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MESENCHYMAL STEM CELLS: A REGENERATIVE HOPE FOR ALZHEIMER'S PATIENTS

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, and neuronal loss. Despite extensive research, effective disease-modifying therapies remain limited. Mesenchymal stem cells (MSCs) have emerged as a promising therapeutic candidate due to their multipotent properties, immunomodulatory capacity, and ability to secrete neurotrophic factors. This review explores various aspects of AD, as well as it explores MSCs mechanisms of action including reduction of neuroinflammation, promotion of neurogenesis, clearance of amyloid-β plaques, and protection against oxidative stress. We also discuss the various sources of MSCs, and methods of delivery.

Keywords: Mesenchymal Stem Cells, Alzheimer's, Patients.

Introduction

In recent years, highly developed countries around the world have been experiencing a demographic shift toward an aging population. Among the diseases commonly diagnosed in the elderly, are neurodegenerative diseases. Notably, Alzheimer's disease (AD) stands out as one of the most frequently observed forms of senile dementia globally **(J. Zhang et al., 2024)**.

AD was first described by Dr. Alois Alzheimer in 1906. The condition's prevalence has steadily increased since then**(Pezeshki et al., 2023),** affecting 55 million people worldwide currently. This number is predicted to double every five years. By 2050, an estimated 152 million people are expected to suffer from Alzheimer's, with the highest rate of increase projected in developing countries **(J. Zhang et al., 2024)**. In developed countries, approximately one in ten elderly individuals (65 and over) and more than one-third of very elderly people(85 and over) suffer from the early and advanced stages of AD, respectively. **(J. Zhang et al., 2024).** In upper Egypt the prevalence of AD is 1% among 50 years old patients and older **(Desoky et al., 2024)**, this increases substantially to 9.7% for 80 years old patients and reaches 9.74 for those aged 80. Interestingly,

early-onset AD is observed at a notably high rate of 7.9% amongst individuals below the age of 65 **(El-Azzab et al., 2023)**.

1. **Pathophysiology of Alzheimer disease**

AD is a progressive neurodegenerative condition which gradually deteriorates cognitive abilities **(Bekiet et al., 2023),** starting with recent memory loss, confusion, and personality changes and impacting all intellectual functions overtime, ultimately affecting a person's ability to perform routine daily activities. **(Ciurea et al., 2023)**. AD has far-reaching effects extending beyond the individual diagnosed, causing significant impacts on family members, caregivers, and society (Gupta et al., 2024). AD is associated with several interacting mechanisms, including the abnormal buildup of proteins, increased inflammation, and neuronal death. **(Jurcău et al., 2022)**. These key mechanisms can be briefly summarized as follows:

a. Amyloid Plaques(Aβ):

Accumulation of amyloid-beta peptides leads to the formation of amyloid plaques, a defining characteristic of AD pathology. **(Adly et al., 2023).** These plaques predominantly accumulate extracellularly in the brain, disrupting neurotransmission **(Yang et al., 2023).** Amyloid-beta originates from cleavage of larger amyloid precursor protein (APP), thereby contributes to neuronal toxicity and inflammatory responses. **(Fanlo-Ucar et al., 2024).**

b. Neurofibrillary Tangles

In AD, tau a protein starts twisting into tangles when hyperphosphorylated, causing microtubule disruption and cell death specifically in areas that control memory like the hippocampus **(Bekiet et al., 2023).**

c. Neuroinflammation

Microglial activation, a hallmark of neurodegenerative processes, triggers chronic inflammation in AD **(Cai et al., 2022)**. encountering amyloid plaques and tau tangles, activated microglial cells release pro-inflammatory cytokines, thereby offering an inflammatory cascade that exacerbates neuronal degeneration and accelerates disease progression **(Yassaghi et al., 2024).**

d. Cholinergic Dysfunction

The initial biochemical manifestation of AD is the depletion of cholinergic neurons **(Giacobini et al., 2022).** The hippocampus, a brain region vital for memory formation (Ahmed et al., 2023), exhibits profound dependence on acetylcholine, a neurotransmitter crucial for cognitive functions, and the loss of acetylcholine-producing neurons within the hippocampus and other cerebral regions is associated with impaired cognitive abilities, notably in the domains of learning and memory.**(Madrid et al., 2021**).

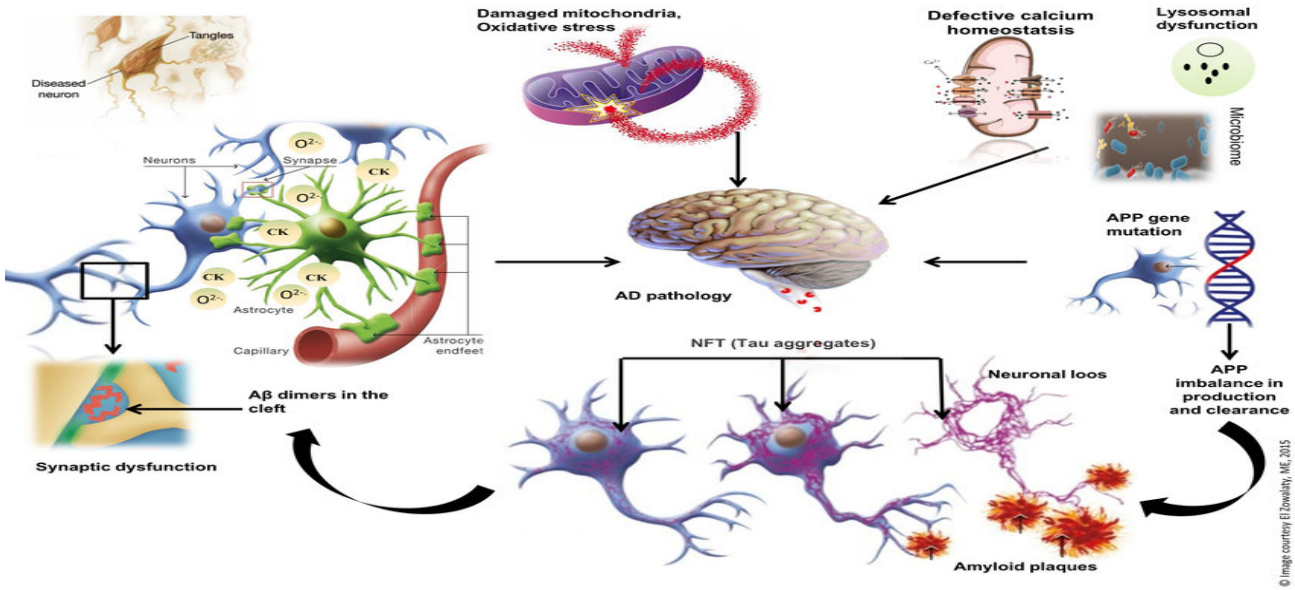

Figure 1: A schematic representation explains the complex pathophysiology of AD, highlighting its multifaceted nature. (Marei et al., 2016)

2. Causes and Risk Factors of AD

The etiology of AD is multifactorial, with its genesis attributed to a confluence of genetic, environmental, and lifestyle factors **(Suresh et al., 2023).**

Genetics: A well-characterized genetic predisposition to AD (AD) is the expression of the apolipoprotein E gene(APOE0) **(Desoky et al., 2024),** which has been implicated in lipid homeostasis and the clearance of amyloid plaques (**Husain et al., 2021**). Furthermore, variations in the TREM2 gene (Triggering Receptor Expressed on Myeloid Cells 2) have been linked to an enhanced susceptibility to AD by modulating brain immunological responses **(Li et al., 2022).** Both are involved in late onset AD **(Eren et al., 2023)**. In contrast, mutations in the APP (Amyloid Precursor Protein), PSEN1 (Presenilin 1), and PSEN2 (Presenilin 2) genes, which are heritable in an autosomal dominant pattern, are associated with early-onset AD **(Bagaria et al., 2022).**

Age: Age constitutes the most substantial risk factor for AD, with its prevalence rising notably with increasing age, particularly after attaining the age of 65 **(Flores-Cordero et al., 2022).** The likelihood of developing Alzheimer's doubles approximately every five years after the age of 65 **(Bomasang-Layno & Bronsther, 2021).**

Family History: A familial predisposition, characterized by the presence of a first-degree relative affected by AD, is associated with an elevated susceptibility to the development of the disease. **(Ramos et al., 2023)**.

Environmental and Lifestyle Factors: Various lifestyle factors have been linked with the risk of AD. These include cardiovascular health (hypertension, high cholesterol, and diabetes), Conversely, physical inactivity and inadequate cognitive stimulation have also implicated, **(Mishra et al., 2025)**. whereas consumption of diets replete with saturated fats, relative to those

high in antioxidants, may contribute to the degenerative processes observed in AD.**(Matías-Pérez et al., 2024).**

3. Symptoms and Stages of AD

AD progresses in stages, from mild memory loss to severe cognitive impairment. AD can be classified clinically into three main stages: early, middle, and late **(Mirakhori et al., 2022).**

The early stage of AD is characterized by minor memory impairment, predominantly affecting the recall of recent episodic events, and occasional confusion. **(Blagov et al., 2022)**. Individuals may also have language difficulties, misplace everyday items, or experience a general decline in their ability to perform familiar tasks **(Siddappaji & Gopal, 2021; Yang, 2020).** The slow decline in visuospatial skills similarly occurs in the initial dementia stages**,** executive dysfunction begins in the predementia stages **(August et al., 2022).** At this stage, the person may still be able to live independently, but the symptoms may become noticeable to family and close **friends.** Neuropsychiatric symptoms like anxiety, apathy, irritability and depressive symptoms may be found **(Salehi et al., 2022)**. Anosognosia often manifests early on (Andrade & Pacella, 2024). Neurologic examination is mostly normal in this phase.

Moderate (middle) Alzheimer's stage is usually the longest period of the disorder and can last for years **(Gupta et al., 2024).** Patients have problems with episodic memory, but they may still remember essential details about their life. All aspects of cognitive functions are affected. Other people can notice symptoms like forgetfulness of events or about one's own private history, mood and behavioral changes especially in challenging situations (eg. massive anxiety, suspiciousness and delusions, compulsive, repetitive behavior, wandering). Patients can't recall their own address or telephone number and are often mistaken about the situation and the date**(Grande et al., 2021)**. Caretakers must help them with daily and personal activities like choosing proper clothing, bathing or preparing meal. In this stage a variety of neuropsychiatric symptoms and changes in sleep patterns may exhibit **(Siddappaji & Gopal, 2021)**.

In severe Alzheimer's disease (late) stage patients commonly need extensive help with their daily activities and personal care. All previous skills continue to worsen. Individuals lose the ability to manage their environment and movement, including the ability to walk and sit. Patients usually become mute, incontinent, and bedridden. Multiple complications arise during this disease period like immobility, deep venous thrombosis, malnutrition, risk of meal aspiration and infections, which often turn in the direct cause of death. Pathologic reflexes are also found in the severe disease phase like root, suck and grasp reflexes **(Thussu et al., 2024).**

Current neuropathological staging models of AD involve an ABC scoring system in which stages are assigned to amyloid-β plaques (A), the Braak stage of tau neurofibrillary tangles (B), and the CERAD (Consortium to Establish a Registry for Alzheimer’s Disease) score of neuritic plaques (C) **(Therriault et al., 2022)**.

4. Diagnosis of Alzheimer’s Disease

Diagnosing Alzheimer’s disease can be challenging because many of its symptoms overlap with other conditions. There is no single test to diagnose Alzheimer's; instead, doctors rely on a

combination of medical history, cognitive testing, physical and neurological examinations, and brain imaging to make a diagnosis **(Reiss et al., 2022).**

Medical History: Assessing the patient's health history, including current and past medical conditions, medications, and family history of neurological diseases **(Hampel et al., 2022).**

Cognitive Tests: A series of tests may be conducted to assess memory, problem-solving, attention, and language. Common tests include the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) **(RANGE, 2023)**

Brain Imaging: Brain imaging techniques such as MRI (magnetic resonance imaging) and CT (computed tomography) scans can provide insights into brain structure and identify any abnormalities. In some cases, positron emission tomography (PET) scans may be used to detect amyloid plaques, a hallmark of Alzheimer's disease**(van Oostveen & de Lange, 2021).**

Biomarker Testing: Performing blood and urine tests to detect infections, metabolic issues, vitamin deficiencies, or thyroid problems that could mimic AD symptoms **(Varesi et al., 2022).**

5. Treatment and Management of Alzheimer's Disease

There is currently no cure for Alzheimer's disease, and no treatment can stop its progression. However, several interventions can help manage symptoms and improve quality of life **(Fymat, 2022).** Some of the treatments are • acetylcholinesterase inhibitors (e.g., tacrine, donepezil, rivastigmine, and galantamine): This increases cell to cell communications by preserving chemical messengers which are limited in AD in brain. • NMDA receptor antagonists (e.g., memantin):- These helps in brain cell communications and slow down the process of degeneration of brain cells or tissues and thus eventually slow down the progression of disease from moderate stage to severe stage **(Jiwtode et al., 2021)**.

Non-Pharmacological Interventions:

While medications can help manage symptoms, non-pharmacological approaches also play an important role in care. These may include cognitive stimulation therapy, physical exercise, and social engagement. Creating a safe and supportive environment that reduces confusion and frustration is crucial in managing the disease **(Huynh et al., 2022)**.

Newer approaches to treatment:

Mesenchymal stem cells (MSC) have recently attracted interest as a potential basis for a cell-based Alzheimer therapy. **(Fymat, 2022).** Mesenchymal stem cells (MSCs) are adult stem cells that can be derived from various tissues such as bone marrow, adipose tissue (fat), and the umbilical cord **(Gholami Farashah et al., 2023)**. (MSCs) can be delivered to the body through various methods as Intravenous (IV) Injection, Intra-arterial Injection, intracranial, Intrathecal Injection, Intramuscular Injection, and intraperitoneal injection **(Bagno et al., 2022)**. MSCs are unspecialized cells that have self-renewal capacity and can be differentiated into many specialized cell types **(Abdelzaher et al., 2025)**, Unlike neural stem cells (NSCs), which can differentiate into neurons **(W. Zhang et al., 2024)**, MSCs do not directly become neurons. However, MSCs have gained attention in Alzheimer's disease (AD) research due to their immunomodulatory, anti-inflammatory, and neuroprotective properties These characteristics make MSCs an appealing

candidate for treating neurodegenerative conditions like AD, where inflammation and neuronal damage play central roles**(Rufino et al., 2022).**.

Key Mechanisms of Action for MSC Therapy in Alzheimer's:

a) Anti-inflammatory Effects: One of the primary mechanisms of MSC therapy in Alzheimer's is the ability to modulate neuroinflammation. MSCs secrete various anti-inflammatory cytokines (e.g., IL-10, TGF-beta) and growth factors (e.g., BDNF – Brain-Derived Neurotrophic Factor, VEGF – Vascular Endothelial Growth Factor) that can help suppress neuroinflammation and promote tissue repair. This reduces the toxic environment that accelerates neurodegeneration in AD **(Xu et al., 2024).**

b) Neuroprotection and Tissue Repair: MSCs release neuroprotective molecules, such as brain-derived neurotrophic factor (BDNF), which helps support the survival and function of neurons. In Alzheimer's, there is a loss of neurons in the brain, particularly in areas related to memory, such as the hippocampus. MSCs can stimulate neurogenesis and encourage tissue repair in damaged areas of the brain **(Wihadmadyatami et al., 2025).** MSCs also produce molecules that can enhance synaptic plasticity, essential for memory formation and learning **(Abdelzaher et al., 2025).**

C) Modulation of Amyloid Beta (Aβ) and Tau Pathology: Some studies suggest that MSC treatment significantly enhances autolysosome formation and Aβ clearance in AD models, leading to increased neuronal survival against Aβ toxicity **(Lu et al., 2025)**. The researchers observed that MSCs upregulated BECN1/Beclin 1 expression, contributing to improved autophagy and Aβ clearance, This could potentially slow disease progression **(Qin et al., 2022)**. MSCs may also help reduce tau-induced neurotoxicity by modulating tau protein aggregation and preventing the spread of tau pathology, which contributes to cognitive decline **(Neves et al., 2021).**

D) protection against oxidative stress: MSCs can secrete exosomes, which are small vesicles containing proteins, lipids, and RNA that can transfer bioactive molecules to neighboring cells. In AD, MSC-derived exosomes have been shown to have neuroprotective effects. These exosomes can help reduce oxidative stress, inflammation and amyloid-beta toxicity, and promote neuronal survival **(Shah et al., 2024).** MSC-derived exosomes can promote the angiogenesis which could help improve blood supply and nutrient delivery to the brain areas damaged by Alzheimer's **(Shah et al., 2024).**

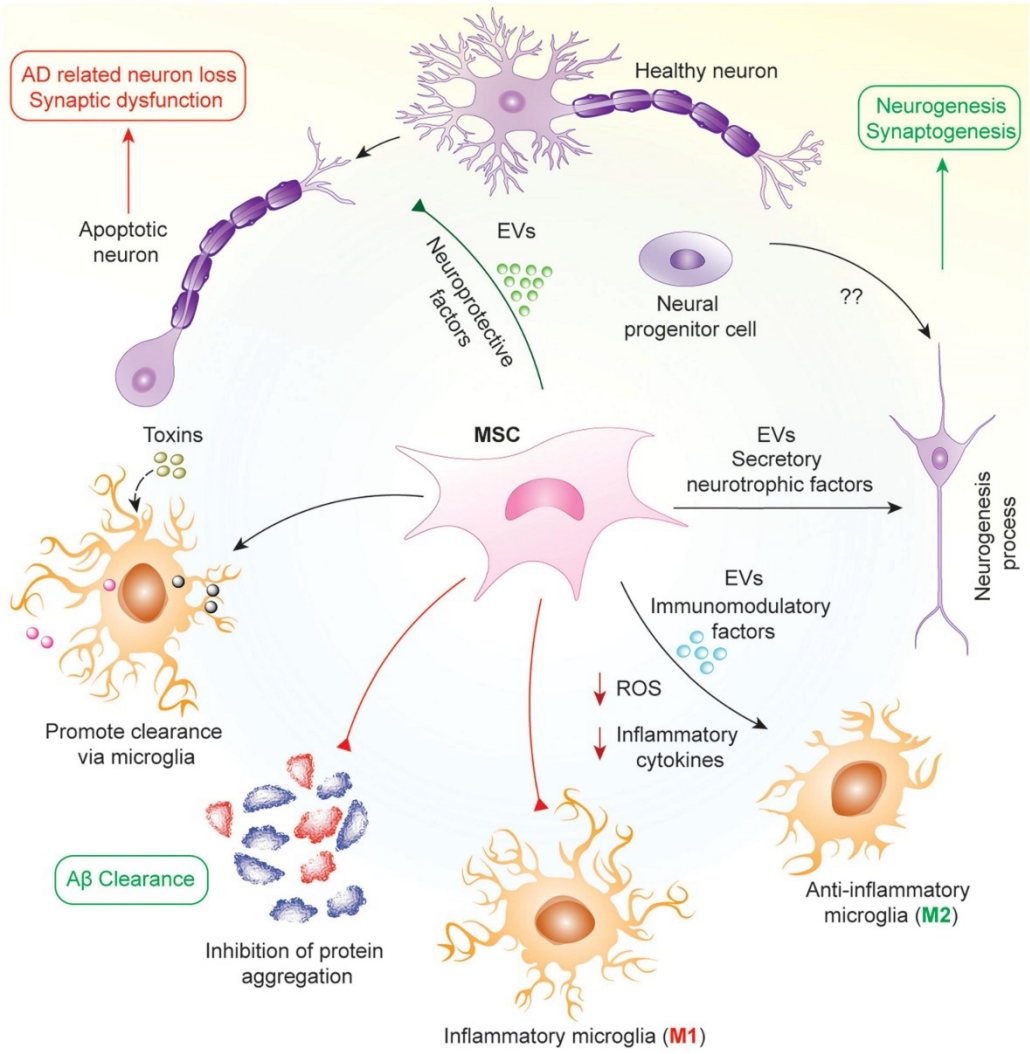

Figure 2. Mechanism of protective effects of MSCs in AD (**Regmi et al., 2022)**.

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