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IS STEM CELL THERAPY EFFECTIVE FOR CHRONIC MIGRAINE?

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ABSTRACT

Migraine is the most common disabling headache globally. As anyone with migraines knows, not all headaches are created equal. Migraine is a common neurological condition as the third most prevalent disease worldwide. According to estimates, community prevalence of migraines is between 15%-25%, being more common in women. Migraine characterized by periodic headaches, which are typically unilateral and are often associated with visual disturbance and vomiting. This condition is believed to be a disturbance in the carotid or vertebrobasilar vascular tree. An initial phase of vasoconstriction causes symptoms of local cortical or brain stem ischemia and this is followed by vasodilation. These changes affect both intra and extracranial arteries and it is dilation of the extra cranial vessels which causes pain by stretching the pain nerve endings in the arterial wall. Pain may be prolonged by secondary muscular contraction. Stem cell therapy has been an area of research for neurological conditions such as Parkinson disease (PD) and stroke for many years. This is based on the rationale that undifferentiated stem cells hold potential to replace or regenerate nerve cells, which do not heal as well as other cells. During stem cell therapy for migraines, stem cells collected from patient's bone marrow are injected into an artery, which allows them to reach the vein at the highest possible concentration. The stem cells replace unhealthy cells with healthy cells, resulting in relief from migraines in many cases.

INTRODUCTION

Migraine present with unilateral throbbing headache and associated symptoms including, nausea, multisensory hypersensitivity, and marked fatigue. (1)

Migraine is a complex neurovascular disorder with a strong genetic component. (2)

Migraine is an episodic neurovascular disorder that is clinically divided into two migraine without aura (MO) and migraine with aura (MA). (3)

Twin and family studies provide evidence of a genetic component in migraine, in particular migraine with aura (MA). (4)

Familial hemiplegic migraine (FHM) mutations are known in three genes, the CACNA1A (FHM1) gene, the ATP1A2 (FHM2) and the SCN1A (FHM3) genes (5)

Many novel ATP1A2 mutations were identified in patients with familial and sporadic hemiplegic migraine. (6)

Migraine, which is not characterized by neuronal degeneration, has also been a target of stem cell therapy in a few small investigational studies. (7)-

Autologous adipose-derived stromal vascular fraction (SVF), which is rich in mesenchymal stromal cells, has been

reported to be effective for the treatment of trigeminal neuropathic pain and chronic migraine and tension-type headaches. (8)

The prospect of regenerative medicine as an alternative to conventional drug-based therapies is becoming a tangible reality by the day owing to the vigorous commitment of the research communities in studying the potential applications across a wide range of diseases like neurodegenerative diseases and diabetes, among many others (9)

Recent research reporting successful translation of stem cell therapies to patients have enriched the hope that such regenerative strategies may one day become a treatment for a wide range of vexing diseases (10)

In fact, the past few years witnessed a rather exponential advancement in clinical trials revolving around stem cell-based therapies. Some of these trials resulted in remarkable impact on various diseases (11).

A case of Epidermolysis Bullosa manifested signs of skin recovery after treatment with keratinocyte cultures of epidermal stem cells (12).

Also, a major improvement in eyesight of patients suffering from macular degeneration was reported after transplantation of patient-derived induced pluripotent stem cells (iPSCs) that were induced to differentiate into pigment

epithelial cells of the retina (13).

However, in spite of the increased amount of publications reporting successful cases of stem cell-based therapies, a major number of clinical trials have not yet acquired full regulatory approvals for validation as stem cell therapies. To date, the most established stem cell treatment is bone marrow transplants to treat blood and immune system disorders (14,15)

Hematopoietic stem-cell transplantation (HSCT) is a complex treatment procedure, which was originally developed for treating hematological malignancies (16)

Although the exact mechanism of action has not yet been precisely defined, the rationale is to erase the aberrant cells with a conditioning regimen (17)

As an ancillary effect, the applied myelotoxic agents deplete bone marrow-inherent stem cells and reduce the mature lymphocyte pool (18)

Reported effects of stem-cell transplantation were the quantitative and qualitative restoration of T and B cells, as well as a change in cytokine and chemokine profiles. (19,20)

History

“Once development was ended...in the adult centers, the nerve paths are something fixed and immutable. Everything may die, nothing may be regenerated,” wrote Santiago Ramón y Cajal, a Spanish neuroanatomist and Nobel Prize winner and the father of modern neuroscience. This statement was the central dogma in neuroscience for a long time. However, in the 1960s, neural stem cells (NSCs) were discovered. (21)

Scientists discovered ways to derive embryonic stem cells from early mouse embryos nearly 30 years ago, in 1981.

Characteristics of a migraine

Migraine attacks come without warning, maybe either frequent or relatively rare, and affect patients at any age. For some, migraines begin during childhood. For others, they begin later in life. Some patients can go for years between attacks, while in other cases they can occur far more frequently. Some patients experience migraines several times per month, while others suffer only one or two attacks per year the migraine attacks can last for several hours or even days. Migraines cause extreme pain and symptoms that can be debilitating. Events associated with migraines can vary. For example, some patients with a traumatic brain injury may suffer from migraines. Other patients report that exposure to certain types of light can either trigger an attack or make one worse.

Clinical Features

The condition usually starts after puberty and continues until middle life. The first symptom is due to vasospasm This is commonly a sensation of white or colored lights, scintillating spots, wavy lines or defects in the visual fields. Weakness of one half of the body may be experienced or there may be numbness of both hands and around mouth. These symptoms may last up to half an hour, and followed by headache usually begins in one spot and subsequently involves the whole of one side of the head. This may be the same or the opposite to the visual or sensory symptoms. The pain usually severe and throbbing and is associated with vomiting, photophobia, sweating, the patient taking to bed in a darkened room.

The Trigeminal System--scrutiny

The trigeminal system represents one of the most important anatomic and functional area for the study of migraine pathophysiology. The trigeminal nerve is the largest cranial nerve, having a large sensory root and a smaller motor root. The trigeminal nerve emerges from the dorsal and median

raphe nuclei located in the brain stem and bears a trigeminal or gasserion ganglion at its base. The peripheral processes of trigeminal ganglion neurons constitute the three sensory branches - ophthalmic, maxillary and mandibular, of the trigeminal nerve. These three branches distribute to pain and temperature receptors on face, forehead, eyelids, nose, pinna, tongue, teeth, cerebral blood vessels (trigeminovascular system), dura mater (membrane that surrounds the brain) and in the posterior area of head and neck. (22)

Signals from activated nociceptors innervating the cranial blood vessels are transmitted to the trigeminal bipolar neurons, and further relayed to thalamic and cortical areas (23)

The signal from the perivascular neurons is transmitted by endogenous mediators, including the vasoactive neuropeptides calcitonin gene-related peptide (CGRP), substance P, neurokinin A, and pituitary adenylate cyclase-activating peptide (PACAP), as well as release of vasoactive inflammatory mediators such as nitric oxide, coincident with inflammation in the meninges (24,25)

Sensitization of pain relevant brainstem regions, including peripheral trigeminovascular neurons to dural stimuli, is thought to produce the characteristic sensation of throbbing pain in migraine (26,27)

Stem cell therapy--Probing

Migraine patients may gain relief from stem cell therapy. Stem cell treatment normally works when the stem cells are injected into the body via an intra-arterial manner, so they reach the brain in a higher concentration. The cells develop into healthy blood cells which then replace the unhealthy blood cells in the body. Stem cell therapy can be a great alternative to the many migraine and headache treatments available.

During stem cell therapy for migraines, stem cells collected from patient's bone marrow are injected into an artery, which allows them to reach the vein at the highest possible concentration. The stem cells replace unhealthy cells with healthy cells, resulting in relief from migraines in many cases. Migraine is a prevalent neurological disorder that is often underestimated for its impact and consequences (28)

According to the global burden of disease, migraines are one of the top causes of disability worldwide (29)

It is estimated that migraines affect around 20% of people at some point in their lives (30)

They affect women more than men and appear with re-occurring intense headaches and altered sensory and motor manifestations (31)

Attacks of migraines seem to follow an evolving phenomenon that occurs over time mirroring the phases that are each marked with certain symptoms as a result of certain neural mechanisms (32)

The mechanisms behind this evolutive process are only partially known, but neuroinflammation and central sensitization, influenced by genetics and epigenetic factors, are proposed to play an important role (33,34)

Serotonergic neuromotor system--Migraine Investigation

Migraine is defined as recurrent attack of headache that are commonly unilateral and accompanied by gastrointestinal and visual disorders. Migraine is more prevalent in females than males with a ratio of 3:1.

Serotonin is a key molecule in the neurobiology of migraine.

(35)

Various studies have implicated serotonin in the pathogenesis of migraine (36)

Serotonin vasoconstricts the nerve endings and blood vessels and in this way affects nociceptive pain.

Comings postulated that low serotonin levels dilate blood vessels and initiate migraine.

Migraine sufferers often report that the headaches stop after they have vomited. Vomiting stimulates intestinal motility and raises blood serotonin. (37)

Serotonin (5-hydroxytryptamine, 5-HT) synthesis involves the rate limiting enzyme, tryptophan hydroxylase (TPH) and is mainly degraded by the action of monoamine oxidases. (38,39)

Tryptophan hydroxylase activity in rat brain base arteries has been suggested to be a marker of serotonergic innervations

Chronic Migraines Could Be Treated with Stem Cell Therapy

Stem cell therapy is being considered as a treatment for a wide variety of conditions. Chronic migraines can be especially challenging to treat because the causes can widely vary. Stem cells are now being researched as a treatment method for chronic migraines that have stopped responding to traditional treatment methods. (40)

Brain alterations in migraine

A variety of imaging techniques have revealed both structural and functional brain alterations in individuals that suffer migraine (41)

Furthermore, clinical and neurophysiological studies have found chronic hypersensitivity to sensory stimuli (42)

Abnormal processing of sensory information in migraines, as well as cortical excitability which may make them more susceptible to CSD (43,44)

Some of these changes may be the result of repetitive exposure to pain or stress, the brain biology of migraine sufferers appears to differ from healthy controls (45)

Migraine may be triggered by a range of external factors, including chemicals, lack of sleep, stress, and skipping meals. However, these triggers only lead to migraine in migraineurs. Some aspects of the altered brain biology are likely to be genetically predetermined.

Human Brain Organoids In Migraine Research:

Organoids of the liver, kidney, intestine, lung, and brain have been developed in recent years. Human brain organoids are used for understanding pathogenesis and investigating therapeutic options for neurodevelopmental, neuropsychiatric, neurodegenerative, and neurological disorders. Migraine is considered a brain disorder with neurological and non-neurological abnormalities and symptoms. (46)

Genetics Of Common Migraine

Monogenic migraine disorders have a large impact on the individuals and families involved, but they are rare. Discovering loci and genes that contribute to common migraine requires different approaches to the Mendelian disorders. (47)

Hemiplegic Migraine

Hemiplegic Migraine (HM) is a rare subtype of MA characterized by episodes of severe migraine and aura

symptoms involving motor weakness or numbness, usually affecting one side of the body (hemiparesis), as well as visual, sensory, or speech disturbances (48)

In some cases, patients experience additional neurological symptoms such as confusion, seizures, memory loss, and coma. Individuals usually fully recover between episodes, although some symptoms may persist for weeks or longer, and some patients can develop permanent ataxia (difficulty coordinating movements), which may worsen with time (49)

In rare cases HM (Hemiplegic migraine) can be fatal after a minor head trauma (50)

How Neurological Stem Cell Therapy Works

All adult stem cells have the aptitude to be transformed into whatever kind of cell the body needs. But those that are stowed in the fat that forms around our upper legs, stomach area and buttocks are particularly potent. Moreover, these highly regenerative adult stem cells are found in particular profusion in our fat, making harvesting not only easier but the sample size much smaller than harvesting from other zones like bone marrow. Neurological stem cell therapy “assigns” new adult stem cells the tasks of becoming the exact varieties of cells required for the re-growth and regeneration of missing, malfunctioning or incapacitated tissue, bone, blood elements or neural cells.

Dealing With Migraines Head-on

--As anyone with migraines knows, not all headaches are created equal. Specialists put the number of different headaches at more than 165, with the migraine variety affecting about 11 people in 100. “A migraine is an intense throbbing or pulsing headache on one side of the head that lasts from four to 72 hours,” said Uwe Reuter, a neurologist at Berlin's Charite university hospital. It can be accompanied by oversensitivity to sounds, light or smells, as well as nausea and vomiting.

Migraine Treatment

There are numerous successful prophylactic treatments for migraine. Phenobarbitone, diazepam, or pizotifen given thrice daily often reduces the frequency of headaches. Other drugs like propranolol, monoamine oxidase inhibitors and tricyclic antidepressants are helpful. Methysergide, a serotonin antagonistic is some time effective but is prone to produce peripheral vasoconstriction, and rarely retroperitoneal fibrosis.

Turning Point In Stem Cell Therapy

The turning point in stem cell therapy appeared in 2006, when scientists Shinya Yamanaka, together with Kazutoshi Takahashi, discovered that it is possible to reprogram multipotent adult stem cells to the pluripotent state. This process avoided endangering the foetus' life in the process. Retrovirus-mediated transduction of mouse fibroblasts with four transcription factors (Oct-3/4, Sox2, KLF4, and c-Myc) (51) that are mainly expressed in embryonic stem cells could induce the fibroblasts to become pluripotent (52).

This new form of stem cells was named iPSCs. One year later, the experiment also succeeded with human cells (53)

Recently, the Food and Drug Administration (FDA) has released regulatory guidelines to ensure that these treatments are safe and effective (54)

Current Regulatory Guidelines For Stem Cell-based Therapies

These guidelines state that; treatments involving stem cells that have been minimally manipulated and are intended for homogeneous use do not require premarket approval to come into action and shall only be subjected to regulatory guidelines against disease transmission. In 2014, a radical

regulatory reform in Japan occurred with the passing of two new laws that permitted conditional approval of cell-based treatments following early phase clinical trials on the condition that clinical safety data are provided from at least ten patients. These laws allow skipping most of the traditional criteria of clinical trials in what was described as “fast track approvals” and treatments were classified according to risk (55).

To date, the treatments that acquired conditional approval include those targeting; spinal-cord injury, cardiac disease and limb ischemia (56)

CONCLUSION

Migraine is a painful recurrence of headache due to variation in the blood flow of cerebral blood vessels. This is caused by activation of ‘trigeminovascular system’, which causes release of vasodilators eg. calcitonin gene-related peptide (CGRP) and diminution of the levels of neurotransmitters like serotonin in trigeminal nerve and cranial vessels. Genetics play an important role in susceptibility, and symptomatology, as well as comorbidity with other traits and conditions. Current research has determined that stem cell therapy could be a potential treatment for patients with chronic migraines. They have been successful in treating other neurological disorders that cause pain in the nervous system. The method of delivery and what form of stem cells are still being perfect, but the initial results have shown some success.

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