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ROLE OF STEM-CELL THERAPY IN THE MANAGEMENT OF AMYOTROPHIC LATERAL SCLEROSIS, A NEURODEGENERATIVE DISORDER: AN OVERVIEW

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a syndrome marked by muscular weakness and atrophy with spasticity and hyperreflexia due to degeneration of the motor neurons of the spinal cord, medulla, and cortex. The symptoms of ALS include progressive weakness in the arms, legs, and trunk; and difficulty in talking, chewing, swallowing, and eventually breathing. The cause of disease is unknown, but the possibility of the illness being associated with a specific genetic defect holds promise of determining the course of the disease. Once this is done, it might be possible to treat the genetic abnormality.

Genetically, there is no way to predict this disease prior to its occurrence. There is an effective therapy; however, patients often benefit from referral to occupational or physical therapy or both. In the present article, we have concentrated on clinical features, morphology, symptomatic approaches, and mainly role of stem cell therapy involved in the management of Amyotrophic lateral sclerosis. The aim of present article is to provide in depth knowledge about latest research going on in the field of stem cell therapy & its utility in the management of Amyotrophic lateral sclerosis.

KEYWORDS

Amyotrophic lateral sclerosis, Lou Gehrig`s disease, Neurodegenerative disorder and Stem-cell therapy.

INTRODUCTON

Amyotrophic lateral sclerosis (ALS) , also known as **Lou Gehrig`s disease or motor neuron disease (MND)**, is a degenerative disorder involving the upper and lower motor neurons of the pyramidal system, with resultant progressive muscle weakness, atrophy (amyotrophy) and spasticity. Most cases of ALS are sporadic. Familial cases, usually inherited in an autosomal dominant fashion, account for 5% to 10% of cases[1]. The cause and pathogenesis of most cases of ALS remain unknown, despite extensive analysis of potential environmental, toxic, infectious, and immunologic factors. The disease affects men slightly more frequently than women and becomes clinically manifest in the fifth decade or later. The pathology of ALS corresponds closely to the clinical features: There is prominent loss of the spinal and brainstem motor neurons that project to striated muscles as well as loss of the large pyramidal motor neurons in layer V of motor cortex, which are the origin of the descending corticospinal tracts. In familial cases, Clarke`s column and the dorsal horns sometimes are affected.[2]

MORPHOLOGY, CLINICAL FEATURES, ETIOLOGY AND SYMPTOMS OF ALS

ALS is characterized by a loss of motor neurons in the anterior horns of the spinal cord, brain stem motor nuclei, and the primary motor cortex of the cerebrum. Grossly, the brain and cord are usually normal, although some atrophy of the primary motor

ROLE OF STEM-CELL THERAPY IN THE MANAGEMENT OF AMYOTROPHIC LATERAL SCLEROSIS, A NEURODEGENERATIVE DISORDER: AN OVERVIEW

cortex (precentral gyrus) may be apparent in severe cases. The anterior spinal nerve roots are usually atrophic. A variety of inclusions are typically seen in residual spinal motor neurons, including ubiquitin-positive hyaline inclusions reminiscent of Lewy bodies and small eosinophilic cytoplasmic structures known as Bunina bodies. Small, ubiquitin- positive inclusions may also be seen in nonmotor areas of the cerebral cortex, particularly in cases of ALS associated with dementia. Degeneration and loss of neurons in the primary motor cortex often cause a loss of corticospinal fibres in the cerebral peduncles, basal pons, and medullary pyramids and especially within the lateral and anterior columns of the spinal cord. Peripheral nerves carrying motor fibres are depopulated, and affected skeletal muscles show evidence of striking denervation atrophy[3].

The onset of ALS is insidious, marked by weakness, clumsiness, and speech difficulties. The disorder is characterized by rapidly progressively weakness, muscular atrophy, spasticity, dysarhthria, dysphagia, respiratory compromise. Sensory function generally is spared, as is cognitive, autonomic, and oculomotor activity. ALS usually is progressive and fatal, with most affected patients dying of respiratory compromise and pneumonia after 2 to 3 years, although occasional individuals have a more indolent course and survive for many years[4].

The etiology and pathogenesis of ALS are unknown. For a subset of the familial cases, the genetic locus has been mapped to the copper-zinc superoxide dimustase gene (SOD1) on chromosome 21. A wide variety of missense mutations have been identified that appear to generate an adverse gain- of-function phenotype. Among the mutations, the A4V mutation is the most common (approaching 50% of cases), is associated with a rapid course, and rarely has upper motor neurons signs. A recessive locus on chromosome 2 has been mapped to a gene encoding a protein termed alsin that has structural homology to proteins involved in GTPase regulation. Other genetic loci for ALS have been mapped but not yet cloned. There is also evidence of roles of glutamate toxicity and protein nitration in the development of ALS pathology. The basis for the selective involvement of motor neurons remains uncertain[5, 6, 7].

INTRO DUCTION ABOUT STEM CELLS

Stem cells are cells found in most, if not all, multi-cellular organisms. They are characterized by the ability to renew themselves through mitotic cell division and differentiating into a diverse range of specialized cell types. The two broad types of mammalian stem cells are embryonic stem cells that are isolated from the inner cell mass of blastocysts, and adult stem cells that are found in adult tissues. In a developing embryo, stem cells can differentiate into all of the specialized embryonic tissues. In adult organisms, stem cells and progenitor cells act as a repair system for the body, replenishing specialized cells, but also maintain the normal turnover of regenerative organs, such as blood, skin, or intestinal tissues.

Stem cells can now be grown and transformed into specialized cells with characteristics consistent with cells of various tissues such as muscles or nerves through cell culture. Highly plastic adult stem cells from a variety of sources, including umbilical cord blood and bone marrow, are routinely used in medical therapies. Embryonic cell lines and autologous embryonic stem cells generated through therapeutic cloning have also been proposed as promising candidates for future therapies.[8, 9] Stem cells, also known as progenitor cells, are cells that have not undergone differentiation to acquire a specific structure or role; they have the potential to self-renew, divide, and differentiate into specialized cell types.[10]

ROLE OF STEM-CELL THERAPY IN THE MANAGEMENT OF AMYOTROPHIC LATERAL SCLEROSIS, A NEURODEGENERATIVE DISORDER: AN OVERVIEW

Stem cells are also sometimes termed "pluripotential" or "undifferentiated" cells because they can differentiate and develop into various cell lines. The differentiation of stem cells into mature cells is tightly regulated; otherwise, intricate plants and animals, with their many interrelated tissues, organs, and systems, could not exist. By contrast, mature or differentiated cells have acquired specific structures and roles, and in many cases have lost the ability to divide and replicate. Also in contrast to stem cells, malignant cells or "dedifferentiated" cells divide in an uncontrolled fashion, and rather than resulting in useful, differentiated, or specialized cells, these types of cells threaten to kill the organism. Stem cell differentiation must be turned on, given direction, and turned off as needed in order to properly supply the basic building blocks of tissues in different organ systems. This requirement for precise regulation applies to an even greater degree to the differentiation of neuronal progenitor cells, because effective neural function depends on establishing precise linkages and interactions between different individual neurons and classes of neurons. By definition, stem cells, including neuronal progenitor cells, are present in embryos. Stem cells may be found in umbilical cord blood. In adults, these cells are present in bone marrow and in other organs in which controlled self-renewal is needed. Neuronal progenitor cells have also been shown to persist into adulthood in specific brain locations near the ventricles where they support ongoing learning and the establishment of new memories through their division, differentiation, migration, and insertion into new circuitry[11].

THERAPEUTIC UTILITY OF STEM CELLS TECHNIQUE IN DISEASE

Medical researchers believe that stem cell therapy has the potential to dramatically change the treatment of human disease. A number of adult stem cell therapies already exist, particularly bone marrow transplants that are used to treat leukemia. In the future, medical researchers anticipate being able to use technologies derived from stem cell research to treat a wider variety of diseases including cancer, Parkinson's disease, spinal cord injuries, Amyotrophic lateral sclerosis, multiple sclerosis, and muscle damage, amongst a number of other impairments and conditions. However, there still exists a great deal of social and scientific uncertainty surrounding stem cell research, which could possibly be overcome through public debate and future research, and further education of the public[12-15].

SYMPTOMATIC TREATMENT AND MANAGEMENT OF ALS

Multi-Disciplinary Approach

The emphasis today is on living positively with Amyotrophic lateral sclerosis. An integrated, multi-disciplinary approach focuses on the triad of

- Diet and supplements.
- Exercise.
- Spiritual and psychosocial support.

This well-rounded program enhances quality of life for people living with ALS as well as for those at risk of developing ALS, and may very likely delays the onset of symptoms. Foods known to nourish the brain, support memory and build overall immunity are especially recommended. Once ALS is confirmed, patients are encouraged to continue this approach, adding other health support therapies as they become necessary, including physical, occupational, and speech therapy[16].

Most people who have ALS disease eventually become physically and mentally disabled. As the

ROLE OF STEM-CELL THERAPY IN THE MANAGEMENT OF AMYOTROPHIC LATERAL SCLEROSIS, A NEURODEGENERATIVE DISORDER: AN OVERVIEW

disease progresses, long-term nursing home care may be necessary.

Because ALS has no known cure, treatment is supportive, protective, and aimed at relieving symptoms. It is extremely important for people with ALS to maintain physical fitness as much as possible, as individuals who exercise and keep active tend to do better than those who do not. No satisfactory treatment is available to stop or reverse ALS, but some approaches can control signs and symptoms. Medications are available to treat the symptoms of ALS. Although the disease's progression cannot be stopped or reversed, therapies and support can partially alleviate symptoms and improve quality of life. Treatments include medication, mental health care, and speech swallowing and physical therapies.

NURSING IMPLICATIONS

Neuromuscular function is monitored to assess the progression of deterioration.Ventilatory status is assessed frequently. The patient is evaluated for respiratory infection, which can be fatal .Nutritional intake and fluid balance are monitored .The skin is inspected regularly for evidence of break-down.

A rehabilitation program is instituted to help the patient maintain independence. Prescribed medications for symptomatic relief are administered, and the patient is instructed in their use. The patient is encouraged to do active exercise and active range -of-motion exercises on unaffected muscle groups; assistance is provided with stretching exercises. Other assistance is provided according to the patient's muscular capacity. As mobility decreases, skin care is provided, the patient is turned and repositioned frequently, and special low pressure mattresses and pads are used to prevent skin breakdown. Equipment such as walker, wheelchair, or special bed is obtained as necessary. Alternative methods of communications are devised for the patient who cannot talk. The nurse helps the patient perform deep-breathing and coughing exercises and uses incentive spirometry, chest physiotherapy, and suctioning as necessary.

The patient having trouble swallowing is positioned upright, and soft, semi- solid foods are offered, with suctioning aspiration. If the patient cannot swallow, nasogastric or gastrostomy tube feedings are provided.

The patient and family are instructed about the signs and symptoms of ALS and about problem management. Referral is made to social and home health care services, hospice care, and available local and national support and information services such as the Amyotrophic Lateral Sclerosis Association.

Desired outcomes include the patient's and family's ability to express feelings about life changes and future losses; to cope appropriately with grief; to make continual adjustments to the home to allow the patient to be independent as long as possible and perform activities of daily living; to maintain the patient's highest degree of mobility, using assistive devices as necessary; and limited or no evidence of complications due to impaired physical mobility[17].

ROLE OF STEM-CELL THERAPY IN THE MANAGEMENT OF AMYOTROPHIC LATERAL SCLEROSIS, A NEURODEGENERATIVE DISORDER: AN OVERVIEW

MEDICATIONS

The table 1 shows commonly used medications for symptomatic treatment of ALS [18-24].

Table .1
Commonly used medications for symptomatic ALS Treatment

Symptoms	Medication
Muscle cramps and spasms	lioresal (Baclofen) tizanidine (Zanaflex) quinine sulfate (Quinine)
Spasticity (stiffness of limbs)	lioresal (Baclofen) tizanidine (Zanaflex) benzodiazepines (Valium)
Excessive crying or laughter	Tricyclic antidepressants (Amitriptyline) Selective serotonin reuptake inhibitors (Lexapro, Celexa, Zoloft, Prozac) valproate (Depakote) lithium (Lithobid)
Urinary urgency or frequency	0xybutynin (Ditropan)
Excessive saliva	Tricyclic antidepressants (Amitriptyline) glycopyrrolate (Pyridium) scopolamine (Scopace) botulinium toxin injection (Botox)
Thick phlegm or post nasal drip	guaifenesin (Robitussin, Humibid) nebulizer treatments
Laryngospasm (throat closing sensation)	benzodiazopines (Valium, Klonapin, Ativan)
Insomnia	Tricyclic antidepressants (Trazodone) zolpidem (Ambien) temazepam (Restoril)

ROLE OF STEM-CELL THERAPY IN THE MANAGEMENT OF AMYOTROPHIC LATERAL SCLEROSIS, A NEURODEGENERATIVE DISORDER: AN OVERVIEW

Depression/anxiety	Selective serotonin reuptake inhibitors (Prozac, Paxil, Zoloft, Celexa, Lexapro) venlafaxjne (Effexor) buproprion (Welbutrin) mirtazepine (Remeron)
Pain	nonsteroidal anti-inflammatory (Motrin, Celebrex, Vioxx) pain medicine (Tylenol, darvon) aspirin narcotics (Vicodin, morphine, oxycontin)
Nausea	prochloperazine (Compazine)
Constipation	stool softeners (Colace) laxatives (Senekot, Ducolax) fiber (Metamucil) enemas

ROLE OF STEM-CELL THERAPY IN THE MANAGEMENT OF AMYOTROPHIC LATERAL SCLEROSIS, A NEURODEGENERATIVE DISORDER: AN OVERVIEW

ROLE OF STEM CELL THERAPIES IN THE MANAGEMENT OF AMYOTROPHIC LATERAL SCLEROSIS

Stem cells could help patients with ALS in several ways. Ideally, they could be induced to differentiate into lower motor neurons in order to replace those neurons that die because of ALS. Perhaps stem cells could rescue dying motor neurons by reconnecting these neurons to partly denervated muscle before it has died completely. Better yet, they could be induced to differentiate into upper motor neurons in the cortex and connect to the lower motor neurons.

Unfortunately, the expectation that stem cells will play such a regenerative role in patients with ALS is unrealistic because of the complexity of the task, which presents obstacles that currently are insurmountable. A more realistic expectation for stem cells is that they play a supportive role in maintaining the viability of or extending the function of surviving motor neurons. The stem cells could be induced to differentiate into supporting cells, glia, or interneurons that might produce factors that would support motor neurons, or perhaps the stem cells themselves might produce such factors[25].

Stem cells have cured rats with an Amyotrophic lateral sclerosis-like disease. The rats were injected with a virus to kill the spinal cord motor nerves related to leg movement, succeeded by injections of stem cells into their spinal cords. These migrated (passed through many layers of tissues) to the sites of injury where they were able to regenerate the dead nerve cells restoring the rats which were once again able to walk.

Recent data from Clement and colleagues show that in chimeric, genetically engineered mouse models, motor neurons carry mutated *SOD1* genes and glial cells carry healthy genes. Survival is extended in these chimeric mice, as compared with nonchimeric mice in which all motor neurons and all glial cells carry mutated *SOD1* genes. This finding suggests that if healthy stem cells could get to the spinal cords of patients with ALS, their survival might also be extended. It remains to be determined whether a mechanism that compensates for a particular genetic error would apply to sporadic patients without that error. Nevertheless, even if this form of therapy were effective only for patients with familial disease, it would be a great leap forward[26].

In previous experiments, intraspinal transplantation of neurons derived from a human teratoma cell line was shown to ameliorate dysfunction and extend survival in G93A *SOD1* transgenic mice. Furthermore, the life span of G93A *SOD1* mice was extended by intravenous administration of human umbilical cord blood. The cells were shown to have migrated into the spinal cord and brain parenchyma and survived 10-12 weeks after infusion. They exerted their beneficial effect even though only a low number of transplanted cells expressed neural antigens[27]. In another study, Sertoli cells, which are not neuronal stem cells, were implanted in the spinal cords of *SOD1* transgenic mice and were shown to provide

temporary protection to motor neurons in their proximity. However, viable Sertoli cells were not present at the time when the animals died[28].

ROLE OF STEM-CELL THERAPY IN THE MANAGEMENT OF AMYOTROPHIC LATERAL SCLEROSIS, A NEURODEGENERATIVE DISORDER: AN OVERVIEW

Preliminary trials with autologous hematopoietic stem cells have been reported in humans. In one, peripheral blood-purified CD34+ cells were injected intrathecally into 3 patients with ALS[29]. None reported side effects after 6-12 months, but no clinical efficacy was reported. In another, 7 patients received intraspinal transplantation of autologous bone marrow-derived stem cells. Minor postoperative adverse events were transient, but muscle strength continued to decline. After 3 months, however, the investigators reported a trend toward slowing of the decline in the proximal muscle groups of the lower limb in 4 patients and a mild increase in strength in 2 patients. Lack of placebo controls and longer follow-up preclude any inferences of efficacy from this study and none were made by the investigators[30].

Stem Cell Research Ethics, Economics, Policy, and Public Health

The ethics of performing human studies at this early stage of stem cell research have been questioned, emphasizing the risks of premature human trials. Reports of stem cell transplantation performed in China without peer review of objective data on each patient before, immediately after, and at specific long-term points following the transplantation do not provide sufficient scientific evidence to demonstrate that the treatment is safe and effective.

"It is critical that scientists and clinicians are cautious, plan rigorous studies, and most importantly focus on key laboratory experiments that will provide answers to the many challenges that still face this therapeutic approach," wrote Lucie Bruijn, PhD, the Science Director and Vice President of the ALS Association. "For this therapy to be safe and have potential in the clinic, it is critical that the appropriate studies are conducted to learn more about the properties and complexities of the various stem cells.

The scientific concerns are 2-fold. First, because the realistic likelihood for success of any individual research effort is low, parallel research in multiple directions is imperative for the field to advance rapidly. The essence of research is trial and error, which operates by identifying ineffective directions and thereby focusing on those that hold promise. It is usually a long time between initiating research and realizing a successful treatment with clinical applications. Therefore, any delay in identification of a potentially effective therapeutic intervention translates into delaying treatments for patients with the diseases in question. Second, excluding particular types of research from federal funding may translate into an exclusion of this research from federal oversight and protections, which might lead to its migration overseas. This may be detrimental to individual patients and to the broader community of patients, clinicians, and scientists.

In November 2004, California citizens approved a referendum measure to issue bonds to fund stem cell research, including embryonic stem cell research at $300 million a year for 10 years. Since then, several other states (Illinois, New Jersey, Maryland, New York, Delaware, and Wisconsin) are considering, or being asked to consider, initiatives for state-funded stem cell research to fill the federal funding gap. This is motivated, in part, by the desire to remain on the forefront of medical research and avert a brain drain toward states that provide an economic environment more conducive to cutting-edge

ROLE OF STEM-CELL THERAPY IN THE MANAGEMENT OF AMYOTROPHIC LATERAL SCLEROSIS, A NEURODEGENERATIVE DISORDER: AN OVERVIEW

research. The ripple effect of the California initiative is expected to result in acceleration of stem cell research nationwide[31].

CONCLUSION

It may be concluded that ALS is a neurodegenerative disorder marked by muscular weakness and atrophy with spasticity and hyperreflexia due to degeneration of the motor neurons of the spinal cord, medulla, and cortex. Genetically, there is no way to predict this disease prior to its occurrence. There is an effective therapy and treatment is only symptomatic; however, patients often benefit from referral to occupational or physical therapy or both. Stem cell research carries promise for patients with ALS and may result in the development of new treatments to slow the progression of the disease. This hope needs to be tempered with caution because of the early stages of stem cell research in general, and in ALS in particular, and because of the track record of the limited efficacy of all pharmacologic interventions in transgenic murine and sporadic human ALS. Meticulous attention to the ethics and scientific rigor of future stem cell research should be supported by clinicians, scientists, and participating patients alike.

More research work and clinical trials should be done in the field of stem cell therapies which would provide a more rational approach in the treatment of ALS.

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ROLE OF STEM-CELL THERAPY IN THE MANAGEMENT OF AMYOTROPHIC LATERAL SCLEROSIS, A NEURODEGENERATIVE DISORDER: AN OVERVIEW

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ROLE OF STEM-CELL THERAPY IN THE MANAGEMENT OF AMYOTROPHIC LATERAL SCLEROSIS, A NEURODEGENERATIVE DISORDER: AN OVERVIEW

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