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A BRIEF REVIEW ON ALZHEIMER'S DISEASE

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Abstract:

Alzheimer's disease is one of the most prevalent dementia that affects nerve cells throughout the brain. 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. Furthermore, using induced pluripotent stemm cells has shown to be a successful method of treating this illness. The goal of this review is to emphasise regarding the stem cell and disease pathogenesis the illness' therapy.

Key words: *Amyloidal protein, dementia, and pluripotent stem cells*

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INTRODUCTION:

The world's population is ageing 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[1]. 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[2]. Memory lapses or difficulty finding the correct phrases are frequently the first indicators of Alzheimer's disease. Language, thinking, decision-making, visuo-spatial 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[3]. 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[4,5]. 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[6].

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 several theories proposed regarding how AD develops, some of which we will discuss in more detail later in this article.

The dominant autosomal mutation in the amyloid precursor protein (APP) gene on chromosome 21 or one of the presenilin genes on chromosomes 1 and 14 appears to be the genetic aetiology of Alzheimer's disease. Additionally, the chance of getting early-onset AD is higher among people who have Down syndrome (trisomy 21). The genetics of AD are more complex and poorly understood, despite this. It is generally known that the epsilon four allele of the apolipoprotein E (APOE) gene, which is located on chromosome 19, increases the risk of sporadic AD[7].

Lower levels of vitamin D (1,25-dihydroxyvitamin D3) were found to be linked to all forms of dementia and Alzheimer's disease, according to studies[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[10,11]. Vitamin D stimulates macrophages in in vitro settings, which improves the phagocytic clearance of amyloid plaques[12,13].

According to several studies, vitamin D may act as a neuroprotectant, and 50 nmol/
L is adequate to reduce the risk of dementia. This knowledge might be helpful in streamlining and lowering the cost of randomised controlled studies examining whether vitamin D supplementation can help older persons postpone or prevent the onset of dementia and AD[14].

Changes in brain

AD cause tissue loss and nerve cell death, and over time, the brain's size decreases, impacting all of the brain's activities. Loss of brain cells in the cortical area harms the brain's capacity for planning, remembering, and thinking. 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 build up of tangles and plaques, which may be the cause of these cell loss. These plaques obstruct cell-to-cell communication and stir up immune cells that attack damaged cells and create inflammation. Tau proteins degrade form tangled strands, or tangles, which block the movement of nutrients and other essential supplies through the cells, resulting in cell death.

CAUSES OF THE DISEASE

Alzheimer's disease is the primary cause of 60% to 70% of dementia cases. It is a chronic neurodegenerative disease that frequently gets worse over time after a mild initial onset. According to one theory, plaques impair proper communication between brain nerve cells. Tangles may interfere with the cells' capacity to take in the nutrients they require. It seems reasonable that more and more neurons—nerve cells that are a component of the nervous system—will go as the Alzheimer's disease worsens.

1. Age: Old age is the single most significant risk factor for the development of Alzheimer's disease.Your likelihood of contracting the illness doubles every five years once you become 65.

2. Down syndrome: Alzheimer's disease is more likely to affect people with Down syndrome. This isbecause the genetic fault that causes Down's syndrome can also cause amyloid plaques to build up in the brain over time, which can lead to Alzheimer's disease in some people.
3. Genetics: Twin and family studies have been analysed, and the results show that between 49% and79% of people with Alzheimer's disease and its memory-related symptoms are inherited from their parents. Familial varieties of autosomal (not sex-linked) dominant inheritance account for roughly 0.1% of instances with onset before the age of 65. This kind of Alzheimer's disease is referred to as early onset familial Alzheimer's disease. Even though AD is rare, only a small percentage of people develop it before the age of 65. Three genes—presenilin 1 (PSEN1), presenilin 2 (PSEN2), and amyloid to precursor protein (APP) have been linked to the onset of AD as a result of mutations in them.

Late-onset Alzheimer's gene

Apolipoprotein E is a gene related with 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[15]. 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.

Apolipoprotein E (APOE)

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 characterised 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- from A. The APP gene can be found in protective versions. A mutation in them results in the generation of too much of a

Amyloid-beta peptide is a harmful protein fragment. 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 leads to the death of brain cells and the onset of Alzheimer's disease symptoms[16].

Diabetes & Alzheimer's

We are aware that some diseases, like diabetes, are linked to our diet, but researchers have discovered a strong 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 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[17].

It has been demonstrated in earlier research that the rise in glucagon-like peptide 1 (GLP-1) contributes to the normalisation of insulin signalling 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[18].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 signalling and whose disturbance can cause dementia[19].

Diabetes and AD are related because both conditions promoted the formation of brain plaques[19]. Our brain gradually shuts down its insulin signalling 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[20].

Children's mental and physical health may be impacted by maternal malnutrition and childhood undernutrition. In maturity, it may result in the onset of type 2 diabetes mellitus, hypertension, insulin resistance, and cardiovascular problems. Malnutrition

in terms of protein has an impact on both CNS and brain development and function. According to neuro-pharmacological research, early episodes of starvation may cause long-lasting modifications in the way that the brain's neural receptors work[21].

The levels and activity of the insulin-PI3-AKT signalling pathway's constituents were observed to decline in Alzheimer's disease in a separate investigation. It was proposed that the primary tau kinase, glycogen synthase kinase-3 beta, would become activated as a result of this reduction in insulin-PI3-AKT signalling. The result could be the creation of intracellular neurofibrillary tangles as a result of aberrant tau hyperphosphorylation[22].

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.

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), two -3 PUFAs (polyunsaturated fatty acids) that are known to be beneficial in the prevention and treatment of dementia and Alzheimer's disease, are increased in concentrations when folic acid is present. The production of pro-inflammatory cytokines is suppressed, NO production is increased, and the neurotransmitter acetylcholine, whose levels are decreased in Alzheimer's disease, is increased in the brain. All of these effects are achieved by EPA and DHA.

The plaques of arterial deposits also contain a rogue protein known as beta amyloid.

Beta-amyloid appears as a dangerous invader and produces inflammation when the body is in "emergency mode" as a result of the immune system's reactivity. If inflammation is the issue, then adding natural anti-inflammatory foods like omega-3 fatty acids and antioxidants to the diet may help to repair the damage done to the brain. Vitamin A, beta-carotene, vitamins C and E, and other antioxidants have been found to be low in AD patients; therefore, getting their concentration back to normal may be the key to healing the condition[20,24].

USING ASTROCYTES

In a study using cultured adult and newborn mice, astrocytes were injected into AD mice's hippocampus. These astrocytes absorb human A immuno-reactive material in vivo and are primarily observed near A deposits seven days later. This study confirms the existence of active A-clearing astrocytes in the brain, which may have significant ramifications for the future design of AD treatment regimens[25].

BY MEANS OF STEM CELLS

While leaving A deposits unaffected, the neural stem cell transplantation causes a significant increase in BDNF-mediated hippocampal synaptic density and improves the spatial learning and memory deficits in AD animals. According to this study, neurotrophin levels could be modulated as a potential strategy for future stem cell-based therapeutics to treat AD[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. Additionally, the hippocampus in the temporal lobes is the region of the AD brain that is most severely affected. These findings suggest that BFCN degradation is a significant contributor to both the genesis of AD and its associated cognitive abnormalities, suggesting that BFCNs may be the optimal donor cells for treating AD-related cognitive symptoms[27,28].

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[29,30].

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 morphologically and functionally incorporated into the endogenous projection system. Importantly, in the behavioural 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.

Utilizing monoclonal antibodies against the cell surface antigens, the researchers from StemCells Inc. were able to successfully separate a highly purified, expandable population of neural stem cells from human brain tissue. Following that, HuCNS-SC cells were created using human neural stem cells that had been processed according to strict guidelines and cGMP standards. These HuCNS-SC cells may engraft, migrate, and develop into neurons, astrocytes, and oligodendrocytes over the long term, according to the meticulous preclinical investigations, which also demonstrate that there is no sign of tumour formation or negative effects.

CELLS WITH INDUCED PLURIPOTENCY

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.

Alzheimer's disease is currently being researched utilising induced pluripotent stem (IPS) cells, a type of stem cell. These laboratory-produced stem cells are created by "reprogramming" specific cells, including skin cells. The IPS cells that are created can create any form of cell in the body. This suggests that they might serve as a source of cells that are typically challenging to obtain, like the neurons found in the brain[31].

Neurons that exhibit some of the hallmarks of Alzheimer's illness have recently been grown in the laboratory using IPS technology by scientists. In order to create IPS cells, the researchers used skin cells from Alzheimer's sufferers. They next devised a strategy for producing neurons in a dish using these IPS cells. The beta amyloid protein is released by the lab-grown neurons, causing plaques to form in the patients' brains. This provides an excellent opportunity for researchers to investigate brain neurons that are comparable to those affected by the illness, e.g. to better understand how and why protein plaques and tangles form, and to look for and test potential medications[31].

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 are 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 (142), total tau, and phosphor-tau-181 in cerebrospinal fluid.

The most widely used diagnostic approach is the ELISA, which measures beta-amyloid (1–42), total tau, and phosphor-tau-181 in cerebral fluid. When compared to healthy individuals, intra-neuronal inclusions of the microtubule related protein tau are much higher with a threshold of > 600 pg/ml[25,31]. Tau is considerably hyperphosphorylated (39 potential sites) in AD, which causes a lack of function and dysfunctional axonal transport. With a cut-off of > 60 pg/ml, tau phosphorylation at position 181 can be detected substantially more easily in AD patients than in controls[22]. In addition, processing of the 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 produced as extracellular A plaque, which is deposition of extracellular A plaque, which is cleaved from amyloid precursor protein (APP) by secretases. With a cutoff of 500 pg/ml, there is a relative drop in the A in AD patients[25,31,32].

Upcoming aspects

Early diagnosis is essential for Alzheimer's disease and other conditions like it. It is crucial to use cutting-

edge technologies to fight Alzheimer's disease because the disease is spreading at an alarming rate. Numerous studies on biomarkers, proteomics, and genomes have recently been undertaken and are continuously being conducted. There are still a number of obstacles to be overcome in spite of these studies. In order to maintain consistency and achieve a significant level of reliability, standardisation of methods and techniques is crucial in the fight against the disease. The availability of technology alone cannot do this.

CONCLUSION:

We have discussed several justifications and potential AD treatment plans in this review. Numerous investigations have demonstrated that the causal metabolic pathways include extracellular amyloid plaques, intracellular neurofibrillary tangles, synaptic degeneration, and neuronal death which finally results in AD as a neurodegenerative condition. At any given age, genetics account for around 70% of the risk of AD. The epsilon 4 allele of the apolipoprotein E gene is the most prevalent genetic risk factor for AD (ApoE). In addition to the genetic and molecular factors, vitamin D deficiency diet, whose active form regulates nerve growth factor appears to be another cause of AD. Additionally, diabetes is caused by a reduction in brain glucose metabolism in AD for three reasons that are currently unknown. We would like to come to the conclusion that stem cell therapy and biomarkers may be new methods for treating and diagnosing AD early on.

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