1. Multiple Sclerosis (MS)

A. Clinical Response: Clinical response demonstrates an increase in methylation on damaged nerve cells and evidence of an improved repair process. In addition to physical examinations prior to stem cell treatment and 6 months post-procedure, laboratory test and imaging results serve as evidence of repair process. Internationally recognized lab tests for monitoring multiple sclerosis include:

- Complete blood count (CBC) with differential
- Cerebrospinal fluid analysis
- Spinal tap
- Evoked potential tests
- Vision evoked potentials
- Quantitative neurological exams
- EEG, MRI, CT scan or PET scan of the brain

2. PRELIMINARIES

A. Background: Multiple Sclerosis is a disease that involves the central nervous system and an abnormal response of the body's immune system against it. The insulating covers of the nerve cells in the brain and spinal cord, also known as myelin, are attacked by the immune system damaging their function. The myelin sheath covering the nerve cells serve as insulators, increasing the speed at which the impulses propagate along the axon. When the myelin sheath is damaged, the nerve impulses traveling to and from the brain and the spinal cord are disrupted, leading to many physical problems.

B. Causes of MS

The exact cause of MS is still unknown, however there are several factors that may play a big role including:

- **Immunological factors:** abnormal immune-cells attack the myelin sheath affecting their function.
- **Environmental factors:** MS is unknown to occur more often in areas closer to the equator. People who live near the equator are more exposed to sunlight therefore acquiring a large amount of vitamin D, which is suggested to play an important role in the development of this disease. Data suggests that exposure to some environmental factors before puberty may influence a person to develop MS. Evidence has also suggested that smoking increases the chances of developing MS,
- **Infectious factors:** Exposure to various viruses, or any other microbe during childhood, is a possible trigger to MS disease. Viruses are well known to cause demyelination and inflammation, making them a possible cause for the development of MS. However there is no clear evidence to have proven this.

C. Treatment options:

MS disease cannot be cured, however medication exist to help control the symptoms. These medications include, but are not limited to the following:

- Corticosteroids – They are prescribed to reduce nerve inflammation.
- Plasma exchange- This treatment is generally used when steroid medications are not effective.
- Beta interferons- The goal of these medications is to reduce frequency and severity of relapse.
- Glatiramer acetate (Copaxamone)- This medication helps block the immune cells from attacking the myelin.
- Mitoxantrone (Novantron)- This is an immunosuppressant drug which prevents immune cells from attacking the nerve cells. This medication is very harmful to the heart and it is associated with the development of blood cancer. It is usually used to treat severe MS patients.
- Muscle relaxants- It is used to reduce muscle stiffness and pain especially in the legs.

![Multiple Sclerosis Diagram](image-url)
3. POTENTIAL BENEFITS OF STEM CELL TREATMENT

MS is a chronic autoimmune disease where the immune cells attack the myelin sheath and nerve cells from the brain and spinal cord. When the nerve cells are demyelinated their function is disrupted leading to severe physical or cognitive problems. Mesenchymal stem cells, found in many tissues in the body including adipose and bone marrow, have the ability to differentiate into different types of cells such as nerve cells and oligodendrocytes (Ghasemi, Razavi, Mardani, Esfandiarl, Salehi, & Esfahani, 2014). Oligodendrocytes have the function to create the myelin sheath around the axons. Studies have shown that demyelination was improved after the transplantation of stem cells, suggesting that stem cell therapy is a potential treatment for MS patients (Ghasemi, Razavi, Mardani, Esfandiarl, Salehi, & Esfahani, 2014). Besides improving the demyelination of the nerve cells, and having immunomodulatory and anti-inflammatory properties, Ghasemi group also observed a recovery in locomotion function. Preclinical trials have also observed the migration of mesenchymal stem cells into the inflamed central nervous system (CNS). The cells may induce the production of neuroprotective agents which help preserve the axons in the CNS (Karussis, Kassis, Kurkalli, & Slavin, 2008).

4. TREATMENT & DELIVERY METHOD REQUIRED

2 Multiple Sclerosis: Treatments and drugs. Mayo Clinic. 2014. Web. 3/20/15

A. Typical Recommended Treatment: Adipose Derived Stem Cells suspended in normal saline.

B. Typical Delivery Method Required: Autologous Ad-SVF containing adult stem cells are infused in 3-5 mL of normal saline and injected intrathecally.

C. Recommended dosing: Recommended repeat dosing MSC’s every 2-3 months. Also recommend intravenous dosing to address systemic symptoms, including muscular, fatigue, bowel/bladder, etc.

5. POTENTIAL RISKS OF STEM CELL INJECTION

There are possibilities for unwanted effects related to the local anesthesia, harvesting procedure, and injection of stem cells. Even with the most established protocol, adequate technique, and careful administration; a medical team may encounter uncontrollable events. Although there is no guarantee of any results, excellent results can be attained. The medical professional provides services in the most responsible, professional and diligent manner, always considering that surgeries imply risks. The risks of complications of adipose tissue harvesting and stem cell infusion are very low. Possible risks include but are not limited to:

- Pain at site of injections
- Bleeding at injection site
- Low-grade fever
- Itching at injection site
- Nerve/muscle injury
- Dizziness
- Swelling of joints
- Hot flashes
- Pain in joints
- Malaise
- Vascular spasm or obstruction
- Bruising
- Allergic reaction
- Nausea
- Allergic reaction

Minor complications may include temporary arm or leg weakness, soreness at the injection site, the temporary increase in symptoms and spinal headache. Extremely rare complications can occur including infection, prolonged bleeding, and paralysis.

6. FREQUENTLY ASKED QUESTIONS

1. What are adult stem cells and how do they work?

They are undifferentiated cells found in tissues in the body, responsible for maintaining and repairing surrounding cells. These tissues include but are not limited to adipose tissue (fat tissue) and bone marrow. They have the ability to differentiate into various cell types, including neurons and oligodendrocytes, and also have the potential to activate the production of anti-inflammatory agents which is what makes them a potential treatment for multiple sclerosis disease. They are undifferentiated cells found in tissues in the body, responsible for maintaining and repairing surrounding cells. It has been proven that there are 500 times more stem cells stored in adipose tissue verse bone marrow, therefore, adipose derived stem cells are far superior.
2. How can stem cell therapy help treat MS?

MS is a neurodegenerative and autoimmune disease where the nerve cells in the brain and spinal cord are affected. The immune cells attack the myelin sheath which acts as an insulator on nerve cells and help propagate the impulses along the axon faster. When the myelin sheath is damaged then the propagation of the impulses is disrupted, leading to various cognitive or physical problems. The motor neurons send impulses to the muscles resulting in voluntary muscle movement. Stem cells may upregulate factors that slow down the progression of the disease. Mesenchymal stem cells are known to have the potential to become neurons and oligodendrocytes, which are responsible for the production of myelin. Not only do stem cells have the ability to induce the production of anti-inflammatory cytokines, they have immunomodulatory properties and may reduce neuronal cell death.

3. How long do you think it would be before I see some improvement?

Stem cells therapy for MS disease is still an ongoing research topic and the results are not guaranteed. However, the response to the treatment varies from patient to patient. Studies have shown patients’ improvement as early as 3 months and 6-12 months after stem cell therapy.

4. Are there any complications associated with this procedure?

Minimal bruising and soreness can be observed due to the liposuction procedure. This will normally last around 1-2 weeks, depending on the patient. Some patients have reported headache or body ache. Other complications have not been observed.

5. How will the stem cells be administered?

For MS disease isolated stem cells will be administered intravenously or intrathecally.

6. Does smoking or drinking affect the therapy?

Smoking and the consumption of alcohol has been shown to be harmful to stem cells. We advise that people do not smoke or drink during their treatment.

7. Will anyone follow up with me after the procedure?

A team member will follow up with you 1 day, 1 week, 3 months, 6 months and 1 year after the procedure. Follow ups help us evaluate the effectiveness of our treatment, and improve treatment protocols. We will be monitoring your progress closely. We are happy to address any issues or questions at anytime.

7. SUPPORTING ARTICLES


The neuroprotective effect of mesenchymal stem cells on an experimentally induced model for multiple sclerosis in mice.

Mahfouz MM1, Abdelsalam RM2, Masoud MA3, Mansour HA3, Ahmed-Farid OA4, Kenawy SA2.

Author information
1 Department of Training Unit and Continuous Education for Pharmacy, Menoufia University, Al Menoufia, Egypt.
2 Department of Pharmacology and Toxicology, Faculty of Pharmacy, Cairo University, Cairo, Egypt.
3 Department of Pharmacology, National Organization for Drug Control and Research (NODCAR), Giza, Egypt.
4 Department of Physiology, National Organization for Drug Control and Research (NODCAR), Giza, Egypt.

Abstract

BACKGROUND:
Multiple sclerosis (MS) is a chronic autoimmune demyelinating neurodegenerative central nervous system disorder. The aim of the present study was to investigate the prophylactic effect exerted by the one-time intraperitoneal injection of mesenchymal stem cells (MSCs) 1 × 106 and 14-day intraperitoneal injection of methylprednisolone (MP) 40 mg/kg in an experimental autoimmune encephalomyelitis (EAE). EAE was induced by intradermal injection of rat spinal cord homogenate with complete Freund’s adjuvant in Swiss mice. Results of MSCs and MP-treated mice showed a significantly milder disease and fewer clinical scores compared to control mice. They suppressed tumor necrosis factor-alpha and myeloperoxidase and increased interleukin 10, whereas thiobarbituric acid reactive substances and nitric oxide brain contents were reduced to comparable levels between treatment groups. Brain content of GSH was significantly higher in MSCs-treated mice than control mice. It is evident that MSCs have relevant prophylactic effect in an animal model of MS and might represent a valuable tool for stem cell based therapy in MS.

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KEYWORDS:
Encephalomyelitis; methylprednisolone; mice; spinal cord; stem cells
PMID: 28557239 DOI: 10.1002/jbt.21936
2. Transplantation of Human Adipose-Derived Stem Cells Enhances Remyelination in Lysolecithin-Induced Focal Demyelination of Rat Spinal Cord

Authors:
Nazem Ghasemi, Shahnaz Razavi, Mohammad Mardani, Ebrahim Esfandiar, Hossein Salehi, Sayyed Hamid Zarkesh Esfahan

Abstract:
Adipose-derived stem cells (ADSCs) are a desirable stem cell source in neurodegenerative diseases treatment due to their ability to differentiate into different cell lineages. In this study, we transplanted human ADSCs (hADSCs) into a lyosphatidylcholine (lysolecithin) model of multiple sclerosis (MS) and determined the efficiency of these cells in remyelination process. Forty adult rats were randomly divided into control, lysolecithin, vehicle, and transplantation groups, and focal demyelination was induced by lysolecithin injection into spinal cord. To assess motor performance, all rats were examined weekly with a standard EAE scoring scale. Four weeks after cell transplantation, to assess the extent of demyelination and remyelination, Luxol Fast Blue staining was used. In addition, immunohistochemistry technique was used for assessment of the presence of oligodendrocyte phenotype cells in damaged spinal cord. Our results indicated that hADSCs had ability to differentiate into oligodendrocyte phenotype cells and improved remyelination process. Moreover, the evaluation of rat motor functions showed that animals which were treated with hADSC compared to other groups had significant improvement (P<0.001). Our finding showed that hADSCs transplantation for cell-based therapies may play a proper cell source in the treatment of neurodegenerative diseases such as MS.

3. Immunomodulation and neuroprotection with mesenchymal bone marrow stem cells (MSCs): A proposed treatment for multiple sclerosis and other neuroimmunological/neurodegenerative diseases

Authors:
Dimitrios Karussis, Ibrahim Kassis, Basan Gowda S. Kurkalli, Shimon Slavin

Abstract:
Bone marrow (BM) derived mesenchymal stem cells (MSCs) (non-hematopoietic, stromal cells) can differentiate under certain circumstances into cells from various neuronal and glial type lineages; they also exert immunomodulatory effects. For potential clinical applications, BM-MSCs offer significant practical advantages over other types of stem cells, since they can be obtained from the adult BM (the patient himself being the donor) and can be easily cultured and expanded posing in parallel a very low risk for development of malignancies. We have shown that BM-MSCs cultured with a cocktail of growth factors (containing FGF and BDNF) differentiate into neuronal/glial lineage cells with a predominance of cells expressing astrocytes' markers. BM-MSCs were effective in suppression of chronic EAE in mice and induced neuroprotection, preserving most of the axons in the CNS of successfully-treated animals. Histopathological studies revealed that MSCs could efficiently migrate into the CNS inflamed tissue (both when administered intravenously and intraventricularly) and differentiated into cells expressing neural–glial lineage markers. Our preclinical results indicate that bone marrow can provide a source of stem cells with a potential for migration into inflamed CNS tissue and differentiation into cells expressing neuronal and glial cell markers. Such an approach may provide a feasible and practical way for in situ immunomodulation, neuroprotection and possibly remyelination/regeneration in diseases like multiple sclerosis. We therefore developed a explorative protocol for the evaluation of this therapeutic approach in a small group of patients with MS and other neurodegenerative diseases.
Journal of the Neurological Sciences 265 (2008) 131–135

4. Experimental and Therapeutic Opportunities for Stem Cells in Multiple Sclerosis

Author:
Rickie Patani and Siddharthan Chandran

Abstract:
Multiple Sclerosis (MS) is an inflammatory demyelinating neurodegenerative disorder of the brain and spinal cord that causes significant disability in young adults. Although the precise aetiopathogenesis of MS remains unresolved, its pathological hallmarks include inflammation, demyelination, axonal injury (acute and chronic), astrogliosis and variable remyelination. Despite major recent advances in therapeutics for the early stage of the disease there are currently no disease modifying treatments for the progressive stage of disease, whose pathological substrate is axonal degeneration. This represents the great and unmet clinical need in MS. Against this background, human stem cells offer promise both to improve understanding of disease mechanism(s) through in-vitro modeling as well as potentially direct use to supplement and promote remyelination,
an endogenous reparative process where entire myelin sheaths are restored to demyelinated axons. Conceptually, stem cells can act directly to myelinate axons or indirectly through different mechanisms to promote endogenous repair; importantly these two mechanisms of action are not mutually exclusive. We propose that discovery of novel methods to invoke or enhance remyelination in MS may be the most effective therapeutic strategy to limit axonal damage and instigate restoration of structure and function in this debilitating condition. Human stem cell derived neurons and glia, including patient specific cells derived through reprogramming, provide an unprecedented experimental system to model MS “in a dish” as well as enable high-throughput drug discovery. Finally, we speculate upon the potential role for stem cell based therapies in MS

5. Stem cell treatment for patients with autoimmune disease by systemic infusion of culture-expanded autologous adipose tissue derived mesenchymal stem cells

Authors:
Jeong Chan Ra, Sung Keun Kang, Seob Shin, Hyeong Geun Park, Sang Aun Joo, Jeong Geun Kim, Byeong-Cheol Kang, Yong Soon Lee, Ken Nakama, Min Piao, Bertram Sohl and Andras Kurtz

Abstract:
Prolonged life expectancy, lifestyle and environmental changes have caused a changing disease pattern in developed countries towards an increase of degenerative and autoimmune diseases. Stem cells have become a promising tool for their treatment by promoting tissue repair and protection from immune-attack associated damage. Patient-derived autologous stem cells present a safe option for this treatment since these will not induce immune rejection and thus multiple treatments are possible without any risk for allogenic sensitization, which may arise from allogenic stem cell transplantations. Here we report the outcome of treatments with culture expanded human adipose-derived mesenchymal stem cells (hAdMSCs) of 10 patients with autoimmune associated tissue damage and exhausted therapeutic options, including autoimmune hearing loss, multiple sclerosis, polymyotis, atopic dermatitis and rheumatoid arthritis. For treatment, we developed a standardized culture-expansion protocol for hAdMSCs from minimal amounts of fat tissue, providing sufficient number of cells for repetitive injections. High expansion efficiencies were routinely achieved from autoimmune patients and from elderly donors without measurable loss in safety profile, genetic stability, vitality and differentiation potency, migration and homing characteristics. Although the conclusions that can be drawn from the compassionate use treatments in terms of therapeutic efficacy are only preliminary, the data provide convincing evidence for safety and therapeutic properties of systemically administered AdMSC in human patients with no other treatment options. The authors believe that exvivo-expanded autologous AdMSCs provide a promising alternative for treating autoimmune diseases. Further clinical studies are needed that take into account the results obtained from case studies as those presented here.

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