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A Review on Alzheimer's Disease

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ABSTRACT:

One of the most prevalent factors contributing to dementia that affects nerve cells across the brain is Alzheimer's disease. This neurodegenerative condition is pathologically brought on by intracellular neurofibrillary tangles and extracellular amyloidal protein, which lead to the development of plaques that impede communication between the nerve cells. Mutations in the APP, PSEN1, and PSEN2 genes have been discovered to be a hereditary risk factor for this condition. Additionally, diet and nutrition have a significant impact on both the progression and prevention of Alzheimer's disease. The biomarker used to identify the disease should be capable of differentiating between dementia's many causes and identifying it at an early stage.Furthermore, using induced pluripotent stem cells has shown to be a successful method of treating this illness. The goal of this review is to provide insight on the disease's progression and its response to stem cell therapy.

Keywords:Amyloidal Protein, Dementia, and Pluripotent Stem Cells

Introduction:

The world's population is aging quickly, and dementia diagnoses are rising. Globally, 35 million individuals are estimated to have Alzheimer's disease (AD) or another type of dementia, and 65 million people are predicted to have dementia-related issues by 2030.

Dementia is a clinical illness associated with a steady decline in brain function that impairs the ability of the affected person to carry out daily tasks adequately. Memory lapses or difficulty finding the

correct phrases are frequently the first indicators of Alzheimer's disease. Language, thinking, decision-making, visuospatial function, attention, and orientation memory loss are some of the symptoms that progressively worsen over time.

One of the most prevalent forms of dementia is Alzheimer's disease. There is no known cause for AD, a progressive multifactorial neurodegenerative brain condition that has both modifiable and immutable risk factors. The most significant non-genetic risk factor is age. The nerve cells in the brain are harmed structurally and functionally. When a disease first manifests, it also affects the connection between nerve cells in brain circuits, which is crucial for memory and other cognitive activities.

Researchers have discovered that those who suffer from Alzheimer's have an unusual buildup of specific proteins in their brains, yet the exact cause of the disease is still unknown. Amyloid beta, one of these proteins, collects in groups to create "plaques." Another protein, known as tau, tangles into protein "tangles." Researchers are still examining whether the symptoms of AD are caused by these changes in the brain. There have been a number of theories proposed regarding how AD develops, some of which we will discuss in more detail later in this article.

The dominant autosomal mutation in either the presenilin gene on chromosomes 1 and 14 or the amyloid precursor protein (APP) gene on chromosome 21 appears to be the cause of the genetic component of Alzheimer's disease. Additionally, there is a higher risk of early-onset AD among those with Down syndrome (trisomy 21). Despite the fact that the genetics of AD are more complicated and poorly understood. The epsilon four alleles of the chromosome 19-located apolipoprotein E (APOE) gene are well recognized to increase the risk of sporadic AD.

Lower levels of vitamin D (1,25-dihydroxyvitamin D3) were found to be linked to all types of dementia and Alzheimer's disease, according to research [8, 9]. 1,25-D3, the active form of vitamin D, controls the expression of neurotrophins such as nerve growth factor, neurotrophin 3, and glial-derived neurotrophic factor as well as the survival, growth, and functionality of neural cells. Vitamin D stimulates macrophages in vitro settings, which improves the phagocytic clearance of amyloid plaques.

Numerous studies have shown that vitamin D may act as a neuroprotectant and that 50 nmol/L is adequate in cases of dementia risk. The cost and design of randomized controlled trials to determine if vitamin D supplements can help older persons postpone or prevent the onset of dementia and AD could be improved with the use of this knowledge.

Changes in Brain

AD causes tissue loss and the death of nerve cells, and over time, the brain's size decreases, impairing all of its activities. The brain's capacity for thought, planning, and memory is harmed by cell loss in the cortical area of the brain. The hippocampus, a region of the brain crucial for the creation of new memories, is where shrinkage is most severe. The ventricles, the fluid-filled spaces in the brain, are growing in size in addition to the region of the

brain shrinking. An AD patient's brain has fewer neuron cells and synapses than a healthy individual, but it has a higher buildup of tangles and plaques, which may be the cause of this cell loss. These plaques obstruct cell-to-cell communication and stir up immune cells that attack damaged cells and create inflammation.Tau proteins break down into tangled strands known as tangles, which prevent nutrition and other vital supplies from moving through the cells, causing the cells to die.

Causes of the Disease

Most dementia cases (between 60% and 70%) are caused by Alzheimer's disease. It is a long-term neuro-degenerative condition that often begins out mildly and progresses over time. According to one idea, plaques prevent nerve cells in the brain from properly communicating. The process through which the cells obtain the nutrients they need may be hampered by tangles. It makes sense that as Alzheimer's progresses, more and more nerve cells, also known as neurons, are lost as the disease progresses.

1. **Age**: The single most important risk factor for the onset of Alzheimer's disease is old age. Once you reach age 65, your chance of getting the ailment doubles every five years.
2. **Down syndrome**: Those who have Down syndrome are more likely to get Alzheimer's disease. Because some people may get Alzheimer's disease as a result of the genetic flaw that causes Down's syndrome, amyloid plaques can accumulate in the brain over time.
3. **Genetics**: According to analyses of twin and family studies, the genetic heritability of Alzheimer's disease (and its memory-related symptoms) ranges from 49% to 79%. With an onset before the age of 65, familial types of autosomal (not sex-linked) dominant inheritance make up about 0.1% of the cases. Early onset familial Alzheimer's disease is the term used to describe this type of the illness. Even though it's uncommon, only a small fraction of people have AD before they're 65. Amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) are three genes that have been related to the development of AD as a result of mutations in them.

Late-onset Alzheimer's gene

Apolipoprotein E is a gene related to AD, which often manifests after age 65. (APOE). This APOE has three different variants, among which the e4 variant raises the risk of Alzheimer's. Other genes linked to AD include SORL1, CLU, PICALM, CR1, and others. Three genes—those encoding presenilins 1 and 2 and the amyloid precursor protein (APP)—can be mutated, and these mutations account for the majority of autosomal dominant familial AD cases.

APP amyloid beta precursor protein

This gene produces a cell surface receptor and a transmembrane precursor protein that secretases cleave into a number of peptides that, when released, bind to the acetyltransferase complex APBB1/TIP60 to promote transcriptional activation and create the protein structure of the amyloid plaques found in the brains of Alzheimer's patients. Chromosome 21 contains this gene. The etiology of AD is linked to the constitutive overexpression of soluble -amyloids, which subsequently leads to the development of amyloid plaques. Due to its limitations and side effects, the anti-amyloid therapy, which consists of the monoclonal antibodies solanezumab, crenezumab, and gantenerumab that target soluble & insoluble A-aggregates, has not been able to improve the clinical results of AD.

APOE apolipoprotein E

This gene produces a protein that binds to a particular receptor in the liver and other peripheral cells and is necessary for the proper breakdown of triglyceride-rich lipoprotein components. This gene, as well as the apolipoprotein C1 and C2 genes, are located on chromosome 19. Type III hyperlipoproteinemia (HLP III), caused by mutations in this gene, is characterized by elevated plasma cholesterol and triglycerides as a result of poor clearance of chylomicron and VLDL remnants.

Most mutations in the APP and presenilin genes result in an increase in the amount of A42, a tiny protein that makes up the majority of senile plaques. Without increasing the amounts of A-42, some mutations just change the ratio between A-42 and the other major forms, particularly A-40. This shows that presenilin mutations can cause disease even if they reduce the overall amount of A produced and may indicate alternative functions for presenilin or a role for changes in the function of APP and/or its fragments aside from A. The APP gene can be found in protective versions.

They produce too much amyloid-beta peptide, a hazardous protein fragment, as a result of mutation. The tau protein malfunctions as these pieces aggregate into amyloid plaques in the brain. The tau protein fragments clump together to create neurofibrillary tangles, which results in the death of brain cells and the onset of Alzheimer's disease symptoms.

Alzheimer's & Diabetes

We are aware that some diseases, like diabetes, are linked to our diet, but researchers have discovered a clear link between the food we eat and Alzheimer's disease and dementia via a similar pathway that causes diabetes 2. As a result, they have renamed Alzheimer's to diabetes 3. Alzheimer's disease causes a decline in brain glucose metabolism. Type 2 diabetes mellitus has been found to increase the risk for Alzheimer's disease more than the other two forms of diabetes, while the reasons for this are still unknown.

It has been demonstrated in earlier research that the rise in glucagon-like peptide 1 (GLP-1) contributes to the normalization of insulin signaling in type 2 diabetes. GLP-1 plays a significant role in both neuronal activity and brain processes. A GLP-1 receptor knockout mouse model was used to test the precise role of GLP-1 receptors in synaptic plasticity and cognitive processes. It was discovered that since the brain's lack of GLP-1 receptor function affects synaptic plasticity and cognitive processes, GLP-1 receptors play a significant role in brain functions.

Researchers mimicked the symptoms of Alzheimer's disease in an animal study by interfering with the brain's insulin signal. Our brains manufacture insulin, which is crucial for healthy brain signaling and whose disturbance can cause dementia.

Diabetes and AD are related because both conditions promoted the formation of brain plaques. Our brain gradually shuts down its insulin signaling as a result of the constant high levels of insulin that result from overindulging in sweets and wheat. According to a study, eating a diet high in fructose and low in omega-3 fatty acids decreases insulin's affinity for its receptor, resulting in chronic insulin resistance as shown by a decline in the phosphorylation of the insulin receptor and its downstream effector Akt in rats after just six weeks.

Both maternal and child malnutrition may have an effect on a kid's physical and mental health. Type 2 diabetes mellitus, hypertension, insulin resistance, and cardiovascular problems can all develop as an adult as a result. The growth and function of the brain as well as the CNS are both impacted by protein-energy deficiency. Early episodes of starvation may cause long-lasting alterations in the function of brain neural receptors, according to neuro-pharmacological research.

In a different investigation, it was discovered that Alzheimer's results in a decrease in the levels and activity of insulin-PI3-AKT signaling pathway components. It was proposed that this reduction in insulin-PI3-AKT signaling could cause the primary tau kinase, glycogen synthase kinase-3 beta, to become active. This could result in inappropriate tau hyperphosphorylation and abnormal neurofibrillary tangle development inside of the cell.

Prevention

Through diet

Without affecting the survival rate, nutritional supplementation may help AD patients live better lives and possibly postpone the onset of dementia [23]. It has been proven that eating things like fish, fruits, vegetables, nuts, and even Indian spices can cut your risk of AD by up to 45%. As mentioned in our assessment, fructose intake should be kept to under 25 g per day. Some studies indicate a reduction in Alzheimer's symptoms with a healthy level of magnesium in the brain. Because of its ability to strengthen the immune system and reduce inflammation, vitamin D also has a positive impact on AD. A diet high in omega-3 fatty acids and vitamin B12 should be consumed.

Polyunsaturated fatty acids (PUFAs) like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are known to be beneficial in the prevention/treatment of dementia and Alzheimer's disease, are more abundant in the blood when folic acid is present. Both EPA and DHA increase NO production, reduce the production of pro-inflammatory cytokines, and raise levels of the neurotransmitter acetylcholine in the brain, which is lowered in Alzheimer's disease.

An aberrant protein called beta-amyloid is also present in the plaques of arterial deposits. When the body is in "emergency mode," beta-amyloid emerges as a poisonous invader and causes inflammation as a result of the immune system's overreaction. If inflammation is the problem, the damage to the brain may be repaired by including natural anti-inflammatory foods like omega-3 fatty acids and antioxidants in the diet. Antioxidants including vitamin A, beta-carotene, vitamins C and E, etc. are shown to be deficient in AD patients; therefore, restoring their concentration to normal could be the key to curing the illness.

Through astrocytes

Astrocytes were injected into the hippocampus of AD mice in a study using cultured adult and neonatal mice. These astrocytes were discovered seven days later mostly in the vicinity of A deposits and absorb human A immunoreactive material in vivo. This result supports the notion that astrocytes function as active A-clearing cells in the brain, which may have significant ramifications for the next formulation of AD treatment regimens.

Through stem-cells

Without affecting A deposits, neural stem cell transplantation causes a significant increase in BDNF-mediated hippocampal synaptic density and corrects the spatial learning and memory deficits in AD animals. In the future, stem cell-based therapeutics to treat AD may be developed using a strategy that involves modulating neurotrophin levels, according to this study's findings [26].

When mesenchymal stem cells from human umbilical cord blood were injected into the hippocampus of AD mice, researchers discovered a decrease in neuronal death, which cured the host mice's memory problems.

The cholinergic blockade interferes with normal human cognitive function since the BFCNs are crucial for learning, memory, and attention, among other elements of cognitive function. Numerous investigations have revealed that the basal forebrain's cholinergic innervation has been severely damaged and that this has led to decreased cholinergic neurotransmission in AD patients' brains, even in those who have the disease at an early stage. Also, the temporal lobes, particularly the hippocampus, are where the AD brain is most severely afflicted. These results show that BFCN degradation is a major factor in the etiology of AD and the cognitive deficits that result from it, indicating that BFCNs may be the best type of donor cells for treating AD-related cognitive symptoms.

Because of the murky molecular underpinnings of the differentiation and development of BFCNs in vivo, the best method for directing the differentiation of pluripotent stem cells into BFCNs in vitro has not yet been identified. Numerous endogenous neurotrophic factors, including bone morphogenetic protein 9 (BMP9), brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and basic fibroblast growth factor (bFGF), have been shown to support cholinergic neurons' survival, growth, and differentiation as well as likely that of BFCNs in the brain.

Transplanted into the NBM of transgenic AD model mice, 5XFAD, and APP/PS1, human and mouse ESC-derived BFCN progenitors were specifically developed in vivo into mature and functioning cholinergic neurons. The basal forebrain cholinergic projection and migration patterns of these exogenous cholinergic neurons were typical, and they were morphologically and functionally incorporated into the endogenous projection system. Importantly, in the behavioral test, AD mice with transplanted BFCN progenitors showed better learning and referencing memory abilities, proving the viability of employing ESC-derived BFCNs for the creation of stem cell treatment for AD.

Using monoclonal antibodies against the cell surface markers, the researchers from StemCells Inc. were able to successfully separate a highly purified, expandable population of neural stem cells from human brain tissue. Then, the human neural stem cells were created in accordance with cGMP standards and given the name HuCNS-SC cells. The thorough preclinical research has demonstrated that these HuCNS-SC cells may live for an extended period of time without showing signs of tumor development or negative effects, and they can also engraft, migrate, and differentiate into neurons, astrocytes, and oligodendrocytes.

Induced pluripotent stem cells

All stem cells are not created equal. Any type of cell in the body can be created by some stem cells. These stem cells, also known as "pluripotent," are present in early embryos. For every type of cell in the body, they serve as the starting point. These pluripotent embryonic stem cells can be kept in reserve for many years in a lab because they can continue to divide and create additional stem cells. They may be the most beneficial kind of stem cells.

Induced pluripotent stem (IPS) cells are a type of stem cell that is currently being used in studies to examine Alzheimer's disease. These stem cells are created in a laboratory by "reprogramming" specialized cells, including skin cells. All of the various cell types in the body can be produced by the IPS cells that arise. They may thus serve as a source of cells that would otherwise be hard to find, such as the neurons in the brain.

Biomarkers

Future treatments would hopefully focus on the disease in its earlier stages before irreparable brain damage or mental decline happened if we could detect Alzheimer's before symptoms appeared. Currently, only clinical examinations can diagnose it, and post-mortem brain pathology can confirm the diagnosis. To enhance diagnosis and hasten the creation of novel treatments, verified biomarkers for Alzheimer's disease must be developed.

Approximately 2.5% of AD cases are genetically predisposed, while the bulk is sporadic (risk age > 60 years). A biomarker that may aid in early detection and distinguish AD from other types of dementia would be excellent.

The most widely used method of diagnosis uses ELISA to evaluate levels of beta-amyloid (1-42), total tau, and phosphor-tau-181 in cerebrospinal fluid. With a threshold of > 600 pg/ml, intra-neuronal inclusions of the microtubule-associated protein tau are much higher than in healthy individuals [25,31]. Tau is substantially hyperphosphorylated in AD (39 locations), which impairs axonal transport and causes dysfunction. With a cut-off of > 60 pg/ml, the detection of tau phosphorylated at position 181 is significantly increased in AD compared to controls [22]. Additionally, the processing of amyloidogenic pathways results in the production of the 42-amino-acid peptide known as A(1-42), which can aggregate in the brain under specific circumstances. This peptide is formed when extracellular A plaque, which is produced by processing amyloidogenic pathways, is deposited. With a cutoff of 500 pg/ml, the A is significantly lower in AD patients.

Future Aspects

Early detection is crucial for diseases like Alzheimer's in order to achieve effective treatment. In order to treat Alzheimer's disease, which is spreading at an alarming rate, it is crucial to use cutting-edge technologies. Numerous studies on biomarkers, proteomics, and genomes have been undertaken recently and are still ongoing. Despite these studies, there are still a number of obstacles to be overcome. Technology alone cannot combat the disease; instead, approaches and practices need to be standardized in order to preserve consistency and attain a respectable level of reliability.

Conclusion

We have discussed several justifications and potential treatment plans for AD in this review. According to numerous studies, the causal metabolic pathways for AD's neurodegenerative nature include extracellular amyloid plaques, intracellular neurofibrillary tangles, synaptic degeneration, and neuronal death. At any given age, genetics is responsible for around 70% of the risk of AD. The epsilon 4 allele of the gene for apolipoprotein E is the most prevalent genetic risk factor for AD (ApoE). A vitamin D-deficient diet, whose active form appears to influence nerve growth factors in addition to the genetic and molecular aspects, appears to be another cause of AD. Additionally, hyperglycemia is caused by a reduction in brain glucose metabolism in AD for three unidentified reasons.Finally, we'd want to draw the conclusion that stem cell therapy and biomarkers may be cutting-edge approaches to treating and detecting AD at an early stage.

References

1.Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, et al. (2013) The global prevalence of dementia: A systematic review and meta-analysis. Alzheimer’s Dement 9: 63.e2-75.e2.

2.Gilman S (2010) Oxford American handbook of neurology. Oxford University Press, Oxford, UK.

3.Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, et al. (2007) Prevalence of dementia in the United States: The aging, demographics, and memory study. Neuroepidemiology 29: 125-132.

4.Ott A, Breteler MM, van Harskamp F, Claus JJ, van der Cammen TJ, et al. (1995) Prevalence of Alzheimer’s disease and vascular dementia: Association with education. The Rotterdam study. BMJ 310: 970-973.

5.Querfurth HW, LaFerla FM (2010) Alzheimer's disease. N Engl J Med 362: 329-344.

6. Selkoe DJ (2002) Alzheimer's disease is a synaptic failure. Science 298: 789-791.

7.Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, et al. (2005) Correlations between apolipoprotein E epsilon4 gene dose and brain-imaging measurements of regional hypometabolism. Proc Natl Acad Sci U S A 102: 8299-8302.

8.Sommer I, Griebler U, Kien C, Auer S, Klerings I, et al. (2017) Vitamin D deficiency as a risk factor for dementia: A systematic review and meta-analysis. BMC Geriatr 17: 16.

9.Gezen-Ak D, Yilmazer S, Dursun E (2014) Why vitamin D in Alzheimer’s disease? The hypothesis. J Alzheimers Dis 40: 257-269.

10. Annweiler C, Montero-Odasso M, Hachinski V, Seshadri S, Bartha R, et al. (2013) Vitamin D concentration and lateral cerebral ventricle volume in older adults. Mol Nutr Food Res 57: 267-276.

11. Fernandes de Abreu DA, Eyles D, Féron F (2009) Vitamin D, a neuro-immunomodulator: Implications for neurodegenerative and autoimmune diseases. Psychoneuroendocrinology 34: S265-S277.

12. Masoumi A, Goldenson B, Ghirmai S, Avagyan H, Zaghi J, et al. (2009) 1alpha,25- dihydroxyvitamin D3 interacts with curcuminoids to stimulate amyloid-beta clearance by macrophages of Alzheimer’s disease patients. J Alzheimers Dis 17: 703-717.

13. Mizwicki MT, Menegaz D, Zhang J, Barrientos-Durán A, Tse S, et al. (2012) Genomic and non-genomicsignaling induced by 1a, 25 (OH) 2-vitamins D3 promotes the recovery of amyloid-b phagocytosis by Alzheimer’s disease macrophages. J Alzheimers Dis 29: 51-62.

14. Littlejohns TJ, Henley WE, Lang IA, Annweiler C, Beauchet O, et al. (2014) Vitamin D and the risk of dementia and Alzheimer’s disease. Neurology 83: 920-928.

15. (2015) Alzheimer's disease genetics fact sheet. National Institute of Aging.
16. Rygiel K (2016) Novel strategies for Alzheimer's disease treatment: An overview of anti-amyloid beta monoclonal antibodies. Indian J Pharmacol 48: 629-636.
17. Hardy J, De Strooper B (2017) Alzheimer's disease: Where next for anti-amyloid therapies? Brain 140: 853-855.
18. Abbas T, Faivre E, Holscher C (2009) Impairment of synaptic plasticity and memory formation in GLP-1 receptor KO mice: Interaction between type 2 diabetes and Alzheimer's disease. Behav Brain Res 205: 265-271.
19.Agrawal R, Gomez-Pinilla F (2012) Metabolic syndrome in the brain: Deficiency in omega-3 fatty acid exacerbates dysfunctions in insulin receptor signaling and cognition. J Physiol 590: 2485-2499.
20.Biessels GJ, Despa F (2018) Cognitive decline and dementia in diabetes mellitus: Mechanisms and clinical implications. Nat Rev Endocrinol 14: 591-604.
21.Das UN (2008) Perinatal and childhood nutrition and its impact on cognitive function and adult diseases 19.
22. Liu Y, Liu F, Grundke-Iqbal I, Iqbal K, Gong CX (2011) Deficient brain insulin signaling pathway in Alzheimer's disease and diabetes. J Pathol 225: 54-62.
23. Navrátilová M, Jarkovský J, Cešková E, Leonard B, Sobotka L (2007) Alzheimer disease: Malnutrition and nutritional support. Clinical and Experimental Pharmacology and Physiology 34: S11-S13.
24. Nield D (2016) Controlling brain inflammation could slow down the progress of Alzheimer's, scientists find. Science Alert.
25. Pihlaja R, Koistinaho J, Malm T, Sikkila H, Vainio S, et al. (2008) Transplanted astrocytes internalize deposited beta-amyloid peptides in a transgenic mouse model of Alzheimer's disease. Glia 56: 154-163.
26. Blurton-Jones M, Kitazawa M, Martinez-Coria H, Castello NA, Muller FJ, et al. (2009) Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer's disease. Proc Natl Acad Sci U S A 106: 13594-13599.
27. Drachman DA, Leavitt J (1974) Human memory and the cholinergic system. A relationship to aging? Arch Neurol 30: 113-121.
28. Drachman DA, Sahakian BJ (1980) Memory and cognitive function in the elderly. A preliminary trial of physostigmine. Arch Neurol 37: 674-675.
29. Knusel B, Michel PP, Schwaber JS, Hefti F (1990) Selective and nonselective stimulation of central cholinergic and dopaminergic development in vitro by nerve growth factor, basic fibroblast growth factor, epidermal growth factor, insulin and the insulin-like growth factors I and II. J Neurosci 10: 558-570.
30. Knusel B, Winslow JW, Rosenthal A, Burton LE, Seid DP, et al. (1991) Promotion of central cholinergic and dopaminergic neuron differentiation by brain-derived neurotrophic factor but not neurotrophin 3. Proc Natl Acad Sci USA 88: 961-965.
31. (2018) Alzheimer's disease: how could stem cells help? EuroStemcell.
32. Humpel C (2011) Identifying and validating biomarkers for Alzheimer's disease. Trends Biotechnol 29: 26-32.