEP, SRA	↓ Aβ plaques, ↑ ACh	None reported
Lepore et al.[28]	ALS	Astrocytes	GRPs	Cervical spinal cord	34 rats	GRP-derived astrocytes	↓ forelimb decline, ↓ microgliosis	None reported
Izrael et al.[29]	ALS	Astrocytes	hESCs	Intrathecal	34 rats	ESC-derived astrocytes	↑ survival, ↓ progression	None reported
Gotkine et al.[30]	ALS (clinical)	Astrocytes	AstroRx® (ESC)	Intrathecal	10 patients	Single intrathecal dose, 100M/250M cells	↓ ALSFRS-R decline rate	No severe adverse events
Proschel et al.[31]	Parkinson's	Astrocytes (GDAsBMP)	GRPs-derived	Intracerebral	18 rats	Delayed transplantation of GDAsBMP	Rescue DA and GABA neurons	None reported
Song et al.[32]	Parkinson's	Astrocytes + NPCs	Engineered astrocytes	Intracerebral	16 rats	Co-grafting with Nurr1+Foxa2 astrocytes	↑ DA neuron survival, ↑ motor recovery	None reported
Windrem et al.[33]	Myelin disorder	Oligodendrocytes	hGRPs	Neonatal brain	20 mice	Neonatal brain injection of hGRPs	Remyelination, ↑ lifespan	Not specified
Wang et al.[34]	Myelin Disorder	Oligodendrocytes	hiPSCs	Neonatal brain	20 mice	hiPSC-derived oligodendrocytes	↑ Myelination, ↑ survival	No tumor formation

ALS: Amyotrophic lateral sclerosis; hESCs: Human embryonic stem cells; GRPs: glial restricted precursors; NEP: Neprilysin; SRA: scavenger receptor A; NPCs: Neural progenitor cells

In the study by Chen et al., using a lentiviral vector that expressed macrophage promoter-driven glial cell-derived neurotrophic factors (GDNF), syngeneic bone marrow HSCs were transduced ex vivo and, then, transplanted to 14-week-old MitoPark mice showing signs of PD symptoms involving progressive motor deficits, with declines in horizontal and vertical locomotor activities.[26] GDNF delivery led to significant restoration of these activities, with up to 46.3% improvement in horizontal activity and 54.9% in vertical activity compared to baseline. Additionally, there was a considerable improvement in non-motor symptoms including cognitive impairment and decreased sucrose preference, with restored sucrose preference levels comparable to normal controls. Both the substantia nigra and the ventral tegmental region showed decreased dopaminergic neuronal loss, with neuron loss decreased to 25–28% as compared to 84% in mice that were not treated. Preservation of dopaminergic terminals in the striatum was observed, with TH+ staining intensity restored to 79-67% of normal levels. Striatal dopamine and its metabolites were also restored to approximately 84% of levels found in normal control mice, compared to a 90% reduction in untreated MitoPark mice. Importantly, no adverse effects were noted in the body weight, general health, or histopathological analyses of major organs, indicating a favorable safety profile for the non-toxic hematopoietic stem cell transplantation (HSCT) approach.[26]

Microglia transplantation can be utilized to restore damaged neurons and promote their survival and functionality in AD. Ban et al. engineered human NSCs to encode the choline acetyltransferase (ChAT) gene, enhancing acetylcholine (ACh) synthesis.[27] Additionally, microglial cells were genetically modified to express neprilysin (NEP) and scavenger receptor A (SRA) genes, enabling efficient degradation and uptake of Aβ. An AD mouse model was developed using an intracerebroventricular injection of Ethylcholine Aziridinium Ion (AF64A), resulting in significant accumulation of Aβ, depleted ACh, and persistent cognitive deficits. The therapeutic potential of these engineered cells was tested through intracerebral transplantation, either as single treatments or in combination, into the brains of the AD model mice. Cognitive function, Aβ burden, and ACh levels were subsequently assessed using behavioral tests, immunoassay, and histological analyses. These treatments effectively reduced Aβ accumulation and recovered ACh levels, addressing both key pathological features of AD. Additionally, the transplanted cells exhibited long-term survival in the brain and expressed their respective functional proteins, further contributing to their efficacy. Notably, combinational therapy showed synergistic effects, with greater improvements in memory, Aβ clearance, and neuroprotection compared to single-cell therapies. The decrease in glial fibrillary acidic protein (GFAP) levels demonstrated the treatments' neuroprotective and anti-inflammatory effects, highlighting their potential as an AD treatment approach.[27]

Yoo et al. showed that cell transplantation at 3 weeks of age, before the onset of Aβ pathology, results in more significant protective effects compared to transplantation at 8–10 weeks of age, after Aβ pathology has developed.[35]

Astrocytes: Astrocytic processes are uniquely positioned to replace absent or damaged host astrocytes by seamlessly integrating into local cellular networks. Astrocytes interact with and regulate various cell types, including neurons, astrocytic replacement has the potential to influence not only astrocytic networks, but also broader aspects of brain activity and function. Recently, astrocyte transplantation has gained attention as a possible treatment for ALS where malfunction of astrocytes has demonstrated promising outcomes in models of age-related neurodegenerative disorders, stroke, and traumatic injury.

In the study by Lepore et al., glial restricted precursors (GRPs) for astrocytes were transplanted into 34 $SOD1^{G93A}$ rats with motor neuron disease that was 90 days old through the cervical spinal cord. GRPs-derived astrocytes demonstrated strong survival in gray and white matter areas up to 80 days after transplantation, when the disease was at its last stage, despite continuous disease progression.[36] Each rat received a total of 9.0 × 10^5 cells (1.5 × 10^5 cells in 6 places), and each animal's 6 transplant sites could be identified. According to quantification (n = 3), 32.2 ± 4.6% of transplanted GRPs survived. There was a slower decline in respiratory and forelimb motor control, less microgliosis, and less loss of motor neurons.[36] In contrast, in another study, transplantation of hGRPs derived from the fetal human brain into 50–60-day-old $SOD1^{G93A}$ rats with ALS showed that the hGRPs differentiated into astrocytes and

survived for 3 months post-transplantation.[28] Nevertheless, there were no obvious therapeutic advantages or motor neuron protection in terms of functional outcomes.[28] Izrael et al. reported that the transplantation of astrocytes derived from human ESCs into cerebrospinal fluid of $SOD1^{G93A}$ rats with ALS also showed longer survival and delayed progression of disease.[29] Further study revealed that the transplantation of hiPSC-derived GRPs increased phosphorylated AKT levels, activating the AKT signaling pathway. This pathway, downstream of VEGF signaling, promotes cell survival in ALS. However, a small proportion of grafts retained positivity for the neural progenitor marker NESTIN at 3 months post-transplantation.[12]

This was a phase 1/lla with an open-label dose to evaluate the therapeutic effects and safety of astrocyte transplantation in patients with ALS. A single dose of intrathecal injection of AstroRx® was given to 5 patients with a dose of $100x10^6$ and 5 patients with a dose of $250x10^6$. Patients were followed up for 12 months post-dose and compared with pre-treatment assessments. The pre-post slope change in ALSFRS-R, which was measured within the first 3 months following therapy, showed that the study had a clinically significant benefit. In the first 3 months after therapy, the ALSFRS-R deterioration rate in the 100 × 10^6 AstroRx® arm decreased from -0.88/month before treatment to -0.30/month (P = 0.039). The rate of deterioration in the 250 × 10^6 AstroRx® arm dropped from -1.43/month to -0.78/month (P = 0.002). In a subgroup of 5 rapid progressors, the effect was substantially more pronounced.[30]

In PD, by preserving and slowing the death of surviving dopaminergic neurons and promoting the development of their axonal nerve terminals, astrocyte transplantation may aid in reinnervating the deafferented striatum. Bahat-Stroomza et al. showed that transplanting astrocytes into the striatum of a PD rat model eventually reduced the contralateral rotations caused by apomorphine.[37] Additionally, rotor-rod performance and the "sunflower seeds" feeding motor test revealed significant behavioral alterations.[37] Proschel et al. investigated the efficacy of a multimodal cell therapy approach with transplantation of in vitro-generated astrocytes ($GDAs^{BMP}$) into a PD rat model.[31] $GDAs^{BMP}$ produces multiple therapeutic agents essential for PD treatment, including brain- and glia-derived neurotrophic factor, neurturin, and IGF1 and IGF2, at levels significantly exceeding those produced by their parental precursor cells (GRPs). $GDAs^{BMP}$ transplantation rescues both dopaminergic neurons and parvalbumin-expressing GABAergic neurons, which are typically lost in PD.[31] Furthermore, Song et al. used co-grafted astrocytes particularly cultured from the ventral midbrain engineered with transcription factors Nurr1 and Foxa2 to investigate the efficacy of NPC transplantation in PD by leveraging the neurotrophic properties of astrocytes to create a supportive brain environment and enhance survival, differentiation, and function of grafted dopamine neurons.[32] Cografting astrocytes with NPCs significantly improved dopamine neuron engraftment and survival for at least 6 months post-transplantation. Nurr1+Foxa2-engineered (Nuclear receptor related-1+ Forkhead Box A2) astrocytes further amplified neurotrophic effects, including increased secretion of neurotrophic factors (e.g., GDNF, Sonic Hedgehog, Fibroblast Growth Factor 8). PD model rats showed significant recovery in motor function, with > 95% reduction in rotation scores when cografted with Nurr1+Foxa2-engineered ventral midbrain astrocytes.[32]

The cerebral ventricles of a rat model of AD developed through infusing amyloid-β (1-42) peptide with autologous enteric glial cells (EGCs), which are related to astrocytes, were transplanted from the rat's appendices. As these cells migrated toward amyloid plaques, the plaque load decreased and the cytokine profile of the brain changed to a less inflammatory state, with lower levels of interleukin-6 (IL6), prostaglandin E2 (PGE2), and tumor necrosis factor-alpha (TNFα) and higher levels of nerve growth factors, brain-derived neurotrophic factors, and GDNF. Furthermore, the therapy improved memory and learning.[38] These findings are supported by a study in a transgenic mouse model of FTD with human P301S tau, where transplantation of NPC-differentiated astrocytes into the cortical gray matter reversed cortical neuron loss.[39]

Treatment for Huntington's disease (HD) has shown promising results with astrocyte transplantation. Mutant huntingtin protein (mtHtt) aggregates in HD, as it does in other neurodegenerative proteinopathies. This aggregation causes progressive neurodegeneration, affecting striatal GABAergic (gamma-aminobutyric acid) medium-spiny neurons first and, then, the cortex. Apart from palliative care, there is currently no cure.[40] Glial pathology's precise significance in striatal neuronal dysfunction and the overall

disease pattern in HD have not been well studied. The absence of in vivo models that allow for an independent assessment of glial and neuronal activity, particularly in human conditions, is the primary reason for this knowledge gap.[40] Benraiss et al. replaced diseased glial cells from RG/2HD neonatal mice through striatal transplantation of astrocyte-GPSc and observed improved motor neuron performance, restoring intestinal potassium homeostasis and slowing the disease progression.[41]

Oligodendrocytes: Oligodendrocytes are essential glial cells, together with astrocytes and microglia. By enveloping axons in a lipid-rich myelin sheath, oligodendrocytes enable rapid saltatory action potential conduction. When myelin insulation is lost in demyelinating illnesses, it impairs brain function and causes axonal conduction to slow down or stop.[42] MS is a common neurodegenerative disorder caused by demyelination, which also occurs in spinal cord injury and white matter stroke. The degeneration or death of oligodendrocytes in neurodegenerative diseases has been brought to light by recent data. Substantial myelin loss that is not repaired by endogenous mechanisms necessitates oligodendrocyte replacement therapy to restore myelin integrity and support neural function. Levison and Goldman injected replication-deficient retroviruses that expressed the β-galactosidase gene into neonatal rats' subventricular zone (SVZ). In the postnatal rat brain, oligodendrocyte precursors are thought to have originated in the SVZ. Labeled cells were shown moving from the SVZ into the ipsilateral hemisphere's white and gray matter after the injection. Migration within the oligodendroglial lineage was directly demonstrated by the identification of a sizable portion of these tagged cells as oligodendrocytes. This suggests that oligodendrocyte progenitors possess migratory characteristics, making them highly suitable candidates for transplantation in MS.[43]

The proof of concept for successful oligodendrocyte replacement has been demonstrated by engrafting human fetal glial progenitor cells into animal models of myelin deficiency, such as the immunocompromised shiverer (shi/shi) × rag2−/− mouse model. Direct injection of these cells into the neonatal brain, targeting major white matter tracts, produced remarkable outcomes: widespread replacement of mouse oligodendrocytes with human oligodendrocytes and significantly prolonged survival in some recipients.[33] Similarly, Nistor et al. in early 2000 transplanted hESCs into a shiverer model of dysmyelination resulting in excellent integration and differentiation into oligodendrocytes and its survival in white matter.[44]

Neonatal shiverer mice, a model of myelin deficiency, were engrafted with human-induced pluripotent stem cells (hiPSC) derived oligodendrocytes, resulting in extensive myelination and significantly increased survival. Notably, the speed and efficiency of myelination were superior to that observed with fetal-tissue-derived oligodendrocytes. Importantly, long-term monitoring revealed no tumor formation in graft recipients up to 9 months post-transplantation. These findings show that hiPSC-derived oligodendrocytes have the potential to be a safe and efficient treatment for diseases involving myelin degeneration.[34]

Oligodendrocyte precursors produced from iPSCs have already been successfully transplanted. It was a time-consuming approach, though, requiring a culture period of 120 to 150 days. As an alternative, a more effective procedure has been developed that allows O4+ oligodendrocyte progenitor cells to differentiate within 75 days.[34]

Clinical challenges in glial transplantation: Multiple cell transplantation into the brain is a potential application of stem cell treatment, especially in glial cell transplantation. This approach offers the dual benefit of replacing both lost neurons and glial cells while allowing the transplanted glial cells to simultaneously support neuronal function. Microglia and astrocytes function synergistically in numerous neurodegenerative diseases, which often contributes to increased neurotoxicity; thus, replacing both cell types could enhance neuroprotection and mitigate disease progression.[45]

To present, no preclinical research has examined combined cell therapy for the brain. However, 2 clinical studies in China explored the intracranial, intravenous, and intrathecal delivery of the 4 fetal-derived cell types of olfactory ensheathing cells, Schwann cells, NPCs, and umbilical cord mesenchymal stromal cells for the treatment of stroke and multiple system atrophy. While both studies showed safety and some patient benefit, ethical and practical concerns limit the feasibility of scaling this approach. Long-term neuroepithelial stem cells have been shown in a recent study to differentiate into both neurons and oligodendrocytes, indicating the capacity to

restore damaged neural circuits and demyelinated axons. This is an interesting alternative as it permits the brain to contain several cell types without requiring simultaneous transplantation.[46,47]

The availability of fetal-derived cells is a challenge, and the potential advantages of therapeutic transplantation through several routes in elderly patients may be outweighed. However, basic and preclinical testing of the idea is still necessary. Given the intricacy of neurodegenerative illnesses and the wide range of symptoms associated with different brain regions and cell types, targeting certain brain regions with several cell types instead of systemic distribution may be a more effective starting point.

Human embryonic precursor cells are frequently seen to be more reliable in exhibiting an accurate astrocytic phenotype than differentiated cells, whose identification is typically ascertained by the expression of generic astrocyte markers like GFAP. However, there are several obvious disadvantages to using human embryonic material, including the limited number of cells that can be created and ethical issues about extending the cell supply. Furthermore, batch-to-batch variability resulting from embryonic variations continues to be a major concern.[48]

Discussion

Cell therapies are an emerging approach to promote tissue regeneration, with the brain being a prime target because certain cell types are lost in many neurological disorders. By replenishing CNS cells, these therapies aim to restore lost functions and alter the progression of diseases.

Numerous investigations have revealed that protective factors are released and integrated into local cellular networks at the implantation site, where they promote plasticity in preexisting cells, which may be a greater contributor to the functional advantages of neuronal transplantation therapy than the restoration of proper axonal circuits.[49]

The glial cell transplantation approach effectively mitigated dopaminergic neuron loss and preserved striatal dopamine levels, suggesting a promising disease-modifying therapy for PD.

In animal models of PD, a number of preclinical studies have shown promising results using microglia transplantation. To determine its potential as a feasible therapeutic option, further study is necessary to determine the safety and efficacy of this strategy in humans. If neurotrophic factor delivery is selected as the therapeutic strategy, the transplantation of genetically engineered cells can be explored as a promising method to achieve sustained delivery and enhance treatment efficacy.[13]

A recently developed approach involves delivering glial cell-derived neurotrophic factor to neurotoxin-induced PD animal models using GDNF-expressing hematopoietic stem cell-derived macrophages. These modified cells are effectively integrated into the brain after transplantation, improving motor function, lowering neuroinflammation, and preventing additional neuronal loss. The inability of peripheral GDNF to pass the blood-brain barrier makes it difficult to administer GDNF-based therapy to the CNS, despite the fact that it has substantial disease-modifying potential for PD. In such cases, studies have found that macrophages serve as a promising cellular delivery system, capable of targeting GDNF directly to areas of neurodegeneration within the CNS. These findings provide a strong rationale for exploring neuroprotective macrophage or microglia transplantation as a potential therapeutic strategy for PD patients.[32]

Human hematopoietic cells, derived from donors or PSCs, can replace microglia, but circulating myeloid-derived microglia-like cells may not fully replicate brain-resident microglia. The long-term impact of these cells, particularly in the context of AD pathology, is unclear. This raises the question of whether authentic microglial cells derived from human PSCs would be a better option.[18]

A single intrathecal administration of AstroRx®, an astrocyte cell-based therapy derived from ESCs to ALS patients, at doses of 100 × 10^6 or 250 × 10^6 cells, has been deemed safe in clinical trials. The first 3 months after the treatment showed a positive clinical benefit. A possible and feasible treatment for ALS is astrocyte replacement based on stem cell transplantation. Critical motor neuron pools that affect ALS patients' survival are addressed by using glial progenitors to target the cervical spinal cord. Respiratory measures remain the most reliable endpoints for ALS clinical trials.[30]

The potential tumorigenicity of grafts remains a significant concern. Kondo et al. utilized the human iPSC line "201B7," previously reported to be safe regarding tumorigenesis.[12] Moreover, no evidence of tumor formation or Ki67-positive grafts was observed. However, a small subset of grafts retained positivity for the neural progenitor marker NESTIN at 3 months post-transplantation.

However, they observed that a small proportion of grafts retained positivity for the neural progenitor marker NESTIN, which indicates cells in an undifferentiated state at 3 months post-transplantation. The risk of tumor formation from the remaining NESTIN-positive NPCs cannot be excluded. Long-term observations are essential to evaluate tumorigenicity in future clinical trials.[12]

The first instance of a multimodal support cell therapy that can aid in the recovery of several neuronal populations associated with PD is GDA^{BMP} transplantation. Dopaminergic neurons and parvalbumin-expressing GABAergic neurons, which are destroyed in PD, are both uniquely restored by this one therapy strategy. Utilizing the beneficial characteristics of astrocytes to treat CNS injury is made possible by the availability of human $GDAs^{BMP}$, which can be generated in therapeutically significant amounts. As a result, GDA^{BMP} therapy may be a new treatment for PD that addresses several pathologies associated with the disease. It may also work well for other neurodegenerative conditions.[31]

Moreover, astrocyte cografting produced dramatic effects, including near-complete behavioral restoration and extensive dopamine neuron engraftments, which persisted for at least 6 months post-transplantation in PD rats. Therefore, astrocyte cografting has been suggested as a viable future alternative in cell therapy methods. Furthermore, by enhancing the brain environment, astrocyte grafting alone may have therapeutic advantages by allowing endogenous dopamine neurons in the substantia nigra to expand axonal outgrowths, release dopamine into the striatum, and rescue striatal GABAergic interneurons.[32]

A significant challenge in considering transplantation for MS is the multifocal nature of the disease where numerous patches of demyelination are interspersed with normal myelinated regions. This pattern is replicated throughout the CNS, making it impractical to directly transplant cells into every individual lesion. Instead, each transplant will need to target groups of lesions. Consequently, transplanted cells must possess the ability to migrate to the demyelinated areas before initiating new myelin formation. Although mature oligodendrocytes are immobile, studies have shown that their progenitors have a significant capacity for migration. These progenitor cells may also be able to move widely across the normal CNS. Preclinical studies suggest that precursor cells can extensively redistribute into lesions, indicating that their natural migratory capacity is sufficient and that transplantation of unmodified cells may be effective.[43] However, it has proved difficult to produce human oligodendrocytes for the study of disease mechanisms; thus, most studies have relied on rat models. Despite constant improvement and refinement, oligodendrocyte differentiation techniques still take several months to create mature human cells free of various glial and neuronal impurities, which presents a challenge.[9]

Delivering a sufficient quantity of cells to the brain is still challenging, regardless of whether progenitor cells are able to migrate to target locations, survive, and develop into the desired cell type. Since the number of cells needed to support neurons or replace glia is currently unknown, experimentation in this area is crucial if the strategy is to be applied to the human brain. Determining the approximate number of glial cells in the target area would be helpful for improving transplantation strategies because glial cell numbers vary across different brain areas.[9]

Conclusion

The transplantation of human glial cells into animal models of neurodegenerative disorders demonstrates significant potential for improving neuronal survival, restoring damaged neural circuits, and mitigating disease progression. Preclinical studies highlight promising findings in the transplantation of glial cells, including astrocytes, microglia, and oligodendrocytes in neuroprotection, modulation of neuroinflammation, and remyelination, which can be harnessed to address the multifactorial pathology of diseases such as ALS, PD, AD, HD, and MS.

While these findings emphasize the effectiveness of glial cell transplantation, challenges remain. Variability in cell survival, differentiation, and targeting to specific disease-affected regions are notable hurdles. Despite promising safety data from animal studies showing promising results, more research is necessary to fully understand how transplanted cells integrate into the host CNS over the long term. Emerging strategies, such as engineering glial cells to enhance neurotrophic factor production, co-transplantation with neural precursors, and the use of iPSCs as a scalable source of glial progenitors, offer promising avenues for enhancing efficacy. However, ethical

and logistical challenges, particularly around the use of fetal-derived cells, must be addressed.

Overall, replacing dysfunctional glia or enhancing glial cell functions holds promise as a therapeutic approach for various brain diseases. While several practical challenges remain, including translating preclinical studies to human applications, further research particularly well-controlled studies that can be easily compared, will pave the way for new treatments for these debilitating and increasingly prevalent disorders.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

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