Cardiovascular health influences Alzheimer's disease risk

Abstract

Alzheimer's Disease (AD) is a common form of dementia due to the death of brain cells, ultimately leading to memory loss. It accounts for about 60 to 80% of cases in the United States. Research suggests that AD has a large genetic component and usually affects people over the age of 65. However, environmental (modifiable) risk factors can also affect the risk of AD. Recent research has called attention to how type II diabetes and coronary heart disease surgeries directly relate to AD. This review paper will discuss the different risk factors for AD, including coronary heart disease, and strategies to minimize disease risk. Its goal is to raise awareness of the risks that can cause a lethal disease that has no proper cure and help bring attention to how genes, environmental factors and genes by environmental factors can increase the risk of AD.

Introduction

Alzheimer's disease (AD), also known as *senile dementia*, is a neurodegenerative disorder with a strong genetic component that is found predominantly in the older population, affecting people over the age of 65 (**ncbi.nlm.nih.gov , 2000**). First defined by Alois Alzheimer in 1906, patients suffering from AD have a disruption in their brain cell-to-cell communication which results in the death of cells and loss of brain function (**nia.nih.gov**).

AD was first considered a rare condition but gradually started being studied as one of the consequences of ageing. Due to this belief and the attached stigma, the research on AD (causes and treatments) was aggressively delayed (**ncbi.nlm.nih.gov , 2000**). More recently, AD patients over the age of 65 are estimated to make up about 16% of the world's population by the US National Institute on Aging (**alz.org , 2021**). Consequently, there has been a shift in research focus towards studying the diagnosis and treatments for this progressive neurological disorder (**mayoclinic.org**).

Hallmarks of Alzheimer's Disease

The two main hallmarks present in defining AD are amyloid-beta (Aβ) plaque and neurofibrillary tangles (**ncbi.nlm.nih.gov , 2019**). The Aβ plaque is formed from the breaking down of different molecular substances, including a large protein called "amyloid precursor protein" (APP). Aβ plaques, such as the amyloid-beta 42, group together to form plaque and collect between the neurons. This perturbs cell-to-cell communication by blocking the synapse between the two neurons, resulting in the disruption of the cell function (**nia.nih.gov**).

Neurofibrillary tangles are a result of the hyperphosphorylation of the protein know as tau. In normal brains, tau protein functions to bind to and stabilize the microtubules and stabilizes them. However, brains affected with AD tau proteins aggregate with one another instead of binding to microtubules. Consequently, the tau aggregates gather to form tangles inside neurons. These tangles harm the synaptic communication between neurons by blocking their transport system (**nia.nih.gov**).

Genetic risk factors of Alzheimer's Disease

A large number of genetic mutations and variants have been associated with AD. Early-onset AD is caused by the inherited mutation in one of the three genes: 'Amyloid precursor protein' (APP) on chromosome 21, 'Presenilin 1' (PSEN 1) on chromosome 14 and 'Presenilin 2' (PSEN 2) on chromosome 1. Even the smallest change in these genes may result in the production of abnormal proteins and play a role in the breakdown of APP, forming amyloid-beta plaques (**nia.nih.gov**). However, early-onset AD only accounts for 10% of all AD cases.

Although the majority of AD cases are late-onset, our understanding of this disease category is much less certain. Although experts haven't found out the specific gene responsible for late-onset AD, research suggests that the APOE gene on chromosome 19 tends to increase a person's risk. The APOE gene is responsible for making the protein that carries the cholesterol in the bloodstream (**nia.nih.gov**). However, genetics can only explain about 20% of all late-onset AD cases. This suggests that there are remaining non-heritable risk factors, such as medical history and environmental conditions that contribute to the disease.

There are many different alleles of APOE that an individual can inherit from each biological parent. APOE ε2 is the rarest allele and provides protection against AD. APOE ε3 is the most common allele is holds a

neutral position, neither increasing nor decreasing the risk of AD. APOE ε4 increases risk of a person developing AD (**ncbi.nlm.nih.gov , 2019**). Almost 25% of people carry one copy of the APOE ε4 allele, and about 3% carry two copies. Although, it is not always necessary that the inheritance of the APOE ε4 allele will cause AD. Studies now suggest that the rare variations of the APOE allele may provide protection against AD but more research is needed to know for sure how these alleles delay the disease onset or lower the risk (**nia.nih.gov**).

Environmental risk factors of Alzheimer's Disease

The substantial amount of disease risk that cannot be attributed to genetics alone, suggests the presence of other, non-genetic risk factors. These conditions include the individual's lifestyle factors - like exercise, diet, tobacco and alcohol consumption – and the environment that individual is exposed to: air pollution and pesticide exposure (**ncbi.nlm.nih.gov , 2019**).

Exposure to *heavy metals and pesticides* have been documented to show a positive link to the risk of acquiring Alzheimer's. The long-term contact with lead has shown to progressively decline mental functions and reduce memory. It could be due to the accumulation and then cause damage to one's nervous system, slowing down its function. *Polluted air* consists of a mixture of organic and non-organic compounds, metals and toxic gases and is associated with a greater risk of AD (**brainblogger.com, 2017**).

Unhealthy lifestyle and the *lack of physical activity* can lead to the development of the Alzheimer's Disease. Studies have shown that the chance of having AD greatly increases as much as 6 times in obese people who have a high blood pressure and cholesterol level (**brainblogger.com , 2017**). Maintaining a healthy diet and avoiding smoking and drinking can protect against any cardiovascular disease which directly correlates to AD (**ncbi.nlm.nih.gov , 2019**). I think regular exercise has been shown to promote neurogenesis, leading to an automatic decrease in the risk of acquiring AD.

Cardiovascular Risk Factors

Risk factors for cardiovascular diseases are very common in the elderly and there have been many studies that draw associations between these risks and the onset of AD and the cardiovascular diseases (**pubmed.ncbi.nlm.nih.gov, 2004**). Cardiovascular diseases such as diabetes, coronary heart disease, and hyperinsulinemia have shown a positive relationship with the risk of developing AD.

Type II Diabetes

Type II diabetes is characterized by the inability to produce or respond to insulin properly. Insulin is a hormone generally produced by the β-cells in the pancreas and helps control the blood sugar levels by converting excess glucose to glycogen, which is stored in our body. An individual with type II diabetes is unable to convert excess glucose to glycogen, resulting in *hyperglycaemia* (high sugar blood levels). Over time, with the decline of the β-cell function, hyperglycaemia results in the development of type II diabetes mellitus (T2DM) (**ncbi.nlm.nih.gov, 2018**).

Research has shown a correlation between T2DM and AD (**ncbi.nlm.nih.gov, 2019**). In 2021, approximately 531 million adults were living with diabetes and it is predicted that by the year 2045, the number of people affected with diabetes will likely exceed about 783 million (**idf.org, 2021**). Due to the suspected link between cardiovascular health and brain function, several studies have investigated the underlying links between T2DM and AD (**ncbi.nlm.nih.gov, 2019**).

Ott et al. investigated the link between type 2 diabetes and AD in a population of 6370 elderly subjects in Rotterdam, Netherlands. The subjects were examined for the presence of T2DM and the non-demented subjects were followed-up for about 2 years. They found out that about 126 subjects were affected by dementia, out of which 89 had Alzheimer's Disease. It was concluded that diabetes (specifically, T2DM) almost doubled the risk of AD (**pubmed.ncbi.nlm.nih.gov, 1999**). Several other studies in The Cade County and Taiwan have also reported similar findings. A few studies such as ones conducted by Shinohara and Sato have also suggested that the correlation between diabetes and AD is bi-directional (diabetes can increase risk for AD but AD can also increase risk of Diabetes (**ncbi.nlm.nih.gov, 2019**).

Bypass Surgeries

Heart surgeries for cardiovascular diseases are also linked with AD. Heart bypass surgeries (or coronary artery bypass graft [**CABG**] surgeries) are used to improve the blood flow to one's heart after the arteries have been blocked due to the coronary heart disease. Here, blood vessels are usually taken from another

area of the body and used as a substitute for the blocked artery and continue to supply oxygenated blood to the heart (**healthline.com, 2019**). There is an alternative to surgically improving one's blood flow. This surgery is known as angioplasty wherein the blocked artery is widened so that oxygenated blood can get through to the heart.

Though bypass surgeries help relieve the symptoms of coronary heart disease, studies suggest an increased memory loss and other damages to brain function following the surgery. A study conducted in 1996 and 1997 suggests that patients undergoing through the bypass surgeries may have a greater risk of developing AD (**webmd.com, 2004**).

Benjamin Wolozin conducted an experiment to explore the correlation between bypass surgery and angioplasty and AD. He and his fellow researchers compared 5216 people who underwent CABG and about 3954 people who underwent percutaneous transluminal coronary angioplasty (**PTCA**) over the course of five years. They noted that about 78 patients who underwent bypass surgery and 41 patients who underwent angioplasty developed the Alzheimer's disease (**sciencedaily.com, 2005**).The study concluded that the risk for Alzheimer's disease is 70% higher in the people who undergo bypass surgery to treat coronary heart disease instead of angioplasty (**webmd.com, 2004**).

To explore the link between bypass surgery and AD, different concentrations of amyloid- β peptide and tau were measured in the cerebro-spinal fluid before and after the patient underwent bypass surgery, along with the evaluation of cognitive functions with the use of psychometric tests. Levels of S100 β present in the cerebro-spinal fluid, which serves as an indicator of cerebral injury, were also assessed (with the help of immune-assays) before and after the patient underwent bypass surgery, along with the evaluation of cognitive functions with the use of psychometric tests. The researchers observed that there was a severe rise in the level of S100β one week after the surgery (S100β serves as an indicator of cerebral injury). They also noted that the level of amyloid-β peptide decreased significantly and the concentration of tau increased over the six months after surgery. These findings suggested that the post-surgical cognitive impairment connected to changes in biomarkers are similar to that seen in AD and a link is proposed (**pubmed.ncbi.nlm.nih.gov, 2010**).

Plausible mechanisms for Alzheimer's Disease and Cardiovascular diseases

Genes

A research report published by the Università of Bologna suggests that Alzheimer's Disease and heart attacks contain similar genetic basis. In 2010, Federico Licastro, an immunologist at the Università of Bologna, conducted an experiment to explore the genetic factors that suggest a common risk to both diseases. The researchers examined the DNA of 1800 people out of which 280 had suffered from a heart attack, 257 had the Alzheimer's Disease and 1307 were healthy patients (the control group). (**sciencedaily.com, 2010**). Individuals were categories into six groups based on their risk levels. Groups 1, 2 and 3 contained the patients with the lowest risk and groups 4, 5 and 6 contained patients with the highest risk of suffering a heart attack. Groups 4 and 6 were the focal point of the experiment as they had a high risk of heart attack and AD suffrage (group 4: under the age of 40 and group 6: between the ages of 40 and 54). They found some overlap between the congenital risks of suffering a heart attack and being affected by Alzheimer's, supporting the claim of a link between heart attacks and the risk of AD. This overlap was seen in 30% of the patients suffering from a heart attack and 40% of the patients with AD and was mostly seen in groups 4 and 6 (**sciencedaily.com, 2010**).

Environment

Smoking

Smoking tobacco is a very common activity around the world. A study conducted in 2014 by Durazzo and Mattson looked at the link between cigarette smoking and the link between AD. They obtained previously published data and original data comparing *in-vivo* amyloid imaging from smoking and non-smoking elders. Smoking was associated with an increased risk of AD, as suggested by smoking-related cerebral oxidative stress, which can potentially promote AD pathophysiology (**ncbi.nlm.nih.gov, 2015**)

Smoking also results in the increase of levels of homocysteine in the blood. Homocysteine is toxic to the arteries and an increase in them has shown a positive correlation between them and AD. Smoking further causes a pique in oxidative stress, resulting in the death of brain cells. Since smoking is very addictive, smokers also have a greater chance of having the APOE4 gene as smoking repeatedly is lethal. (**brightfocus.org, 2021**).

Alcohol

An excess amount of alcohol may lead to brain damage, increasing the risk of developing AD. Reviews conducted by Alzheimer's Disease International found that individuals who drank a large quantity of alcohol in short amount of time were more likely to develop Alzheimer's disease that those who had a moderate alcohol consumption (**alzheimers.org.uk, 2019**).

Another recent study examined more than thirty million Europeans to investigate the major factors affecting AD. The study concluded that alcohol was one of the largest non-genetic risk factor for the Alzheimer's disease. They found that the individuals who regularly over-consumed alcohol we more likely to develop AD than the ones who drank rarely/did not drink at all (**alzheimersorganization.org**).

Large amounts of alcohol consumptions are more likely to result in a decrease in the volume of brain's white matter, which helps transmit signals from on brain region to another. This ultimately results in issues with brain functions (**alzheimers.org.uk, 2019**).

Pesticides

A lot of evidence suggests that long-term exposure to pesticides may cause toxicity on the nervous system and result in an increase in the risk of Alzheimer's disease (**ncbi.nlm.nih.gov, 2016**).

A study was conducted in 2009 to investigate the link between pesticides and AD in about 4000 subjects (65 or older). At the start of the study, they were asked if they had been exposed to pesticides prior to the experiment and if yes, which type of pesticide and for how long. About 750 subjects reported being exposed to pesticides. A standard test (measures the total cognitive functioning) was given at the outset and two other times over a six to a seven-year period. It was seen that about 53% of the people who worked with pesticides had an increase in the risk of AD (**webmd.com, 2009**).

Scientists have found that pesticides contain organophosphates (OPs) which produce long-lasting decrements in neurological and cognitive function (**ucl.ac.uk, 2012**). Exposure to pesticides like DDT promotes the creation of the amyloid beta plaques, resulting in clogs in the neurons of individuals and may further increase the risk in the people who already have a genetic predisposition toward developing AD (**webmd.com, 2014**)

Genes x Environment

Not all individuals with genetic risks for AD end up developing the disease. There are some cases where people with the APOE4 gene make it till the age of 100 or older without developing AD whereas there are some cases where people who do not have the APOE4 gene still end up getting affected by AD. These data suggest additional risks, such as environmental risks, may interact with susceptibility genes to contribute to the risk of AD (**news.usc.edu, 2019)**.

It is plausible that environmental mutagens impact the stability of DNA, and affect AD risk. Genetic mutations can result in the production of abnormal protein that are commonly associated with AD (**nia.nih.gov, 2019**). The Honolulu-Asia aging study looked into the relationship between smoking and dementia in Japanese men. The researchers reported that smoking (mainly tobacco), which is classified as a mutagen, increased the risk of AD as it modified the APOE gene. A relationship between the APOE4 gene and alcohol consumption can also be seen in some groups in the Washington Heights-Inwood Columbia Aging Study (**ncbi.nlm.nih.gov, 2019**). Interestingly, smoking and drinking also affects one's heart vessels and leads to cardiovascular disease (CVD) which further increases the risk of AD (**fda.gov, 2021**). Pesticide DDT exposure and air pollution, notably PM exposure, have also been recognised as possible risk factors in Alzheimer's disease (**ncbi.nlm.nih.gov, 2019**).

Conclusion

The purpose of this review was to explore the relationship between cardiovascular risks and the Alzheimer's Disease. We provide strong evidence that cardiovascular risk factors, such as Diabetes and Coronary Heart Diseases, genes, and environmental factors, such as alcohol and pollution, can contribute to Alzheimer's disease risk. Thus, future research studies investigating the biological mechanisms that link bypass surgeries and other cardiovascular diseases with Alzheimer's are warranted.

To reduce the risk of AD, individuals must live a healthy lifestyle to prevent the onset of cardiovascular diseases. Healthy lifestyles may include a good diet (constituting of foods from all fats, proteins,

carbohydrates, vitamins and minerals in an equal amount), regular exercise and limitation of alcohol and cigarettes (**medlineplus.gov, 2015**).

Although Alzheimer's disease is one of the most ruthless diseases in the world and there is no cure proper cure available treat this lethal dementia, greater understanding of Alzheimer's disease risk can help prevent disease risk.

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