Stem cell therapy in neurodegenerative diseases

From principles to practice

Rajalingham Sakthiswary, Azman Ali Raymond

Abstract

The lack of curative therapies for neurodegenerative diseases has high economic impact and places huge burden on the society. The contribution of stem cells to cure neurodegenerative diseases has been unraveled and explored extensively over the past few years. Beyond substitution of the lost neurons, stem cells act as immunomodulators and neuroprotectors. A large number of preclinical and a small number of clinical studies have shown beneficial outcomes in this context. In this review, we have summarized the current concepts of stem cell therapy in neurodegenerative diseases and the recent advances in this field, particularly between 2010 and 2012. Further studies should be encouraged to resolve the clinical issues and vague translational findings for maximum optimization of the efficacy of stem cell therapy in neurodegenerative diseases.

Key Words

stem cells; neurodegenerative diseases; Parkinson’s disease; Huntington’s disease; Alzheimer’s disease; amyotrophic lateral sclerosis; embryonic stem cells; induced pluripotent stem cells; mesenchymal stem cells; neural stem cells

Research Highlights

(1) Stem cell therapy is probably the only potential treatment modality which offers ‘cure’ for neurodegenerative diseases.
(2) The structural and functional improvements seen in animals need further evaluation prior to extrapolation to humans. Hence, the clinical outcome and long term safety of stem cell therapy in humans with neurodegenerative diseases are still questionable.
(3) Of the 4 types of neurodegenerative diseases described in the literature, there is relatively more evidence for stem cell therapy in Parkinson’s disease and amyotrophic lateral sclerosis compared to Huntington’s disease and Alzheimer’s disease.

Abbreviations

PD, Parkinson’s disease; HD, Huntington’s disease; ALS, amyotrophic lateral sclerosis; ESCs, embryonic stem cells; IPSCs, induced pluripotent stem cells; MSCs, mesenchymal stem cells or mesenchymal stromal cells; SVZ, subventricular zone; SGZ, subgranular zone; GDNF, glial cell line-derived neurotrophic factor; AD, Alzheimer’s disease

INTRODUCTION

Stem cell therapy has revolutionized the field of medicine over the past few decades. Stem cells have been proven to be invaluable in the treatment of numerous diseases affecting various organs in the human body. The list of therapeutic applications of stem cells in clinical practice continues to expand steadily over the years. Neurodegenerative diseases became a landmark in the history of stem cell therapy back in the 1980s when patients suffering from Parkinson’s disease (PD) in Mexico were treated with this form of therapy with
variable outcome\textsuperscript{[11]}. Today, stem cell therapy offers promising hope for almost all forms of neurodegenerative diseases including PD, Huntington’s disease (HD), Alzheimer’s and amyotrophic lateral sclerosis (ALS). The fundamental mechanism underlying all forms of neurodegenerative diseases is progressive loss of structure, function or number of neurons, including death of neurons\textsuperscript{[2]}. At a molecular level, there are many parallels among the different forms of neurodegenerative diseases. Unfortunately, the current available treatment options neither pharmacological nor neurosurgical are efficient in arresting the progression of the neurodegenerative processes. Stem cell therapy, on the other hand, enables regeneration of neural tissue which ameliorates neurodegeneration occurring at different levels of the neuronal circuitry. We searched the electronic databases of the PubMed and the Cochrane Library for related studies encompassing basic sciences, translational, clinical and epidemiological research. In this review, we have summarized the principles, clinical applications and the recent progress of stem cell therapy in neurodegenerative diseases.

**TYPES OF STEM CELLS**

**Embryonic stem cells (ESCs)**

ESCs are pluripotent and retain the ability to self-renew indefinitely with the capacity to differentiate into almost all cell types of the central nervous system. These cells are currently being used as an inexhaustible source of neurons to perform experiments involving new candidate drugs in neurodegenerative diseases\textsuperscript{[3]}. The first clinical application of ESCs-derived tissue in the central nervous system was oligodendrocytes in the treatment of spinal cord injury. The initial approval for this clinical application by the Food and Drug Administration (FDA) in January 2009 (http://www.geron.com/products/productinformation/spin_alordinjury.aspx) was put on hold after preclinical studies showed a higher frequency of epithelial cysts within the grafted spinal cords compared to the rodent studies. The subsequent applications for clinical trials using ESCs-derived tissues are still awaiting approval\textsuperscript{[4-5]}. In 2011, Nistor et al\textsuperscript{[6]}, for the first time described a method for producing human neuronal progenitors in large quantity and high purity from ESCs. The human neuronal progenitor population produced displayed characteristic neuronal-specific markers and spontaneously differentiated into neuronal subtypes in vitro, i.e. cholinergic, serotonergic, dopaminergic, noradrenergic, and medium spiny striatal neurons. In this recent study, the ESCs derived human neuronal progenitors, when transplanted into the injured spinal cord and integrated into host tissue, matured into a variety of neurons.

Translating ESCs into novel therapies in neurodegenerative diseases needs careful consideration as it is associated with the risk of tumour formation. This threat is due to the persistence of nondifferentiated cells that undergo malignant transformation and genetic instability following prolonged time in culture\textsuperscript{[7-8]}.

**Induced pluripotent stem cells (IPSCs)**

The main breakthrough in regenerative medicine is the reprogramming of adult somatic cells to acquire similar characteristics as ESCs. These cells are referred to as IPSCs. Although the initial reprogramming required retroviral transfer into fibroblasts of four transcription factors, subsequent research demonstrated that fewer factors might suffice\textsuperscript{[9-11]}. Such reprogrammed cells now offer the promising avenue to generate autologous dopaminergic neurons for transplantation in PD patients. Of note, the IPSCs platform has a distinct advantage over ESCs in the sense that IPSCs are autologous and therefore the transplantation does not require immunosuppressive agents\textsuperscript{[12]}. However, similar to ESCs, an important risk of IPSCs is tumour formation. The differentiation of IPSCs into mature neurons is more difficult than ESCs. Hence, the clinical application of IPSC in neurodegenerative diseases is still not feasible in the near future owing to the lack of in-depth research evaluating its therapeutic safety among human subjects\textsuperscript{[8]}.

Vierbuchen et al\textsuperscript{[13]} in 2010 through their elegant work demonstrated that it may be possible to transform fibroblasts from adult mice into mature neurons without the intermediate step of IPSCs. This strategy which is not only ethically acceptable, may also overcome the risk of tumour formation.

**Mesenchymal stem cells or mesenchymal stromal cells (MSCs)**

MSCs, with pluripotent differentiation capacity, are an ideal source for cell transplantation in neurodegenerative diseases. The International Society for Cellular Therapy proposed a panel of markers for the identification of MSCs which include CD44, CD73, CD90, and CD105\textsuperscript{[14]}. The exact regulating mechanism underlying MSC proliferation and differentiation remains vague. This critical issue has to be addressed for safe translational clinical application. Increasing depth of MSCs knowledge has led to a few successful FDA-approved phase I–III clinical trials for bone and cartilage diseases. MSC-derived functional neurons appear more promising in neurodegenerative diseases compared to ESCs given the less related ethical and immunorejection problems\textsuperscript{[15]}. In preclinical studies of neurodegenerative diseases,
MSCs were delivered via either intracerebral or intrathecal injection. Following transplantation, MSCs promote neuronal growth, decrease apoptosis, reduce release of free radicals, and suppress inflammation. At present, there are ongoing clinical trials evaluating MSCs in the treatment of amyotrophic lateral sclerosis, traumatic brain injury, and stroke. In a recent study by Gong et al. (2011), immortalized mesenchymal stem cells were generated by using SSR#69 retrovirus expressing simian virus 40 large T (SV40T) antigen. Immortalized MSCs outperformed primary MSCs by demonstrating higher proliferation capacity and anti-senescence ability in addition to basic features of primary MSCs. Senescence was a serious drawback in MSCs application prospects for cell-based regenerative medicine. This study highlighted that immortalized MSCs were a superior alternative to MSCs in neuronal differentiation and neuroregeneration.

**Neural stem cells (NSCs)**

NSCs can be produced from fetal or adult central nervous tissue via the dissection of specific brain regions. Several growth media facilitate the proliferation of such cells when supplemented with mitogens such as epidermal growth factor and fibroblast growth factor 2. NSCs have the capacity to differentiate into oligodendrocytes, neurons, and astrocytes. A study by Huang et al. in 2012, demonstrated for the first time that NSCs can synthesize d-serine. d-Serine, the co-agonist of N-methyl-D-aspartate receptors, has been recognized as an important gliotransmitter in the central nervous system. d-serine has been shown to regulate neurogenesis by promoting NSC differentiation into neurons. Degradation of endogenous d-serine in their study, on the other hand, significantly inhibited the proliferation and neuronal differentiation of NSCs. Low oxygen conditions and hypoxia-inducible factor 1 alpha were identified to be critical for NSC development. These conditions were successfully used to expand epidermal growth factor/fibroblast growth factor 2 responding cells for a period of more than a year. In vitro studies have proven that newborn neurons in the brains of rodents can integrate into the existing neuronal circuitry and receive functional input.

**Evolving Concepts of Neurogenesis**

It has become convincingly apparent that neurogenesis in the central nervous system of primates, including humans occurs throughout life. About 9,000 to 10,000 new cells are generated daily in the rodent hippocampus of which up to 90% differentiate into neurons. This capability has been clearly demonstrated particularly at two locations: the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus. Neurons born in the SVZ, migrate through the rostral migratory stream to the olfactory bulb and become granule neurons and periglomerular neurons. As the precursors migrate towards their destination, three well-defined processes take place i.e. proliferation, cell death/survival, and differentiation. Neurons born in the SGZ, on the other hand, migrate and become dentate granule cells in the granule cell layer of the dentate gyrus. Recent studies have proven that newborn neurons in the brains integrate into the existing neuronal circuitry and receive functional input.

Adult neurogenesis is regulated by various physiological and pathological factors at all levels from the proliferation of NSCs to maturation of the neurons. Apart from aging, the known down-regulating factors of neurogenesis are stress, glucocorticoids and inflammation. Conversely, the up-regulating factors are estrogen, antidepressant drugs and growth factors such as brain-derived neurotrophic factor (BDNF) and insulin growth factor 1. There are still controversies on whether neurogenesis occurs at sites other than the SVZ.
and SGZ\[44\].

Over the past decade, the field of regenerative medicine has witnessed remarkable progress in the concepts and understanding of neurogenesis. There are a few basic principles derived from recent studies which were summarized by Zhao et al in 2008\[44\]. (1) Neurogenesis is conserved in all mammalian species. (2) The process of neurogenesis is readily influenced by numerous external factors. (3) Adult neurogenesis shares similar mechanisms with embryonic neurogenesis. (4) The mechanisms of SVZ and SGZ neurogenesis are quite different, despite sharing certain common regulators. (5) The activities of newborn neurons from both SVZ and SGZ are critical for effective neurogenesis.

Although the processes described above occur throughout the life span of humans, there is a sharp decline from youth to the aged brain. In 2012, Encinas et al \[45\] pointed out that NSC deforestation is the culprit leading to age-related decline in hippocampal neurogenesis. Deforestation through differentiation of NSCs into astrocytes contributed to the diminishing pool of quiescent neural progenitors in the dentate gyrus\[46-47\].

The "NSC deforestation model" explained that in terms of frequency, astrogliogenesis occurred parallel to neurogenesis. Recently, Cunningham et al \[48\] discovered that hypoxia-inducible factor-1alpha played a central role in the survival of NSCs through Notch and Wnt/beta-catenin signaling pathways. Hypoxia-inducible factor-1alpha is a mediator of adaptive cellular responses to hypoxia through regulation of cellular metabolism and angiogenesis. These molecules are involved in the maintenance of the ideal vascular environment of the NSCs niche enhancing the repair of the brains.

The fundamental mechanism for the observed improvements after stem cell therapy in the central nervous system is believed to be neuroprotection. Neuroprotection is achieved through the secretion of growth factors \textit{i.e.} brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, and nerve growth factor. Genetically engineered stem cells in recent studies have the tendency to overexpress growth factors which in turn enhance their neuroprotective capacity\[49\]. The outcome of stem cell therapy can be improved through the combination with other adjunct therapies. For example, stem cell therapy with erythropoietin demonstrated synergistic effects on neurogenesis in a rat model\[50\]. Exploration of other strategies in this regard has been sparse. Post stem cell therapy, the survival of stem cells can be jeopardised by poor vascularisation, inflammation or rejection mediated by the immune response of the host\[49\].

Despite the remarkable advance in our scientific knowledge and understanding of stem cell biology, there are still many hurdles to cross and multiple challenges to overcome. Unfortunately, the vast majority of studies are based on animal models. Researchers have not answered the compelling question of whether human stem cell populations will exhibit similar functional properties to their murine and rodent counterparts. Translating stem cell therapy to the neurology clinics is not possible without the identification of a suitable source of stem cells for therapeutic applications. Different neurological conditions are better suited to a certain cell type than others. For example, NSCs are a good option for spinal cord injury whereas MSCs are better for multiple sclerosis. The cost, time and labor intensive nature of stem cell therapy limit its use especially in developing and third world countries. A potential solution for this concern is the use of broad spectrum stem cell therapy with multipotent adult precursor cells (MAPC cells). These cells are currently being tested in neural pathologies\[53\].

**EXPERIMENTS AND EXPERIENCES OF STEM CELL THERAPY IN NEURODEGENERATIVE DISEASES**

**PD**

PD is typically a disease of the basal ganglia characterized by progressive degeneration of dopaminergic neurons in the substantia nigra. The depletion of dopamine in the nigrostriatal pathway leads to motor dysfunction. The current available therapies for PD address symptoms but do not cure this illness. Over the past two decades, preclinical and clinical trials in PD patients have demonstrated that stem cell therapy of human embryonic mesencephalic tissue has the capacity to reinnervate the striatum. PD, in fact, has emerged as the best-suited neurodegenerative diseases for stem cell therapy\[52-53\]. The essence of stem cell therapy in PD is the ability of stem cells to differentiate into dopaminergic neurons. Through genetic engineering, dopaminergic neurons were obtained from rat NSCs, mouse fibroblasts and human ESCs\[1, 54\].

Soldner and colleagues’ finding that fibroblasts from PD patients can be reprogrammed to differentiate into dopaminergic neurons was a turning point in the clinical area of PD\[52\]. ESCs, NSCs and bone marrow stem cells (BMSCs) all successfully survived when grafted in animal models of PD\[53-54\]. Of note, not only were ESCs found to release significant amounts of dopamine but both ESCs and NSCs derived from the embryonic ventral mesencephalon produced promising functional outcome\[54-55\].

There were a few double-blinded trials presented with
negative results\cite{56-57}. In those trials, patients who were transplanted with fetal tissues did not improve significantly especially the older patients\cite{56-57}. These inconsistent results could be due mainly to variation in the collection of stem cells\cite{56, 58-60}. Several factors have been proposed to influence the development of dopaminergic neurons such as orthodenticle homeobox 2 (OTX2), orphan nuclear receptor-related factor 1 (Nurr1), tyrosine hydroxylase, fibroblast growth factor 8 (FGF8), engrailed genes (En1, En2), Wingless (Wnt), (Fox) A2 and neurogenin (Ngn). Figure 1 summarizes the sources of stem cells and factors regulating stem cells differentiation in PD.

A recent study demonstrated that multipassaged neural precursor cells from human ESCs had reduced life span\cite{61}. Forced expression of Bcl-XL and SHH is believed to be able to tackle this problem\cite{61}. A few studies have looked into generating dopaminergic neurons by overexpression of Nurr1 in stem cells\cite{62-65}. Introducing Nurr 1 into stem cells resulted in motor function improvement with ESCs but not with NSCs\cite{65-66}. Intriguingly, in the presence of stromal cells, dopaminergic neurons had improved survival and were better incorporated in the striatum\cite{67-68}. A more recent study published in 2012, stated that stem cell therapy with human amniotic fluid stem cells and MSCs ameliorated bladder dysfunction in a PD rat model. In this study, cystometric parameters improved as early as 14 days after stem cell therapy\cite{69}. Besides, glial cell line-derived neurotrophic factor (GDNF) has been implicated in the survival of ventral midbrain dopaminergic neurons. Treatment of midbrain NSCs with GDNF increased the sphere diameter of the stem cells, and reduced the expression of caspase 3 while enhancing the expression of Bcl-2\cite{70}. Deileidi et al \cite{71} in 2011 reported for the first time that Oct-4 induced pluripotency caused successful differentiation of adult NSC into functional midbrain dopaminergic neurons in the SVZ of the brains. Dopaminergic neurons produced from Oct4-reprogrammed NSCs improved motor deficits in a rat model of PD. Despite the impressive potential of stem cell therapy in PD, it carries the serious risk of graft-induced dyskinesias. Politis et al \cite{72} in their study found that positron emission tomography after 14 years posttransplantation revealed an elevated serotonin to dopamine transporter ratio in the grafted striatum. This was compatible with serotoninergic hyperinnervation which was the underlying mechanism for graft-induced dyskinesias.

HD

HD is a fatal progressive neurodegenerative diseases of autosomal dominant inheritance due to an expansion of cytosine-adenine-guanine repeats in the Huntingtin gene (\textit{htt}). Mutated \textit{htt} induces a preferential loss of medium spiny neurons of the striatum giving rise to motor, cognitive and emotional deficits. Experiments utilizing stem cells in HD is barely a decade old. Research on neural regeneration has been less intense in HD compared to PD with fewer preclinical and clinical trials. Nevertheless, there is convincing evidence that NSCs confer behavioral benefits in phenotypic models of HD\cite{73-74}. Dey et al \cite{75} in 2010 reported that MSCs, harvested from mouse femurs which were genetically engineered to over-express BDNF or nerve growth factor reduced behavioral deficits in the YAC 128 mouse model of HD. The transplanted mice showed less neuronal loss in the striatum on immunohistological examination. This study highlighted that intrastriatal transplantation of MSCs that over-express BDNF may create a conducive environment within the striatum that retards neurodegenerative processes. Ebert et al \cite{76}, on the other hand, identified mouse NSC act as growth factor (GDNF) delivery vehicles to the brains of murine models of HD. GDNF has shown promising results in HD by reducing neuronal death and the resultant motor impairment. Snyder et al \cite{77} in their study discovered that the implantation of human multipotent stromal cells from bone marrow (hMSCs) into the dentate gyrus of the hippocampus of mice models of HD was shown to enhance proliferation and neural differentiation of endogenous NSCs for up to 30 days post stem cell therapy. Interestingly, these effects were seen despite

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**Figure 1** Sources of stem cells in Parkinson’s disease (PD).

Factors regulating stem cells differentiation into dopaminergic neurons are orthodenticle homeobox 2 (OTX2), orphan nuclear receptor-related factor 1 (Nurr1), tyrosine hydroxylase (TH), fibroblast growth factor 8 (FGF8), engrailed genes (En1, En2), Wingless (Wnt), (Fox) A2 and neurogenin (Ngn). NSC: Neural stem cells; ESC: embryonic stem cells.
the rapid disappearance of the implanted hMSCs over 3 to 15 days.
In HD monkeys, dental pulp stem cells were a potential source of personal stem cells for therapeutic purposes. dental pulp stem cells had multipotent differentiation capabilities. The advantage of this source of stem cell is they are true personal stem cells and can be readily isolated from individuals at any age[78]. It is rational to speculate that stem cell therapy with personal stem cells would require less intensive immunosuppressive therapy post transplant in humans.
Lin et al[79] concluded from their study that human bone marrow-derived MSC based stem cell therapy in HD offered neuroprotection and neurorestoration through neural differentiation, neurotrophic support capability and anti-apoptotic effects. Mice models showed significant improvement in motor dysfunction as early as 10 weeks after stem cell therapy. Post transplantation, there were increased levels of laminin, Von Willebrand factor, stromal cell-derived factor-1, and its receptor Cxcr4. Almost all studies on stem cell therapy in HD are animal based (Figure 2) and hence this area is still at its infancy. The applicability of the findings of the studies described earlier in humans is still a gray area. For the time being, stem cell therapy with regard to HD, is still far from being practiced in the neurology clinics worldwide.

Figure 2  Stem cells evaluated in the recent preclinical studies of Huntington’s disease.
MSC: Mesenchymal stem cells or mesenchymal stromal cells.

ALS
ALS is an adult-onset disease which is usually sporadic. ALS is characterized by the death of upper and lower motor neurons with subsequent muscular paralysis and atrophy. Unfortunately, despite the advent of modern medicinal chemistry, there is only one approved treatment i.e. riluzole, which has modest therapeutic effects[80-84]. Compared to other neurodegenerative diseases, there are certain features of ALS that makes it more challenging to experiment stem cell therapy. The most important aspect is the unknown pathogenesis followed by the lack of knowledge on how the disease spreads in the human body. Choosing the ideal site to implant stem cell is difficult without answers to the above[80, 82]. Theoretically, the objective of stem cell therapy in ALS is substitution of motor neurons. The fundamental strategies of stem cell therapy in ALS consist of the regulation of inflammation and the expression of neurotrophic factors. Stem cells modified to release GDNF improved motor function in transgenic rats[83-84]. In 2010, the FDA approved a clinical trial with NSCs in patients suffering from ALS. The phase I of the trial, at Emory University, assessed the safety of implanting NSCs into the spinal cord of 18 affected patients. A year later, FDA approved the continuation of the trial[80, 85]. More recently, Martinez et al described the safety of stem cell transplantation into the frontal motor cortex of 67 patients with ALS[86]. This was probably one of the largest human studies in the history of stem cell therapy in neurodegenerative diseases. Autologous stem cell therapy into the frontal motor cortex was found to be safe with encouraging results of 90% survival at 1 year[86]. Similarly, surgical implantation of MSC into the dorsal spinal cord was well tolerated with no immediate or long term complications during a follow up period of 9 years[87]. Both these human studies, however, focused on the safety rather than the clinical benefits. Hence, stem cell therapy in ALS is still in a preliminary stage. The ideal cellular type and optimal anatomical site for implantation which would yield favorable clinical outcome are yet to be determined.

Alzheimer’s disease (AD)
AD is the most common form of dementia accounting for more than half of all dementias. It is characterized by the insidious onset of dementia and, histologically, by senile plaques and neurofibrillary tangles[88]. There is accumulating evidence that the pathogenesis of AD involves oxidative stress and inflammation[89-90]. Most patients only seek treatment at an advanced stage of the disease with neuritic plaques, neurofibrillary tangles, and neurodegeneration. To arrest the disease progression at this stage, clinicians are expected to adopt a multifaceted approach aiming to promote cell survival and substitute the lost neurons[89]. Using the mouse models of AD, Blurton-Jones et al[91] in 2009 reported that NSCs transplanted in the hippocampus improved memory deficits via BDNF mediated response. The role of BDNF in ameliorating cognitive function was further emphasized by Nagahara et al[92] in the same year. Furthermore, observations from animal studies have pointed out that
transplanted SC migrate and differentiate into cholinergic neurons, astrocytes, and oligodendrocytes. Apart from replacement of the lost neurons, stem cells stimulate endogenous neural precursors, promote structural neuroplasticity, inhibit proinflammatory cytokines, suppress neuronal apoptosis and express growth factors\[93\].

Kern et al\[94\] in 2011 discovered that implantation of NSCs into the hippocampus of aged Down syndrome mice resulted in a significant decrease in the tau/reelin-positive granules. The authors of the study suggested that changes in granule density could be used to assess the effectiveness of novel therapies such as stem cell therapy. Generation of patient-specific iPSCs associated with AD is in progress. Researchers are working on creating stem cell lines from patients with amyloid precursor protein duplications, tau mutations and preselenin-1. In this regard, cholinergic cells of the nucleus basalis are a reasonable initial target\[95\].

FUTURE DIRECTIONS AND RESEARCH AGENDA

Neurorestoration is a concept which is evolving at an accelerated pace over the past decade. A very recent study identified up to 106 of either ongoing or planned neurorestorative clinical trials. The vast majority of the trials were targeting one of the following diseases: multiple sclerosis, stroke, PD and ALS\[96\].

In future, researchers should attempt to identify the ideal SC type and route of administration for each neurodegenerative diseases. Clearly, a tailored approach is required for each neurodegenerative diseases to effectively salvage the neuronal networks. Besides, less invasive methods of stem cell implantation across the blood brain barrier are being explored.

CONCLUSION

Neurodegenerative diseases have devastating sequelae with conventional pharmacological therapies and to date stem cell therapy is probably the only potential treatment modality which offers ‘cure’ for neurodegenerative diseases. The vast majority of studies are in animal models. Thus, there is still paucity of data on clinical outcome and long term safety of stem cell therapy in humans with neurodegenerative diseases. The structural and functional improvements seen in animals need further evaluation prior to extrapolation to humans. Of the four types of neurodegenerative diseases described above, there are relatively more studies on PD and ALS compared to HD and AD. Prior to the clinical applications of stem cell therapy in neurodegenerative diseases, several issues need to be addressed. The cost, safety, manpower requirement and post-transplant monitoring are some of the many concerns.

Author contributions: Rajalingham Sakthiswary was involved in the manuscript composition and performed the literature search. Azman Ali Raymond contributed to the conceptual framework and critically appraised the article.

Conflicts of interest: None declared.

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