**Stem Cell Therapy and Neurodegenerative Diseases**

**Abstract**

Neurodegenerative diseases are a blight on modern society, creating financial and emotional burdens that, if left uncured, will continue to be a scourge on a large part of the ageing population. These diseases, such as Alzheimer’s and Parkinson’s, are characterized by pathological events in the brain that cause neurons to die or not function properly. Finding a definitive cure that reverses the symptoms of neurodegenerative diseases could eliminate a significant danger of the modern world's relatively recent increased life expectancy. Stem cell therapy, using stem cells as a treatment, poses a potential solution to neurodegenerative diseases. In this paper, we discuss Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis, Huntington's, current treatments, and each disease's potential to be cured by stem cell therapy.

**Introduction**

Neurodegenerative diseases are caused when nerve cells within the brain or the nervous system lose their function over time and slowly begin to die [1]. These types of diseases are usually age-related and sometimes affected by genetics. They are also incurable, with the only treatments being medication that relieves the pain. Neurodegenerative diseases like Alzheimer's can affect a person's cognitive function, such as memory and ability to do simple tasks independently [1 ]. Other neurodegenerative diseases like Parkinson's or Huntington's disease primarily affect the body's motor functions [1].

Neurodegenerative diseases affect many people. Alzheimer's affects around 6 million people in the U.S. [2 ]. There are also 1 million people with Parkinson's disease in the U.S. [3]. These numbers are expected to increase significantly in the coming years. 500,000 people are predicted to be diagnosed with Alzheimer's this year [2 ]. These statistics mean someone is diagnosed with dementia every 5 seconds [2]. If not stopped, over 150 million people worldwide are expected to have dementia by 2050. These diseases worldwide cost more than 1 trillion dollars in health care.

*Stem cell therapy* is a promising treatment method involving stem cells, which are undifferentiated cells that can develop into other cell types. Stem cells also can renew themselves, and they also have the potential to build every type of tissue in the body. This ability is very promising as it means stem cells can become brain and nerve cells, which could significantly affect the future treatment of neurodegenerative diseases. Many types of stem cells are known today. Embryonic stem cells, or ESCs, are stem cells taken from unused embryos and used for science. Induced pluripotent stem cells, also called iPSCs, are pluripotent stem cells made in the lab by reprogramming normal cells. Pluripotent refers to the ability of the cell to change into any cell in the body, as opposed to multipotent, which means they can only change into a select few. Adult stem cells are cells within the mature body, but only in small amounts. These stem cells exist naturally to replace the damages that occur to the body. There are many different types of adult stem cells, including Hematopoietic Stem Cells (HSCs), Mesenchymal stem cells (MSCs), Neural stem cells (NSCs), Epithelial stem cells (ESCs), and Skin stem cells (SSCs) [4].

**Neurodegenerative Disorders and Current Therapies**

The following paragraphs will explore some neurodegenerative diseases and their typical therapy modes and delve into stem cell therapy. This information is summarized in Table 1.

**Table 1**: **Current Treatment and Availability of Stem Cell Therapy for Various Neurodegenerative Disorders**

| Neurodegenerative Disease | Current Treatment | Stem Cell Therapy |
| --- | --- | --- |
| Alzheimer's Disease | Mild AD: rivastigmine, donepezil, and galantamine  Severe AD: memantine  Aducanumab: A promising new medication that changes the course of the disease. | Yes: Endogenous and Exogenous repair  Only types being tested are MSCs |
| Parkinson’s Disease | Most cases: Carbidopa-levodopa and Dopamine agonists | Yes: Pluripotent stem cell therapy |
| Huntington’s Disease | Relieve Symptoms: tertabenzibnem, deutetrabenazine, haloperidol, fluphenazine, amantadine, and levetiracetam. | Yes: The use of NSCs, MSCs, and iPCs |
| Amyotrophic Lateral Sclerosis | Riluzole: Effective medication that extends the lifetime. | Yes : to promote endogenous repair |

*Alzheimer’s Disease*

Alzheimer's disease is the most common neurodegenerative disease [2]. This disease is usually fatal and is characterized by symptoms like memory loss, mood changes, and wandering [5]. One significant change in the brain when undergoing Alzheimer's is the accumulation of beta-amyloid plaques (protein fragments) around the neurons in the brain and tau tangles ( tau being a type of protein) inside the neurons. These tau proteins block the nutrition and other molecules on the way to the neuron. The beta-amyloid plaques could damage the neurons by interfering with synaptic transmission between neurons [6]. These changes are the reason behind the destruction of the neurons. Changes such as smaller plaques can cause damage to neurons by interfering with synaptic transmission. The destruction of neurons typically happens in the part of the brain that controls memory, the entorhinal cortex and the hippocampus [6]. It affects the cerebral cortex and, eventually, most of the brain. Because Alzheimer's is becoming more and more common as life expectancy increases, it is imperative that a cure stops progression as well as reverses the symptoms. Stem cell therapy has a good potential as a cure because a treatment utilizing them can undo the reason symptoms appear, neuron loss, by introducing new cells that can replace them.

Because Alzheimer's is a complicated and severe disease, multiple treatments could help. In cases of mild or moderate Alzheimer's, medicines such as rivastigmine, donepezil, and galantamine could reduce the symptoms of the disease [3]. While not fully understood, these diseases are thought to stop the breakdown of acetylcholine, a chemical in the brain that is essential for memory and cognitive abilities. Another treatment is aducanumab, the only treatment that changes the course of the disease by targeting beta-amyloid proteins. For more severe cases, memantine is prescribed to decrease symptoms so the patient can maintain functions for longer [3].

As of now, stem cell therapy for people with Alzheimer's is still being developed and is not available for widespread use, but stem cell therapy does hold promise as a cure for this disease. One theoretical approach for therapeutic stem-cell treatment is endogenous repair. This approach uses stem cells to stimulate the hippocampus's neurogenesis, which plays an essential role in learning and memory [6]. This method may cancel or slow down the memory loss problems related to Alzheimer's. Another approach is through exogenous cell therapy, which are methods that aim to repair cognitive functions that are lost in Alzheimer's by restoring the neurons that were lost with stem cells [6]. Because of inconsistency, the only stem cell therapy tested in human trials are MSC-based ones. While those trials do not directly show progress for the therapy, it is thought that the reason is because of the observation methods, as MSCs are proven to work in animal tests.

*Parkinson’s Disease*

Parkinson's disease is the second most common neurodegenerative disease. People with this disease are found to have lumps of the protein alpha-synuclein called Lewy bodies. These bodies cause the destruction of nerve cells in the basal ganglia, the part of the brain that controls movement. The destruction of cells produces less dopamine, which is essential for the body's movement [7]. The loss of dopamine results in the recognizable symptoms of Parkinson's disease, which are tremors in hands, arms, legs, jaw, and head, muscle stiffness, slowness, and impaired balance and coordination [3]. Parkinson's disease is a good target for upcoming stem cell therapy procedures because it can target and replace the loss of the midbrain dopamine neurons.

As of today, Parkinson's disease is incurable, but several medications could help control symptoms associated with the disease. The lack of disease-altering medication is because many of these medications are substitutes for dopamine or increase dopamine production. Carbidopa-levodopa is one of the most effective medications [3]. This is because the chemical is converted to dopamine inside the brain. It can be taken through inhalation or infusion. Dopamine agonists are another type of medication[3]. Instead of promoting dopamine, these medications replicate dopamine's effects on the brain. Even though it is less effective than dopamine, it is more stable and reliable than carbidopa-levodopa. MAO B inhibitors are another medication given to people with Parkinson's disease [3]. This type of medication helps to protect the dopamine in the brain from breaking down.

Stem cell therapy also holds great promise for Parkinson's disease, specifically pluripotent stem cells. This is because the disease's primary cause of symptoms is the destruction of mDA neurons, or the neurons responsible for creating dopamine. Using stem cell transplants from hPSCs could generate functional mDA cells in the brain. In addition to many "proof of concept" studies that show that the physical effects of Parkinson's could be treated, many animal studies also show that non-motor functions can be restored, too [7].

*Huntington’s Disease*

Huntington's disease is another neurodegenerative disease affecting 50,000 Americans and occurs in about 6 in every 100,000 people [8]. This disease is spread through a defective gene in chromosome 4 of 25. This disease is a dominant trait, so if inherited, the person will eventually develop the disease [9]. The defective gene encodes extra repetitions of the huntingtin protein (named after the disease), which causes approximately double the number of repeats than in a normal gene [10], suggesting that it may be used for actions like chemical signalling, transportation, binding materials, and preventing apoptosis. It could also help to repair damaged DNA [11]. The defective gene causes neurons to break down gradually and die. The disease can occur at any time in a person's life if inherited. The symptoms of Huntington's disease include mood swings, depression, and in some cases, suicidal thoughts. It also causes problems with judgment, attention, and other cognitive problems. Uncontrolled movements in the fingers, feet, or torso are also signs of chorea, which not everyone with Huntington's disease develops [10].

Like most neurodegenerative diseases, Huntington's disease also does not have a treatment that can alter the course of the disease. The only treatments given to patients with this disease are medications, physical therapy, speech therapy that help suppress movement disorders and drugs and psychotherapy to help with mental health problems [12]. Common medications used to treat physical symptoms include tertabenzibnem, deutetrabenazine, haloperidol, fluphenazine, amantadine, and levetiracetam [12].

Because Huntington's disease is related to the destruction of neurons in the basal ganglia caused by a mutation in the huntingtin protein, it is likely that stem cell therapy could help, as it possesses the potential to replace the neurons destroyed. The use of stem cell therapies like NSCs, MSCs, and iPSCs as a treatment is shown to have positive results, improving the motor functions of animal tests [13].

*Amyotrophic Lateral Sclerosis*

ALS, also known as amyotrophic lateral sclerosis, is a neurodegenerative disease that affects and destroys neurons and nerve cells in the spinal cord. The disease's symptoms most often occur between 55 and 75, with men more likely to develop the disease [14]. Some studies suggest that military veterans are more likely to develop this disease. While 90% of cases are sporadic, meaning they occur at random, around 10% are considered to be inherited [15]. The defective genes inherited might concern functions like the processing of RNA, the recycling of protein, and the shape of motor neurons. It is also speculated that exposure to toxic substances, physical trauma, diet, and other factors could play a role in sporadic ALS. However, many scientists think that it is caused pathogenetically [16]. The disease mainly affects the motor neurons in the primary motor cortex, brainstem, and spinal cord.

ALS is also an incurable disease, but the treatments could slow the progress of the symptoms and provide comfort to the patient. One medication that treats ALS is Riluzole, which could increase the patient's life expectancy by 5 to 6 months. Edaravone helps the patient by slowing the decline of daily function, which ALS usually causes. Therapies are also used to treat people with ALS. These include breathing care, physical therapy, speech therapy, psychological support, and other things to provide comfort [14].

While direct replacement of cells through stem cell therapy in ALS does not seem likely to be effective, the use of stem cells to promote astrocytes which will, in turn, stimulate endogenous repair to the spinal cord and neurons. This is because astrocytes are shown to cause neurodegeneration when their function is interrupted. The promotion of astrocytes may reverse the effects of motor control by ALS [17].

**Methods**

Existing literature was initially chosen based on finding the fundamental papers in the field. These were selected through the utilization of crucial search words, including "stem cell therapy", "neurodegenerative disease current treatments", and "stem cells for treatment". Building upon this, additional papers were obtained utilizing more complex search terminology and search patterns in stem cell therapy for neurodegenerative diseases such as "Alzheimer's" and "iPCSs" for more in-depth research. Careful consideration was used to identify what papers demonstrated how stem cell therapy can solve neurodegenerative diseases and how they work. All in all, websites were scoured for various papers that covered methods thought to be crucial to identifying ways to treat neurodegenerative diseases using stem cell therapies. The significant websites accessed included PubMed, CDC.gov, and NCBI.gov.

**Future Directions**

Neurodegenerative diseases are severe diseases that have no satisfactory conventional treatments. With a rising average life expectancy, the average person is more likely to be diagnosed with these diseases now than ever. Stem cell therapy for these types of diseases is in the works, but they still have a ways to go. For example, many animal experiments have shown successful implementation of stem cells but had little to no effect on the disease itself [6]. Furthermore, the process of stem cells and how they function is still needed to be studied. These issues must be addressed soon to ensure that stem cell therapy gets approved for clinical trials. There also needs to safeguard against the body treating the stem cells as foreign threats, which could cause much harm and nullify the effects of the treatment.

**Conclusions**

Common neurodegenerative diseases like Alzheimer's, Parkinson's, ALS, and Huntington's are fatal and, as of now, incurable. These diseases could be the bane of a post-industrial country such as the US, whose population is getting older rapidly. The use of traditional medicine has thus far proven futile, as the only results of these treatments are a slightly increased lifetime and the elimination of some of the symptoms. Methods such as using MSCs to replace the cells lost from the disease seem to have much potential impact, and diseases with more unique characteristics could be cured with more specialized use of stem cells. The cure for neurodegenerative diseases could help to unshackle the expected lifetime of an average human being and would increase the quality of life in many places. It seems the future of that cure hides within stem cell therapy.

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