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MINI REVIEW

Alzheimer's disease and the recent advances in tissue engineering for it's treatment: A mini-review

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ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia among elderly individuals and accounts for 60 to 70% of patients affected by all forms of dementia globally. AD is a significant public health concern, as it shows an increased prevalence and incidence rates. Based on the current trends, the global population above 65 is estimated to almost double, and the number of individuals over 85 will increase to more than thrice by the year 2050. Pathophysiological processes and genetic factors leading to the accumulation of beta-amyloid and neurofibrillary tangles are being studied. Various tissue engineering methods have shown promise in identifying the disease process early and delaying the pathophysiological and genetic processes leading to cognitive decline.

There are various innovative tissue engineering methods showing promises in the diagnosis and treatment of AD, such as 3D bioengineered neural tissue models derived from 'human induced pluripotent stem cells, nanocarrier-mediated small interfering RNA (siRNA) delivery methods, carbon-based nanomaterials, and scaffold innovations that help to create realistic models of neuronal tissues and to use advanced drug delivery systems using nanoparticles in patients with AD.

Keywords

Tissue engineering, bioengineering, public health, elderly, geriatric

Introduction

Alzheimer's disease (AD) is a 'progressive neurodegenerative disorder' that mainly affects the brain, leading to a gradual decline in memory, thinking, and reasoning skills. AD is identified as the most common cause of dementia, especially among the elderly, accounting for 60 to 70% of all dementia cases globally. [1] Symptoms of this disease typically begin with a mild loss of memory. They can progress to severe cognitive impairment, reducing the person's ability to perform everyday activities and are characterised by the accumulation of 'amyloid plaques' and 'neurofibrillary tangles' in the brain tissue, inhibiting neurotransmission and leading to the death of brain cells. [2]

AD usually manifests in individuals above 65 years of age, although an early-onset form of the disease can occur when a person is in their 30s to mid-60s, even if rarely. [3] As the disease advances, it can cause significant changes in the behaviour and personality of the individual, confusion, impaired judgment, and difficulties with language and communication. [1] While there is no permanent cure for AD at present, available treatment modalities are helping to reduce the symptoms temporarily and to reduce the progression rate of the disease. [4] AD is a significant public health concern, as it shows an increased prevalence and incidence rates globally. [5]

Global trends in AD

Incidence rates of AD and other forms of dementias had increased by 147.95% from the year 1990 to 2019, with a total of 2.92 million cases of AD and other dementias (95% CI: 2.49 million to 3.37 million) in the year 1990 and a total of 7.24 million cases (95% CI: 6.22 million to 8.23 million) in the year 2019. [6] It is estimated that the global population over 65 will almost double, and the number of individuals over 85 is expected to increase more than thrice by the year 2050. [5]

Epidemiology of AD

Almost 67% of all clinically diagnosed patients of AD and other forms of dementia are females, according to reports from the US [7] and from most of the European countries. The reason for this gender difference was attributed to the increased life expectancy of women. [8] The increased age-standardized incidence rates (ASIRs) are associated with an increase in sociodemographic Index (SDI), indicating that higher SDI regions (regions with higher 'per capita income', 'average educational attainment' and 'total fertility rate') reported higher incidence rates of dementia. For instance, countries like Turkey and Kuwait reported some of the highest age-standardized prevalence rates (ASPRs), while India and Nigeria had some of the lowest. Global statistics from the year 1990 to 2019 showed an increase in the burden of AD. The prevalence trend was higher among the elderly population from countries with high SDI. [6] Another research carried out among the members of the Leisure World Cohort Study in California found that the disease incidence rates increased exponentially with age. Incidence was 12.7% per year among the 90-to-94-year age group, which increases to 21.2% per year among those between 95 to 99 years. Incidence increased further to 40.7% per year in the 100+-year age group. [9] Prevalence of AD among those aged 65 to 74 years, 75 to 84 years, and those aged 85 years and above were 5%, 13.2% and 33.4%, respectively. [10] When COVID-19 entered the ranks of the top ten causes of death, AD was the seventh leading cause of death in the United States during 2020 and 2021. AD remains the fifth leading cause of death among Americans aged 65 years and above. Between the years 2000 and 2021, mortality due to diseases such as stroke, cardiovascular diseases, and HIV decreased, while the reported mortality due to AD increased by more than 140%.

An estimated 6.9 million Americans who are aged 65 years and higher are currently living with AD. This number is expected to reach 13.8 million by the year 2060 if no newer medical breakthroughs to prevent or cure AD are introduced. The register of death certificates showed a total of 119,399 deaths from AD in the USA in 2021. [10]

Impact of AD on caregivers

According to the research findings published by the 'Alzheimer's Association', caregivers of patients with AD exhibit high levels of stress. Increased caregiver stress is detrimental to the patients' and caregivers' quality of life. [11] Caregiving for dementia was found to be not covered under health insurance, and the overall financial burden was valued at 346.6 billion US Dollars in the year 2023. These costs extend to the unpaid caregivers' elevated levels of risk for the development of emotional distress, which in turn might result in various adverse physical and mental health outcomes. Caregivers report high-stress levels related to coordinating care, expenses and maintaining their health. [10]

Risk factors of AD

Key risk factors for the development of AD include:

- Age: The research shows that the risk of developing AD increases significantly as age advances. [10]
- Gender: Women are disproportionately affected by AD. One in five women at the age of 45 years has a lifetime risk of developing AD, while one out of 10 men of the same age has the same. [12]
- Family history of AD: Another strong predictor for AD is family history. The research published by the 'Alzheimer's Association' revealed that those who had a close relative with the disease were more prone to develop AD. The risk increases when more than one family member has the disease
- Lack of sleep, smoking habits, hypertension or diabetes are some of the major modifiable risk factors which can increase the risk of development of AD. [13]
- Health conditions: Factors such as obesity, atherosclerosis, and cardiovascular diseases were linked to higher disease burdens, particularly among different genders. [13]

Pathophysiology of AD

Research has identified the accumulation of beta-amyloid (Aβ) plaques and neurofibrillary tangles in the brains of AD patients as a significant role in the pathophysiology of AD. Neurofibrillary tangles are made up of 'hyperphosphorylated tau protein'. Accumulation of these proteins results in neuron degeneration and cognitive decline in patients.

Excess accumulation of 'Amyloid Beta' (Aβ) and 'hyperphosphorylated tau' proteins are the hallmark lesions of AD. The 'loss of synapses' and defect in neurotransmission are directly proportional to the disease severity. Experiments conducted outside the human body suggest that Aβ and 'hyperphosphorylated tau' proteins can have both direct and indirect cytotoxic effects, which can inhibit neurotransmission, 'axonal transport', 'signalling cascades', 'organelle function', and 'immune response' in many ways resulting in synaptic loss and inhibition of the release of neurotransmitters. [14]

Key pathological features of AD

'Amyloid Plaques' are the results of the aggregation of Aβ (amyloid β) peptides, particularly the Aβ42 variant, which is derived as a result of the cleavage of 'amyloid precursor protein' (APP) by β and γ secretase enzymes. An imbalance between the production of Aβ and its clearance results in toxic deposition of beta amyloids, leading to synaptic dysfunction and death of neurons. [15] The presence of amyloid plaques is often seen as an early lesion in AD pathology, which may occur decades before the appearance of clinical manifestations. [14]

'Neurofibrillary Tangles' (NFTs) are made of 'hyperphosphorylated tau' proteins. NFTs disrupt the microtubule network, essential for neuronal transport and function. This destabilisation leads to neuronal cell death and correlates with the cognitive impairment associated with AD. Tangles typically begin in the temporal lobes and spread to other cortical areas as the disease progresses. [16]

Neurodegenerative Processes in AD

The degeneration and neuronal loss primarily affect cholinergic neurons in the basal forebrain and neocortex, reducing acetylcholine levels, a neurotransmitter vital for learning and memory. [17] Both amyloid plaques and NFTs contribute to synaptic loss, which is critical for cognitive functions. The extent of synaptic loss correlates with the severity of cognitive decline. [18] Activation of microglial cells and astrocytes, which happens in response to amyloid deposition, results in chronic inflammation, further exacerbating neuronal damage, thus contributing to the progression of AD. [19]

Genetic factors in AD

Several genes are implicated in the pathophysiology of AD. Mutations in the amyloid precursor protein gene (APP), 'Presenilin 1 gene' (PSEN1) and 'Presenilin 2 gene' (PSEN2) are found to be linked to the familial forms of AD, leading to increased production of Aβ (amyloid β). [20] The 'apolipoprotein E' (APOE) gene 'ε4 allele' is a variant of the APOE gene found to be the most potent 'genetic risk factor' for developing AD, influencing amyloid metabolism and deposition. [21] Newer tissue engineering methods for studying the pathology of AD and treating AD. Recent advances in tissue engineering methods for treating AD have shown some promise. [22] Some of those methods are discussed below.

Bioengineered neural tissue models

A significant advancement is the development of 3D bioengineered neural tissue models derived from 'human induced pluripotent stem cells' (iPSCs). 'Induced Pluripotent Stem Cells' (iPSCs) are somatic cells which are genetically reprogrammed to behave as embryonic stem cells, thus allowing them to differentiate and grow into any other type of cells, such as neurons and glial cells which are relevant to the treatment of Alzheimer's. [23]

These models utilise silk-based scaffolds to create functional neural networks that can remain stable and active for extended periods, up to two years or more. These scaffolds are made using silk fibroin derived from silkworms. These scaffold models are bio-engineered and are helping researchers to study the pathology of AD. These models help study beta-amyloid and tau protein accumulation in a controlled environment that resembles human brain tissues. These 3D bioengineered neural tissue models approach can help overcome the limitations associated with traditional cell cultures and animal models. It provides insights into various neurodegenerative processes in a more physiologically relevant environment. [24, 25]

Nanocarrier-mediated small interfering RNA (siRNA) delivery method

The nanocarrier-mediated small interfering RNA (siRNA) delivery method is an innovative tissue engineering method that uses nanoparticles for the targeted delivery of siRNA to treat the genetic factors contributing to AD development. Nanoparticles effectively cross the blood-brain barrier and deliver the siRNAs to the brain tissues, inhibiting the specific genes involved in AD progression. [26] Even though the trials for testing this bioengineering method are still in preclinical stages, this approach shows promise for developing and administering molecular targeted therapies that could lead to newer methods in precision medicine for treating AD. [27]

Carbon-based nanomaterials

Another promising bioengineering method integrates carbon-based nanomaterials for treating patients with AD. These materials enhance drug delivery systems to the brain tissues and provide neuroprotective effects to the patients. Carbon-based nanomaterials have been found to have a better ability to target neuronal tissues without compromising the stability

of the therapeutic agents. Thus, these materials can improve the clinical and cognitive outcomes of patients with AD. [28]

Scaffold innovations

Recent research conducted in bioengineering has explained the use of collagen scaffolds with microchannels, which can help promote the differentiation and regeneration of neuronal tissues. [29] Collagen-based scaffolds can be engineered to release various neurotrophic factors in a controlled manner. This, in turn, can support the growth and repair of neural tissues which are badly affected by AD. [30]

Conclusion

This review article sheds light on AD and various tissue engineering methods that can help us better understand and treat it. These methods help create realistic models of neuronal tissues and use advanced drug delivery systems using nanoparticles. Newer tissue engineering methods can enhance therapeutic efficacy and pave the way for newer, innovative treatments for AD.

Abbreviations

Age-standardised prevalence rates (ASPRs), Alzheimer's Disease (AD), amyloid precursor protein (APP), amyloid-beta (Aβ), apolipoprotein E (APOE), induced pluripotent stem cells (iPSCs), neurofibrillary tangles (NFTs), Presenilin 1 gene (PSEN1), Presenilin 2 gene (PSEN2), small interfering RNA (siRNA), Socio-Demographic index (SDI)

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Authors' contribution

a. Study planning: AS, SS

b. Manuscript writing: AS, SKKA, KBL, KM, SS

c. Manuscript revision: AS, KM and SS

d. Final approval: AS, SKKA, KBL, KM, SS

e. Agreement to be accountable for all aspects of the work: AS, SKKA, KBL, KM, SS

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References

1. Alzheimer's disease fact sheet [Internet]. National Institute on Aging. [cited 2024 Dec. 10]. Available from: https://www.nia.nih.gov/health/alzheimers-and-dementia/alzheimers-disease-fact-sheet
2. Alzheimer's disease [Internet]. Mayo Clinic. [cited 2024 Dec. 10]. Available from: https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/symptoms-causes/syc-20350447
3. What happens to the brain in Alzheimer's disease? [Internet]. National Institute on Aging. [cited 2024 Dec. 10]. Available from: https://www.nia.nih.gov/health/alzheimers-causes-and-risk-factors/what-happens-brain-alzheimers-disease
4. Alzheimer's disease: Causes, symptoms, treatment & stages [Internet]. Cleveland Clinic. [cited 2024 Dec. 10]. Available from: https://my.clevelandclinic.org/health/diseases/9164-alzheimers-disease
5. United Nations Department of Economic and Social Affairs, Population DIvision (2019) World Population Prospects 2019: Highlights. ST/ESA/SER.A/423 [cited 2024 Dec. 10].
6. Li X, Feng X, Sun X, Hou N, Han F, Liu Y. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2019. Front Aging Neurosci. 2022 Oct 10;14:937486. https://doi.org/10.3389/fnagi.2022.937486
7. Alzheimer's Association. 2013 Alzheimer's disease facts and figures. Alzheimers Dement. 2013 Mar;9(2):208-45. https://doi.org/10.1016/j.jalz.2013.02.003
8. Mielke MM, Vemuri P, Rocca WA. Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. Clin Epidemiol. 2014 Jan 8;6:37-48. https://doi.org/10.2147/CLEP.S37929
9. Corrada MM, Brookmeyer R, Paganini-Hill A, Berlau D, Kawas CH. Dementia incidence continues to increase with age in the oldest old: the

90+ study. Ann Neurol. 2010 Jan;67(1):114-21. https://doi.org/10.1002/ana.21915
10. 2024 Alzheimer's disease facts and figures. Alzheimers Dement. 2024 May;20(5):3708-3821. https://doi.org/10.1002/alz.13809
11. Caregiver stress [Internet]. Alzheimer's Disease and Dementia. [cited 2024 Dec. 10]. Available from: https://www.alz.org/help-support/caregiving/caregiver-health/caregiver-stress
12. Alzheimer's Disease – Facts and Figures 2024. Alz.org. [cited 2024 Dec. 10]. Available from: https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf
13. What are the causes and risk factors of Alzheimer's and other dementias? [Internet]. Alzheimer's Disease and Dementia. [cited 2024 Dec. 10]. Available from: https://www.alz.org/alzheimers-dementia/what-is-alzheimers/causes-and-risk-factors
14. Rajmohan R, Reddy PH. Amyloid-Beta and Phosphorylated Tau Accumulations Cause Abnormalities at Synapses of Alzheimer's disease Neurons. J Alzheimers Dis. 2017;57(4):975-999. https://doi.org/10.3233/JAD-160612
15. Chen, Gf., Xu, Th., Yan, Y. et al. Amyloid beta: structure, biology and structure-based therapeutic development. Acta Pharmacol Sin 38, 1205–1235 (2017). https://doi.org/10.1038/aps.2017.28
16. Roberta Epis, et al. Searching for new animal models of Alzheimer's disease. European Journal of Pharmacology. Volume 626, Issue 1, 2010, Pages 57-63, ISSN 0014-2999, https://doi.org/10.1016/j.ejphar.2009.10.020
17. Hampel H, et al. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. Brain. 2018 Jul 1;141(7):1917-1933. https://doi.org/10.1093/brain/awy132
18. Nelson PT, Braak H, Markesbery WR. Neuropathology and cognitive impairment in Alzheimer disease: a complex but coherent relationship. J Neuropathol Exp Neurol. 2009 Jan;68(1):1-14. https://doi.org/10.1097/NEN.0b013e3181919a48
19. Di Benedetto G, et al. Role of Microglia and Astrocytes in Alzheimer's Disease: From Neuroinflammation to Ca2+ Homeostasis Dysregulation. Cells. 2022 Sep 1;11(17):2728. https://doi.org/10.3390/cells11172728
20. Lanoiselée HM, et al. APP, PSEN1, and PSEN2 mutations in early-onset Alzheimer disease: A genetic screening study of familial and sporadic cases. PLoS Med. 2017 Mar 28;14(3):e1002270. https://doi.org/10.1371/journal.pmed.1002270
21. Di Battista AM, Heinsinger NM, Rebeck GW. Alzheimer's Disease Genetic Risk Factor APOE-ε4 Also Affects Normal Brain Function. Curr Alzheimer Res. 2016;13(11):1200-1207. https://doi.org/10.2174/1567205013666160401115127
22. Poudel P, Park S. Recent Advances in the Treatment of Alzheimer's Disease Using Nanoparticle-Based Drug Delivery Systems. Pharmaceutics. 2022 Apr 11;14(4):835. https://doi.org/10.3390/pharmaceutics14040835
23. Abelseth E, Abelseth L, De la Vega L, Beyer ST, Wadsworth SJ, Willerth SM. 3D printing of neural tissues derived from human induced pluripotent stem cells using a fibrin-based bioink. ACS Biomater Sci Eng. 2019;5(1):234–43. https://doi.org/10.1021/acsbiomaterials.8b01235
24. Huang X, An Y, Yuan S, Chen C, Shan H, Zhang M. Silk fibroin carriers with sustained release capacity for treating neurological diseases. Front Pharmacol. 2023 May 5;14:1117542. https://doi.org/10.3389/fphar.2023.1117542
25. Babu PJ, Suamte L. Applications of silk-based biomaterials in biomedicine and biotechnology. Engineered Regeneration. 2024;5(1):56–69. https://doi.org/10.1016/j.engreg.2023.11.002
26. Imran Sajid M, et al. siRNA drug delivery across the blood-brain barrier in Alzheimer's disease. Adv Drug Deliv Rev. 2023 Aug;199:114968. https://doi.org/10.1016/j.addr.2023.114968
27. Amiri A, Barreto G, Sathyapalan T, Sahebkar A. siRNA Therapeutics: Future Promise for Neurodegenerative Diseases. Curr Neuropharmacol. 2021;19(11):1896-1911. https://doi.org/10.2174/1570159X19666210402104054
28. Yazdani S, et al. Carbon-Based Nanostructures as Emerging Materials for Gene Delivery Applications. Pharmaceutics. 2024 Feb 18;16(2):288. https://doi.org/10.3390/pharmaceutics16020288
29. Pai V, Singh BN, Singh AK. Insights into Advances and Applications of Biomaterials for Nerve Tissue Injuries and Neurodegenerative Disorders. Macromol Biosci. 2024 Dec;24(12):e2400150. https://doi.org/10.1002/mabi.202400150
30. Iyad A Hammam, Ryan Winters, Zhongkui Hong. Advancements in the application of biomaterials in neural tissue engineering: A review. Biomedical Engineering Advances, Volume 8, 2024, 100132, ISSN 2667-0992, https://doi.org/10.1016/j.bea.2024.100132