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A systematic review on the role of stem cells in the treatment and diagnosis of neurological diseases such as MS in overweighting patients with endoscopy point

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Abstract

Currently, the role of stem cells in the treatment and diagnosis of neurological diseases such as Alzheimer's and MS have been systematically investigated. Alzheimer's disease (AD) is the most common dementia in the elderly population. Alzheimer's disease is a permanent and progressive brain disorder that causes heavy social and financial losses worldwide. In a recent study, the topic was investigated by reviewing more than 80 articles and searching for the keywords "stem cells", "neurological diseases", "Alzheimer's" and "MS". The results of a recent study on MS patients showed that current treatments for AD patients can only reduce symptoms, but cannot completely prevent neurodegeneration. Therefore, there is no long-term improvement. Stem cells are undifferentiated cells that have the ability to produce many different types of cells in the body. A large amount of data shows the therapeutic potential of stem cells for a variety of neurological diseases. Numerous studies have shown that neuronal and glial cells have been successfully differentiated from various stem cells. The results of a recent study have shown that the progenitors of nerve cells that enter the body in this way migrate to the brain and settle especially in the white matter of the brain. Also, regarding MS disease, about 80% of the patients have not relapsed after 2 years of treatment. While stem cell therapy in MS is often associated with severe side effects, no patients died and the procedure was deemed safe. Therefore, treatment of this highly active type of MS with stem cells may be better than some DMT-modulating treatments. Disease-modifying therapy (DMT) is used as an approach to disease control. This treatment helps slow the progression of the disease.

Key words: MS disease, Alzheimer's disease, nerve cell, side effects, permanent disorder.

Introduction

Stem cells are the raw materials of the body [1]. Cells from which all other cells with special functions are produced. These cells have many applications in the treatment of many diseases [2-4]. Due to the unique ability of stem cells, these cells are an attractive topic in biology and medical sciences today [5]. Also, research in this field has increased our knowledge about how an organ grows and develops from a single cell, and more importantly [6], it has helped to understand the mechanism of replacement of healthy cells with damaged cells. These cells are the basic materials of the body [7]. These cells divide under suitable conditions in the body or in the laboratory and form more cells called daughter cells [8]. Daughter cells either turn into new stem cells, or they turn into specialized and differentiated cells with a more specialized function, such as blood cells, brain cells, heart muscle cells, or bone cells [9]. No other cell in the body has the natural ability to produce new cells. Of course, these cells are not only used to make replacement nerve cells for transplantation. They can be used in other ways, especially as a support for the patient's cells and a controlling or regulating effect on the patient's central nervous system [10]. In fact, many consider the reason for this to be some stem cells that are uniquely useful in the disease. For example, in MS disease, stem cell transplantation is possible, in the production of substances that support the survival or recovery of damaged nerve cells [11]. They are also effective in this disease by reducing inflammation. This may prove a valuable approach, regardless of the ability of such cells to become replacement neurons. Likewise, much work has been done with cells of this type in the laboratory. A number of well-designed and well-designed studies have been conducted in a small number of patients to demonstrate that the procedure is feasible and well tolerated [12].

In a recent study, the topic was investigated by reviewing more than 80 articles and searching for the keywords "stem cells", "neurological diseases", "Alzheimer's" and "MS". The results of a recent study on MS patients showed that current treatments for AD patients can only reduce symptoms, but cannot completely prevent neurodegeneration [13].

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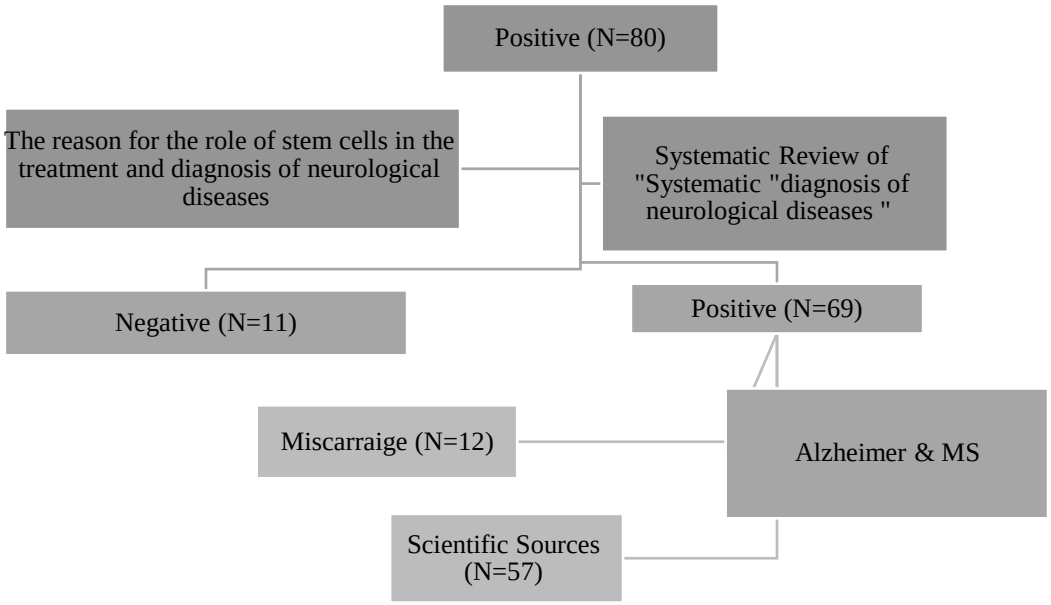

Figure 1. Flow chart of included subjects

Special feature of stem cells

Stem cells are cells that have not yet differentiated. This means that they have not yet been assigned a specific function in the body [14]. At first glance, stem cells are little different from normal body cells. However, they have two very special talents: they can divide and differentiate. So, they can create exact copies of themselves. Plus, they can be defined in a specific cell. Thus, they form, or repair, tissue [15].

Types of stem cells

Researchers classify stem cells based on their potential to differentiate into other cells. Embryonic cells are the strongest type. Because their task is to become any type of cell in the body. The complete classification includes the following:

1- Capable: this type of cells can be differentiated into possible types of cells. The first few cells that appear when the zygote begins to divide are viable [16].
2- Multipotent: these cells can become almost any type of cell in the body. Early embryonic cells are multipotent [17].
3- Multipotent: these cells can be separated into a family of closely related cells. For example, adult hematopoietic stem cells can become red or white blood cells or platelets [18].
4- Oligopotent: These can differentiate into several different cell types. Adult lymphoid or myeloid cells can do this [19].
5- Unototent: These can only produce cells of one type that are their own. However, they are still stem cells. Because they can renew themselves [20]. For example, we can refer to muscle cells in adults. Embryonic cells are considered pluripotent instead of being potent. Because they cannot become part of the extraembryonic membranes or placenta [21].

The effect of stem cells on spinal cord lesions

Currently, post-accident care for spinal cord injury patients focuses on extensive physical therapy, occupational therapy, and other rehabilitation therapies [22]. A number of published articles and case studies confirm the possibility of treating spinal cord injury with stem cells derived from human umbilical tissue and cells derived from bone marrow [23].

The possibility of combined treatment of allogeneic stem cells for spinal cord injury

Many articles and studies have examined and confirmed the effect of this case. This treatment has resulted in improvement in the following cases [24]:

- ✓ Improve your ASIA score.
- ✓ Improve bladder or bowel function [25].
- ✓ Improve sexual performance.
- ✓ Increase muscle control [26].

Through the administration of mesenchymal stem cells derived from umbilical cord tissue, we have observed improvements in spinal cord injury patients treated at our centers [27].

Very complex spinal cord injuries

Inflammation occurs, nerve tissue is destroyed and wounds are created that prevent the growth of nerve cells. Stem cells can help solve all these problems [28-30]. They can replace dead tissue, generate new nerve cells and create a regenerative environment [31].

The effect of stem cells on neurological diseases

These cells can be used in the treatment of various nervous system diseases such as stroke, Huntington's disease, Parkinson's disease, lateral sclerosis, amyotrophic, multiple sclerosis and Alzheimer's disease [32].

MS

Although the underlying cellular and molecular mechanisms of stem cell therapy in patients with MS are not understood, they have yielded encouraging results [33]. For example, by intravenous injection, mesenchymal cells are able to move in brain lesions and improve the survival rate of brain cells [34]. Also, the injection of mesenchymal cells reduces the severity of the disease and improves the quality of life of MS patients [35]. These cells can be easily isolated from different body sources including blood [36], fat tissue and bone marrow, umbilical cord blood and placenta. Many studies have analyzed the safety and efficacy of tests related to cells derived from these different sources [37]. The injection of mesenchymal cells derived from bone marrow has been revealed to improve the severity of the disease [38], the cognitive functions of patients and the quality of life due to the neuronal protection and anti-inflammatory properties of the cells. Studies have shown that adipose-derived MSC therapy is a safe method that improves MS disabilities, such as problems with sex and social activities [39]. Researchers found that stem cells from adult adipose tissue are one of the most suitable cells for the treatment of MS [40]. This is because adipose tissue is easily isolated, produces a high volume of cells per unit area, and has relatively cheap extraction costs [41]. In addition, umbilical cord-derived mesenchymal cells are attractive therapeutic options. Because they come out of the context that is easily accessible and there is no moral dilemma [42]. In recent research, it has been determined that hematopoietic stem cell transplantation can prevent the progression of MS disease for 4 to 5 years in 70% to 80% of patients [43].

The effect of stem cells on Parkinson's disease

In recent years, research has been conducted on the use of nerve cells derived from aborted human fetuses [44]. Obviously, the cell source for treating the disease in this way is very limited and brings many problems [45]. Meanwhile, a suitable and effective alternative for Parkinson's disease cell therapy is dopaminergic progenitor cells derived from fetal cells, which can function as a renewable resource with high capacity, and this method is being researched [46].

The effect of stem cells on Huntington's disease

Huntington's symptoms include a severe decrease in muscle control, emotional disturbance, and interference in brain cells [47]. This disease is related to the cranial nerve and provides an excellent model for cell replacement therapy [48]. Most of the diseases related to the brain nerves are currently incurable and often the treatments that are able to affect the main pathogenic factors need a lot of time. This brings into focus strategies such as cell replacement therapy [49]. For this reason, in the last two decades, there has been a great interest in the treatment of neurological diseases such as Huntington's disease with the method of cell replacement [50].

Are stem cells effective?

According to current research, the effect of using these cells can cure 70 types of diseases in the future [51].

Importance of cell banking

Stem cell banking is very important and has the following advantages:

- ✓ Cell storage for a long time without significant change [52].

- ✓ Possible decrease and increase in detection of cell contamination [53].
- ✓ Reduction of cell transplant costs [54].

Problems of using stem cells

There are several obstacles to using these cells for treatment. Because it is very difficult to detect and identify stem cells, especially for adults [55]. Also, the responses of the body's immune system can reduce its usefulness. Using these cells can cause cancer, poisoning, infection, reduced immunity and even death [56]. For this reason, this method should be used when other treatments have not worked. The most powerful include powerful embryonic stem cells as well as induced cells that have the ability to divide [57], reproduce and transform into different types of cells. This power is also their greatest weakness [58]. Once injected into the human body, the cells can begin to multiply uncontrollably, potentially causing tumors to grow [59].

How to do the process

The cord blood sample collected after entering the cord blood bank is checked by the quality control unit, and if permission is obtained, it is processed in the laboratory [60]. The sample is first evaluated in terms of volume and number of cells, and in the next step, if the necessary conditions are met, it enters the process of cell separation [61]. Otherwise, the contract will be canceled by notifying the family and the return fee will be returned according to the contract. Microbial and viral tests are performed on the samples that meet the minimum standard conditions [62]. Finally, it is stored for a long time in special freezing tanks at a temperature of minus 196 degrees Celsius. The frozen sample is used only once for transplantation [63].

How do induced pluripotent stem cells produce?

The signals in the body tell the cell by changing some genes, some genes are on and some genes are off. To produce the resulting competent stem cells, scientists re-introduce signals to these cells, which remain as stem cells in the early embryo [64]. These turn off the genes that tell the cell to be specialized and turn on the genes that tell the cell to be basic [65].

What are the limitations of these treatment methods?

Many people have ethical problems with using human embryos for scientific study. Also, the ability of embryonic stem cells to reproduce endlessly means that they may develop mutations that can interfere with their development [66], or allow them to divide to the point where they cause damage. Finding suitable medical applications for embryonic cells is challenging. MS is a disease involving the central nervous system [67], which, in addition to the destruction of myelin, causes the loss of axons over time, and there is no definitive treatment [68]. Spontaneous repair and demyelination occur early in the course of MS. Recent researches have shown that cell therapy has the potential to restore the central nervous system and may also have an anti-inflammatory effect. Stem cells have the ability to transform into other cells and tissues [69]. These cells are obtained from different places for therapeutic use and have different types:

1- HSCs (hematopoietic stem cells): are stem cells that exist in blood and bone marrow [70].

2- MSCs (mesenchymal stem cells): are a group of stem cells that exist in different tissues such as bone marrow, skin and fat.

3- NSCs (Neural stem cells): specialized stem cells responsible for myelin repair in the brain and can be obtained from other types of stem cells such as MSCs and hESCs [71].

4- iPSCs (induced pluripotent stem cells): they are obtained through genetic engineering and have the ability to transform into different cells.

5- hESCs (human embryonic stem cells): stem cells obtained from the umbilical cord.

Treatment with autologous hematopoietic stem cells

In this treatment method, a high-dose nervous system suppressant is first used to remove and destroy active autonomous B and T cells, and as a result, the immune system can be revived. During the treatment, stem cells are taken from the patient's blood, multiplied and frozen. These stem cells are at the beginning of their process and are not defective or diseased. The patient's defective and unhealthy immune system is then destroyed by chemotherapy, and then the previously collected stem cells are injected through the blood to restore the immune system [72].

Treatment with MSCs

Mesenchymal stem cells have an immunomodulatory role and suppress the proliferation of T cells and cause the induction of regulatory T cells and affect the growth function of dendritic cells and suppress B cells and inhibit the function of NK cells. In a number of studies, intrathecal injection of mesenchymal cells taken from the bone marrow and multiplied has shown relatively good effects in patients with advanced MS [73].

What is HSCT cell therapy for MS?

Stem cells can become different types of cells in the body. Hematopoietic stem cells make blood cells. Some doctors use a type of stem cell therapy called hematopoietic stem cell transplantation (HSCT) to treat RRMS, but more research is needed to know how well HSCT works against it.

In HSCT, doctors give you drugs to help you make more bone marrow stem cells. Then they take some blood from you and store the stem cells in it to use later [74]. Next, you will receive high doses of chemotherapy and other powerful drugs to severely suppress the immune system. This is done in the hospital and you may need to stay there for up to 11 days. The doctor puts the stem cells into the bloodstream so they can turn into new white blood cells and help your body build a new, healthy immune system [75]. You will also receive medicines such as antibiotics to help fight infections and other illnesses until your immune system can do its job again. Treatment usually lasts a few weeks, but recovery may take several months. Treatment for MS varies from person to person, but when treatment is successful, your immune system should be back to full strength within 3 to 6 months [76].

What is the treatment of MS with stem cell transplant?

For several years, researchers have been trying to treat MS using stem cells, and several clinical trials are being conducted in this regard [77]. Living body cells are used in cell therapy. Cell therapy was first used 50 years ago to treat leukemia by transplanting bone marrow hematopoietic stem cells from a healthy person to a cancer patient. Now, stem cells are used to treat many diseases, including heart, autoimmune, neurological and cartilage diseases. In the clinical trial of treating MS using cell therapy, by injecting medicine into the patient's body, the body produces more bone marrow stem cells [78].

Then blood is taken from the patient and blood stem cells are stored. In the next stage, by using chemotherapy, the patient's immune system is severely weakened. In the final stage, doctors re-introduce the patient's blood stem cells to become new white blood cells and help the body build a new healthy immune system [79]. The results of cell therapy for MS patients have been promising so far. For example, in a clinical trial on 24 people, about 70% of the patients had no more symptoms of MS five years after treatment [80]. In another trial, 10 patients with MS with an average age of 33 years underwent cell therapy and stem cells were injected into the spinal canal of the patients [81-83]. The injection of stem cells improved the symptoms in more than half of the patients after one year. In another trial, 25 patients with an average age of 34 years were injected with stem cells inside the spinal canal [84]. After one year, cell therapy improved the course of the disease in the patients. These results have increased the hope of finding a definitive treatment using stem cells for MS [85].

Table 1. Forest plot showed the role of stem cells in the treatment and diagnosis of neurological diseases such as MS in overweighting patients with endoscopy point

Raw	Study	Year		Proportion	Wight 98%	Weight %
1	Tahernia et al.	**2022**		0.92	[0.39 – 1.06]	5.03
2	Taban et al.	**2023**		0.87	[0.54 – 1.02]	6.02
3	Susanabadi et al.	**2021**		0.88	[0.63 – 1.01]	5.57
4	Shiva et al.	**2023**		0.60	[0.25 – 1.08]	6.13
Heterogeneity t^2=0.02, I^2= 0.00, H^2=1.02				0.95	[0.22 – 1.07]	
Test of Θ= Θ, Q (4) =5.55, P= 0.74						
1	Sharifi et al.	**2012**		0.84	[0.27 – 1.08]	6.08
2	Sharifi et al.	**2024**		0.76	[0.52 – 0.22]	5.82
3	Shahsavarinia et al.	**2022**		0.11	[0.54 – 0.89]	5.85
4	Rostami et al.	**2020**		0.39	[0.12 – 0.99]	6.09
Heterogeneity t^2=0.14, I^2= 0.11, H^2=0.42				0.77	[0.19 – 1.00]	

Test of Θ= Θ, Q (4) =3.35, P= 0.34						
1	Pourhanifeh et al.	**2020**		0.92	[0.39 – 1.06]	3.03
2	Palagini et al.	**2020**		0.87	[0.54 – 1.02]	8.33
3	Otaghvar et al.	**2024**		0.99	[0.63 – 1.01]	7.50
4	Namanloo et aL.	**2022**		0.68	[0.25 – 1.08]	6.03
Heterogeneity t^2=0.14, I^2= 0.00, H^2=1.02				0.87	[0.22 – 1.07]	
Test of Θ= Θ, Q (4) =3.55, P= 0.12						

Conclusion

Alzheimer's is a progressive neurodegenerative disease that eventually leads to dementia. According to global statistics, the number of people with Alzheimer's disease worldwide was 46,800,000 in 2015, and it is estimated that this number will almost triple by 2050. According to the Alzheimer's Association report, one person in the United States is diagnosed with Alzheimer's every 66 seconds. This disease occurs mostly in people over 65 years old and some of its symptoms include memory loss and behavioral and cognitive disorders. Alzheimer's disease is caused by the gradual accumulation of beta-amyloid (Aβ) plaques outside brain neurons, twisted and tangled filaments of tau proteins in neurons, neuronal cell apoptosis, and synapse dysfunction. Therefore, the aim of treating this disease is to improve and adjust these factors.

So far, the definitive treatment for this disorder is not known, but the use of stem cells is a new method for Alzheimer's treatment, and several experimental studies and clinical trials have been conducted on the transplantation of mesenchymal stem cells from the umbilical cord tissue (HUC-MSC) with satisfactory results. As mentioned, one of the main pathological signs of Alzheimer's is the deposition of extracellular Aβ plaque in the brain. In almost all studies that transplanted HUC-MSCs into animal models, a reduction in Aβ plaques was observed. In 2016, Xie et al investigated the effect of Wharton gel mesenchymal stem cells (WJ-MSCs) in the treatment of Alzheimer's disease and reported that transplantation of WJ-MSCs significantly reduced the deposition of Aβ, Aβ40 and Aβ42 in the cerebral cortex and hippocampus of mice. In 2013, Yang et al showed that HUC-MSCs transplantation significantly reduced Aβ deposition and soluble Aβ levels in Alzheimer's mice. In another 2018 study, Li et al showed that autophagy plays an important role in the degradation of amyloid precursor protein and presenilin. These proteins are essential for the production of Aβ. In treated mice, studies have shown that with HUC-MSC injection, a decrease in the levels of amyloid precursor protein, presenilin and Aβ was observed, but this process was stopped by inhibiting autophagy in the treated animals. However, in 2017, Si et al. found no significant difference in Aβ levels between treated and control groups of mice. They stated that HUC-MSCs transplantation does not regulate the expression of Aβ-producing or degrading factors, and cognitive improvement may be due to other regulatory pathways such as reduction of oxidative stress markers and neurogenesis in transplanted patients. Another noteworthy point in Alzheimer's disease is inflammation, which occurs as a result of increasing Aβ levels. In 2016, Xie and his colleagues showed that, due to the anti-inflammatory properties of MSCs, HUC-MSCs transplantation reduces inflammation in Alzheimer's patients. Other effective factors in Alzheimer's disease are cell apoptosis and synaptic dysfunction.

HUC-MSCs transplantation reduces cell apoptosis and effectively improves synaptic function. The results of a research show that stem cells are undifferentiated cells that have the ability to produce different types of cells in the body. A wide range of information shows the ability of stem cells to treat a variety of neurological diseases. In this review article, the possible beneficial effects of stem cells for the treatment of nervous system diseases are presented. Stem cells have been proposed for the treatment of various acute and chronic diseases of the nervous system, such as hemorrhagic and ischemic stroke, Parkinson's disease, Huntington's disease, lateral sclerosis, amyotrophic, multiple sclerosis and Alzheimer's. Stem cells have been frequently investigated in laboratory studies and can be considered as new developing strategies for the treatment of nervous system diseases in the near future. Researchers have investigated this issue in research called the ability of stem cells in the treatment of nervous system diseases. In this research, which was conducted by Masoumeh Thaqalul Islam, assistant professor of the Department of Anatomical Sciences and Cell Biology of Mashhad University of Medical Sciences, and Seyed Mahmoud Hosseini, assistant professor of the Department of Physiology of Mashhad University of Medical Sciences, it is stated that stem cells are undifferentiated cells that have the ability to reproduce and produce cells.

They retain the precursor. As a result, they can differentiate into different types of cells in the body in response to specific stimuli. Our knowledge about these cells is growing rapidly and has recently opened new perspectives in regenerative strategies of the nervous system during acute diseases such as stroke, ischemic and hemorrhagic, brain injury, as well as chronic neurodegenerative diseases such as Parkinson's, Korea He has had Huntington's, lateral sclerosis, amyotrophic lateral sclerosis, multiple sclerosis and Alzheimer's disease. In this research, it has been stated that cell therapy is an interesting and effective strategy in the treatment of neurological diseases and so far, embryonic stem cells, neural stem cells, mesenchymal stem cells and other cells have been used in the treatment of neurological diseases. A variety of stem cells are generated throughout mammalian development, and there are several sources of these cells that may be useful in the treatment of these neurological diseases. Based on this research, embryonic stem cells derived from the internal cell mass of the fetus can be extracted and cultured before intrauterine replacement. In certain areas of the brain of adult mammals, such as the subventricular zone located in the lateral ventricles, the sub granular layer of the dentate gyrus of the hippocampus, the cerebral cortex, the cerebellum, and the spinal cord, there are neural stem cells that have the ability to self-renew and can also grow in the right conditions of the culture environment and in response to the different growth factors present in it to differentiate into specific phenotypes of neurons and glial cells. In addition, bone marrow, umbilical cord blood and adipose tissue can also be available and easy sources to obtain stem cells. Researchers say about the inclusion criteria for this study, adult mammalian adipose tissue, which is easily available, has stem cells that can differentiate into neurons, types of glial cells, and active endothelial cells, similar to cells derived from bone marrow. Umbilical cord blood also contains a population of stem cells that have the potential to transform into blood and nerve cell lines and is considered an available and inexpensive cell source. Embryonic stem cells are cells that have the ability to multiply and differentiate into different types of cells, including nerve cells, but in using them, it should be noted that in uncontrolled conditions, these cells may be tumorigenic, and on the other hand, in the result of different passages can undergo genetic and epigenetic changes. In this research, it is stated that in addition, it should be noted that these cells may be rejected by the immune system. Neural stem cells are mature stem cells that are multipotent and have the ability to differentiate into neurons and glial cells, and they can be obtained from the spinal cord and forebrain. Compared to embryonic stem cells, these cells have advantages, such as their non-rejection by the immune system and the absence of genetic and epigenetic changes. Therefore, embryonic stem cells can be considered as a suitable source in cell therapy in neurological diseases. The authors of this article say that other stem cells, including mesenchymal stem cells, have less proliferation and differentiation capabilities compared to embryonic and neural stem cells, but since they are autologous, they have received special attention for the treatment of a number of neurological diseases. This article examines how cell therapy can be used to treat diseases related to the nervous system.

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