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Role Of Wharton's Jelly Mesenchymal Stem Cells In The Treatment Of Alzheimer's Disease

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Abstract:
Alzheimer's Disease (AD) is an incurable, neurodegenerative disorder that predominantly affects a large number of the world's elderly population. It is a neurological ailment that begins slowly and gradually impairs behavioral and mental abilities. The current review discusses the pathology of AD and the neuroregenerative potential of human Wharton's Jelly Mesenchymal Stem Cells (WJ-MSCs) in the treatment of AD. Stem cells exhibit unique and potentially promising regenerative abilities and are being researched as a cure for varied diseases, including AD. Mesenchymal Stem Cells (MSCs) harvested from Wharton's Jelly (WJ), of the human umbilical cord are multipotent, safe, ethically viable, and non-controversial. The review focuses on the current evidence related to the application of WJ-MSCs, in preclinical trials, as a potentially promising cure for this debilitating disease.
Keywords: *Wharton's Jelly, Mesenchymal Stem Cells, Alzheimer's Disease, neurodegenerative*

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I. Introduction

A progressive neurodegenerative disorder, Alzheimer's disease (AD), accounts for 60 – 70% of all cases of dementia (Mielke, 2018).[1] AD is characterized by memory loss, cognitive deficits, and behavioral changes including the ability to carry out daily tasks.[2] AD primarily affects individuals over 65 years of age, though early-onset cases affect 1 in 20 people aged 40-65 years.[3] This debilitating disease is a major cause of death worldwide affecting more than fifty million people. With the number of dementia cases expected to double by 2030 and triple by 2050, it will have a significant global impact.[4] AD disease is diagnosed based on symptoms and signs, with memory impairment being clinically significant. Worldwide, there are approximately 7.7 million new dementia cases yearly, equating to one new case every four seconds.[5] Advanced age is the primary risk factor.[6] Genetic factors, including rare mutations in APP and PSEN1/2 genes responsible for early-onset familial AD and APOE ε4 allele responsible for late-onset sporadic AD, play a significant role.[6] Other risk factors include female gender, low education, family history of dementia, and cardiovascular conditions. Traumatic brain injury and aluminium exposure have been associated with increased risk, though their roles remain controversial.[3,7] Diagnosis can involve cognitive tests, brain scans, and in some cases, lumbar punctures or PET scans.[3] Patients could be in a pre-clinical period without exhibiting any overt symptoms for 8-10 years.[8] The average survival time of patients, post-diagnosis, ranges from ≅ four years for men and ≅ six years for women.[9]

This prognosis significantly diminishes the quality of life, making it markedly poor even if the patient has not succumbed to the disease. At present there is no cure for AD, and the pathogenesis is also poorly known. In addition, the development of new drugs for its treatment has high failure rates. According to Liu et al. (2020)[10], almost all advanced clinical investigations that have been undertaken to date that have targeted specific AD-related pathways have failed, in part because of the enormous number of neurons that have already been damaged in the brains of AD patients.

Conventional therapies available for the treatment of AD focus on addressing neurotransmitter deficits. Cholinesterase inhibitors (ChEIs) are approved for low to moderate Alzheimer's, while memantine, an NMDA receptor antagonist, is used for the treatment of moderate to severe cases.[11,12] These treatments provide modest symptomatic benefits in cognitive, behavioural, and global measures.[12,13] ChEIs and memantine can be safely combined for additional symptomatic relief.[11,12] However, the effectiveness of these therapies has been questioned, leading to increased research into disease-modifying treatments.[13] New approaches aim to interfere with pathogenic processes such as amyloid β plaque deposition, neurofibrillary tangle (NFT) formation, inflammation, and oxidative damage which disrupts cellular physiology, cholesterol accumulation, and deposits.[14] These symptomatic treatments aim to counterbalance neurotransmitter disturbances but do not modify disease progression. The earlier FDA-approved drugs focused on symptom relief by boosting neurotransmitter activity (acetylcholine and glutamate), however, they did not alter the disease's underlying pathology. These drugs result in slowing progression for about 6 months but do not extend to all patients.[15] While these treatments offer some relief by improving neurotransmitter function, the development of disease-modifying therapies remains a critical priority in AD research. Ongoing research seeks to develop more effective therapies that can slow or prevent

disease progression. Aducanumab (Aduhelm), approved in 2021, is the first drug to target the underlying biology of Alzheimer's by reducing amyloid-beta plaques in the brain.[16]

In 2015, regenerative medicine entered more focused clinical trials aimed at treating Alzheimer's disease. Regenerative medicine leverages the therapeutic properties of stem cells to repair and rebuild damaged tissues or organs. Based on their potential for differentiation into specific cell types, stem cells are categorized as totipotent, pluripotent, multipotent, or unipotent. According to their origin, stem cells are classified into different categories; examples include embryonic stem cells (ESCs), perinatal stem cells (cells obtained during the period immediately before and after birth), and tissue-derived (somatic) stem cells.[17] Perinatal stem cells differ from embryonic stem cells in that they do not lead to the formation of tumors when transplanted. Wharton's Jelly is a mucous connective tissue in the human umbilical cord, which can be ethically harvested as it is discarded after birth. This logistical benefit makes Wharton's Jelly (WJ) an attractive source of stem cells for transplant therapy.[18] Moreover, Wharton's Jelly contains high amounts of primitive mesenchymal stem cells (MSCs), which are more effective in treating various conditions compared to MSCs from adult tissues as they exhibit higher pluripotency than adult stem cells, with evidence indicating their ability to generate cells from all the three primary germ layers. The current review article will discuss the potential of WJ-MSCs in the treatment of Alzheimer's Disease.

II. Pathophysiology Of Alzheimer's Disease

Alzheimer's disease is believed to result from an accumulation of amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein in the brain. Due to abnormal chemical shifts, tau detaches from microtubules and attaches to other tau molecules. Eventually, these strands combine to form tangles inside of neurons.[19] These tangles impair synaptic transmission between neurons by blocking the neuron's transport mechanism. Newly available evidence suggests that complex interactions between abnormal tau and beta-amyloid proteins may result in brain changes linked to Alzheimer's disease. Certain memory-related brain regions appear to have a buildup of abnormal tau. Beta-amyloid collects between neurons to create plaques, and when its levels get closer to a tipping point, tau begins to spread quickly across the brain.[19] These pathological processes of Alzheimer's disease start over a decade before noticeable cognitive decline. About 20% to 40% of cognitively healthy older adults already show elevated amyloid accumulation.[20] The accumulation of Aβ plaques in the hippocampus is a significant factor in neuronal cell death. These plaques composed of amyloid-beta (Aβ) peptides induce oxidative stress, which in turn damages neurons and disrupts synaptic function, leading to cognitive decline and memory loss.

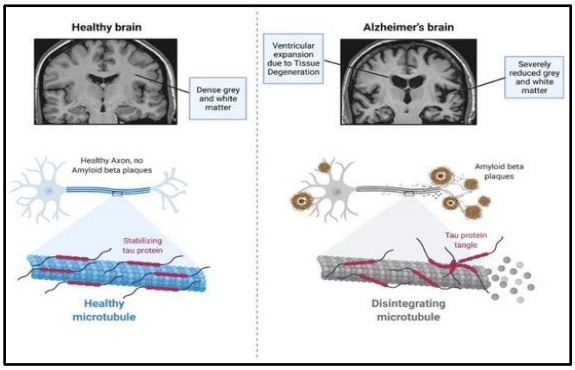

Figure 1: Pathophysiological differences between a healthy and an AD brain.[21]

These pathological changes trigger a cascade of events, leading to neurodegeneration with subsequent neuronal and synaptic loss, which results in macroscopic brain atrophy. Despite debates regarding the pathophysiology of AD, the amyloid cascade hypothesis is widely accepted. This hypothesis posits that the buildup and aggregation of amyloid-beta (Aβ) initiates a series of pathological events culminating in AD.[22] Additionally, neuroinflammation has been shown to play a significant role in the pathological process of AD. Microglia are the key orchestrators of this inflammation. In AD, the excessive activity of microglia aggravates tau pathology, induces proinflammatory cytokines' release, and causes neuronal injury. Proliferation, apoptosis, angiogenesis, inflammation, and immunomodulation are some of the processes implicated in the pathogenesis of AD. It is proposed that stem cell transplantation may modify these processes, thereby restoring neurological function and leading to an improvement in neurobehavioral outcomes.[23]

III. Treatments

Alzheimer's disease (AD) has no known cure and its causes are poorly understood. Drug development for AD has been highly unsuccessful with most advanced clinical trials failing primarily due to an extensive loss

of neurons by the time AD is diagnosed. Treatment strategies primarily address neurotransmitter imbalances. Cholinesterase inhibitors (ChEIs) are prescribed for mild to moderate cases while memantine (a class of drugs which inhibit the NMDA receptor) is used to treat severe to moderate AD. Although these drugs provide limited relief from symptoms, they do not slow or stop further progression.

Newer approaches, such as anti-amyloid drugs, aim to target underlying disease processes like amyloid β plaques, neurofibrillary tangles, and inflammation.[24] Developing therapies that modify the disease course remains a top priority in AD research. Stem cells have the inherent ability to heal and regenerate.[25] In Alzheimer's disease treatment, stem cell therapy shows potential for alleviating symptoms and reducing amyloid-β protein deposition, which current treatments cannot achieve.

Wharton's jelly, found in the umbilical cord, is a promising source for stem cell therapy. This mucous connective tissue cushions and protects the umbilical vessels. Ethically, harvesting Wharton's jelly is non-controversial since the umbilical cord is usually discarded after birth, and its collection does not harm the fetus or newborn. Unlike embryonic stem cells, WJ-MSCs do not form tumors when transplanted. These stem cells are more effective and potent as compared to stem cells from adult tissues as they are rich in primitive MSCs. Additionally, WJ-MSCs are more suitable for transplant therapy as compared with bone marrow-derived MSCs as they have lower immunogenicity and are easier to isolate.[26]

WJ-MSCs can differentiate spontaneously into neurons and glial cells as expressed by neuron-specific enolase (NSE) and β-tubulin markers.[27] WJ-MSCs release extracellular vesicles which contain catalase. The catalase helps protect neurons in the hippocampus against synapse damage and oxidative stress caused by Aβ oligomers.[28] Furthermore, WJ-MSCs secrete neurotrophic factors that promote neuronal survival and reduce inflammation.

IV. Preclinical Studies

Xie et al. (2016)[29] explored the curative potential of WJ-MSCs to alleviate memory deficit and reduce Aβ deposition in APP/PS1 double-transgenic mice. Following intravenous transplantation of WJ-MSCs, significant improvements were observed in spatial learning and memory, along with a reduction in Aβ deposits and the levels of soluble Aβ. WJ-MSC treatment also increased anti-inflammatory IL-10 expression while down-regulating pro-inflammatory cytokines IL-1β and TNFα and microglial activation. Their findings suggest WJ-MSCs could play a crucial function in the treatment of AD by modulating neuroinflammation.

Eslami et al. (2021)[30] conducted a trial to study the effect of intranasal delivery of WJ-MSCs in rats injected with amyloid β 1–42 into the hippocampus to induce Alzheimer's disease. A group of these rats was administered intranasal human WJ-MSCs fourteen days after they had been induced with AD. Gene expression levels, apoptosis apoptosis-related factors were measured to evaluate memory performance. Gene expression analysis of the hippocampus in the WJ-MSC group showed higher levels of neurotrophic factors linked to improved memory retention. The WJ-MSC group also showed lower levels of pro-apoptotic factors which are associated with neural cell death.

Behavioural evaluations were conducted to evaluate anxiety-like behaviour, spatial and passive learning, and memory. The Passive Avoidance Test[31], showed that the WJ-MSC treated group had significant improvement in memory retention compared with the AD group. The Morris water-maze (MWM) test, which is designed to measure working memory and cerebral and locomotory function, indicated enhanced spatial memory and learning in the WJ-MSC treated group.[32] Histological evaluations revealed fewer damaged neurons in the MSC-treated group as compared to the untreated AD group.

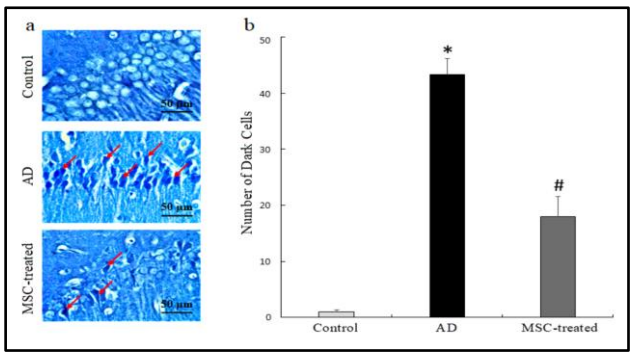

Figure 2: Research findings of Nissl staining of the hippocampus.[30] Areas marked Red represent the dead cells.

Another preclinical trial by Ali et al.(2023)[33] investigated the effectiveness of WJ-MSCs in treating AD in rats by inducing a group of rats with aluminium chloride (AlCl) to mimic AD symptoms and evaluating their cognitive functions with an AlCl-induced group administered with MSCs.

Tests conducted 30 days post-treatment showed a significant reduction in amyloid accumulation in the hippocampus and cortex of the brain and lower RYR3 gene expression (associated with calcium accumulation in neurons) in the MSC-treated group in comparison with the AlCl-induced group without treatment. Behavioral evaluations, including the Y-maze test, conducted 30 days post-treatment indicated that MSC treatment improved cognitive function.

V. Safety Considerations

Mehling, et al. (2022)[34] conducted a study that retrospectively analyzed subjects treated with WJ-MSCs. They were evaluated for six months for any adverse events, following intravenous, intrathecal, or intraarticular administration of WJ-MSCs for various conditions including neurological and osteoarthritic ailments. Of the 22 patients evaluated, 9.3% experienced, mild and transient chills and headaches which were resolved without any concern. Extensive blood profiling of a single patient indicated no hematological safety concerns. The study supports the safety of WJ-MSCs in humans, encouraging further clinical trials. In 2017 the US Federal Drug Administration issued an extensive framework to be followed during the development of regenerative medicines. They have proposed "an efficient, science-based process for helping to ensure the safety and effectiveness of these therapies".[35,36]

VI. Conclusion

Researchers have found that WJ-MSCs can help treat AD pathologies of amyloid-beta plaque accumulation, tau protein hyperphosphorylation, and neuroinflammation. In pre-clinical trials using AD rat models, WJ-MSCs have been seen to promote neuroprotective and regenerative effects through secretion of neurotrophic factors which enhance cognitive functions. Wharton's jelly has considerable potential in regenerative medicine as it is rich in growth factors, extracellular vesicles, cytokines, and hyaluronic acid which contribute to its anti-inflammatory properties, and promote healing, regeneration and tissue repair.[37]

WJ-MSCs contain high levels of collagen, sulphated proteoglycans, and other extracellular matrix components, contributing to tissue regeneration and reducing neuronal loss. These properties highlight the potential of WJ-MSCs in treating Alzheimer's, a degenerative disease. Multiple preclinical studies in AD rat models have demonstrated the effectiveness of WJ-MSCs in the treatment of Alzheimer's. The potential benefits of Wharton's Jelly in the treatment of AD warrant further clinical research.

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