Review Article ISSN (O):2395-2822; ISSN (P):2395-2814

Decoding the Molecular Ties between Cerebrovascular Disease and Alzheimer's

Simran Agarwal[1], Mir Saleem[2]
[1]Nova Southeastern University, Florida, USA.

Received: June 2020
Accepted: June 2020

ABSTRACT

Alzheimer's disease (AD), is a progressive disease in which a patient becomes senile, unable to recall memories or perform important mental functions. Cerebrovascular Disease (CVD) results in damage in the brain due to a shortness of blood supply. Usually, the shortness is due to a block in major blood vessels. Most of the time, medical doctors promote similar lifestyle changes to patients due to the risk factors associated with both of these diseases. The purpose of this literature review is to understand mechanistic ties between the incidences of AD and CVD. Firstly, this paper analyzes the correct medical terminology between AD, CVD, and vascular dementia. Both CVD and AD are known to cause dementia. Some newly found causes of these diseases are analyzed. Some studies stress that depression can cause the onset of AD, but CVD can cause the onset of depression. Molecular markers are also analyzed. Recent discoveries have also suggested that non-insulin dependent diabetes mellitus is a risk factor of vascular disease. As a result, not only should healthcare providers emphasize the risk associated with age, but healthy eating a strict diet with iron rich foods and physical activity should be among recommendations that make up a lower risk of patients acquiring AD, CVD, and other types of dementias.

Keywords: Alzheimer's disease, Cerebrovascular Disease.

INTRODUCTION

Alzheimer's Disease (AD) can be characterized as a progressive and a chronic neurodegenerative disorder that affects the central nervous system. This diagnosis is known to be one of the leading neurodegenerative cause of dementia and is the most common form.[1] AD can lead to the impairment of memory, language, and thought. With increasing age, there is increasing prevalence of AD.[2] Cerebrovascular Disease (CVD), results in damage of the brain due to an insufficient supply and flow of blood. The brain can be permanently or temporarily delayed due to ischemia or bleeding in one or more cerebral vessels. Some classified symptoms of a cerebrovascular disease incidence include speech difficulties, numbness or drooping of one side of the face, and muscle weakness. Scientific literature, recent case studies, and epidemiological data are studied to explore the significance and association between Cerebrovascular disease and Alzheimer's disease. Prevention methods have also been discussed.

Alzheimer's Disease (AD):

Alzheimer's Disease (AD) is characterized by two major neural structures that cause distinctive damage: neuritic (senile) plaques and neurofibrillary tangles.[3] This includes the presence of Beta-amyloid within the plaques, tau protein within the tangles, all combined with neuronal loss. These extracellular protein deposits spread to a variety of structures within the brain. This disease is associated with aging and symptoms typically begin with the loss of forming memories and recalling events. Forming memories is facilitated by the hippocampus and surrounding areas, and research shows that this structure is one of the first to be affected as prognosis of the disease is progressed. In a patient with AD, the overall brain structure compared to a healthy brain, is severely shriveled due to the increased loss of volume due to cell death.

With AD comes many various types of vascular pathology which shapes the aged human brain. These include: Cerebral amyloid angiopathy (CAA), Cerebral atherosclerosis, Small Vessel Disease (SVD) or microvascular degeneration, Blood-brain barrier (BBB) dysfunction causing white matter lesions (WML's), microinfarctions, and microbleeds.[4] All of these come with the consequence of damaging cerebral vessels eventually leading to neuronal injury and cognitive impairment. Time of occurrence for symptoms to show vary from patient to patient, with most of the patients being elderly. Some of these key events include: severe cognitive impairment, the inability to dress, eat, and wash, institutionalization, and death.[5] For many years it is assumed that the pathogenesis of Alzheimer's is related to the Amyloid-beta peptide (Aβ).[6] This peptide is produced by the cleavage of APP by β- and γ-secretases in the endoplasmic reticulum, trans-Golgi and endosomal-lysosomal systems, and via exocytosis is brought

Name & Address of Corresponding Author
Simran Agarwal, MA
Nova Southeastern University, Florida.
USA.

within the extracellular space where it binds to receptors. Studying this peptide is important to understand the severity of AD and dementia and the presence of various other peptides.[6] The Amyloid Cascade Hypothesis states the increase of these peptides causes the cascade, resulting in synaptic dysfunction and memory loss paired with damage to brain structures. New research published from in the Neuroscience Forefront Review suggests that Alzheimer's Disease pathogenies may be a negative feedback loop between Aβ and specific receptors, including the alpha7 nicotinic acetylcholine receptors (α7-nAchRs).[6] This theory presents that a buildup of Aβ peptides results in decreased function of these receptors, which essentially leads to memory loss and dysfunction of synapses. Overtime, this study explains that a buildup of this receptor will lead to abnormal protein levels, and essentially, "cellular exhaustion" away from normal homeostasis.[6]

Melatonin hormone levels are consistent within the body to regulate an internal circadian rhythm.[7] This hormone is controlled in a similar fashion as N-acetyltransferase within the suprachiasmatic nucleus (SCN). Patients with Alzheimer's show a decreased volume and total cell number of SCN, which can be related to the disorientation of time, sleep disorders, delirium, and difficulty with regulating the body's natural alarm clock.[7] A recent study concluded that patients show a rate of increase up to 36.4%, in which these individuals show no melatonin rhythm and Alzheimer's disease.[7]

Until the 1970s, dementia caused by AD was thought to be untreatable and not much research was done.[8] This posed a threat to the diagnoses and management of Alzheimer's. Ethical issues hindered research due to principles of non-maleficence and beneficence. The use of drugs to modify disease progression presents these issues. Today, drugs that target symptoms can be administered orally or trans-dermally, and further research will hopefully provide for disease-modifying drugs that targets the early stages of AD.[9]

Cerebrovascular Disease:

Cerebrovascular Disease (CVD), results in abnormal blood flow to the brain. Often, patients of CVD have experienced either a stroke, carotid stenosis, vertebral stenosis and intracranial stenosis, aneurysms, and vascular malformations. With stroke being the third leading cause of death, it is very crucial to determine the causes and effects associated with CVD in order to prevent further damage. Often, CVD can result in either permanent or temporary damage. Majority of the cerebrovascular problems, such as CVD, can be detected through the following tests: angiography, carotid ultrasound, computed technology (CT) scan, Doppler ultrasound, electroencephalogram (ECG), lumbar puncture, magnetic resonance imaging (MRI), and magnetic resonance angiogram (MRA).

According to the Ad Hoc Committee for the Classification and Outline of Cerebrovascular Disease most common after stroke symptoms include: weakness, clumsiness, sensory alterations on limbs, speech disturbance, loss of vision, or homonymous hemianopia.[10] Some other symptoms or warning signs of stroke include dizziness, nausea, vomiting, severe headache, confusion, numbness, abnormal speech, loss of balance and vision. Ischemia is usually due to a buildup of fat and cholesterol deposits in the form of plaque. Ischemic stroke is one of the most common, in which there are two types: thrombotic and embolic. Thrombotic strokes occur when a blood clot blocks an artery to disrupt blood flow. Embolic strokes occur when plaque or thrombus (blood clot) travels from its original site down to an artery to stop blood flow. The extent of damage is reflected upon how downstream the embolus has moved. Hemorrhagic stroke is mainly caused by hypertension, a rupture of an aneurysm, vascular malformation, or due to a complication with anticoagulation medication. The hemorrhage can be classified by intracerebral or subarachnoid. Treatment usually involves surgery to control the bleeding. A Transient Ischemic Attack (TIA), is a temporary cerebrovascular event that causes no permanent damage. Usually, a patient will exhibit stroke-like symptoms, as an artery is temporarily blocked. There are no treatment options for the TIA itself, but these patients will be treated for carotid artery disease or other cardiac problems to further prevent a major stroke later on.

Vascular Dementia:

Vascular Dementia (VaD), is dementia associated with CVD or ischemic brain injury. Vascular Dementia, alongside Alzheimer's disease, are the two most common types of dementia.[11] There are similarities among symptoms as well as pathology. Recent studies estimate that 10-50% of cases of dementia are vascular dementia. There are many problems when characterizing CVD as a cause of dementia, especially in elderly patients. There is no accepted neuropathologic pathway or framework for diagnosis. There is also no agreement for one definition of vascular dementia.[12] Given these challenges, researchers have identified various similarities in clinical, imaging, epidemiological, and neuropathologic aspects of CVD and cognitive impairment, given dementia and AD.

Alzheimer's and Parkinson's Disease Dementia Comparison

Parkinson's disease dementia (PDD) shows some of the major symptoms associated with Alzheimer's disease. Various clinical trials have demonstrated the hypothesis of a cholinesterase inhibitor, such as rivastigimine, can improve some of the cognitive

defects associated with both AD and PDD.[13] Cholinergic system defects are profound in Parkinson's disease alone (PD). The defects lead to impairment in cognition which then progresses to dementia. Clinical drug trials found that there are differing patterns of impairments between the two diseases, even though both diseases involve cholinergic deficiencies.[13] Greater understanding of the progression and various severity of each disease state can allow professionals to better diagnose a patient and provide the best alternative care despite the route of progression.

Newly Found Causes:

A recent study targeted Income as a cause of cerebrovascular disease in New York. According to the Department of Neurology at the State University of New York at Buffalo, CVD is most common within Western New York, where measures of age-, gender-, and race-adjusted CVD hospitalization data is collected and analysed.[14] This measure indicates the prevalence of a nontraditional socioeconomic factor. Results show that with higher income, comes higher levels of cerebrovascular disease prevalence. Within the State of New York, there is a variance with high and low clusters of CVD with increasing income.[14]

Incidence rates of CVD is thought geographically. Urban and rural areas both can be affected when it comes to CVD, while some may think that healthcare varies in two distinct areas. A recent study in western Canada, specifically Alberta, was conducted. Results show that between the 1999-2000 fiscal year, the rate of cerebrovascular disease per 10,000 was similar between urban (13.24) and rural (13.82) areas. Rural residents often report their incidents in urban area emergency departments, which results in CVD killing more rural patients. Overall mortality is similar in both of these dwellers.[15] Between 60%-90% of patients with AD will show varying degrees of cerebrovascular pathology via autopsy results.[11]

Vitamin D and Calcium may be associated with a wide-range of outcomes, but there is scarce literature on their effects on CVD. One research in February 2012, studied and reported a review of cerebrovascular disease (defined as any fatal or non-fatal ischemic stroke, hemorrhagic stroke or transient ischemic attack) by circulating vitamin D (25-hydroxy vitamin D [25(OH)D] as active metabolite) and calcium levels. Results from selected studies showed that higher circulating levels of Vitamin D is associated with a decreased risk of CVD. On the contrary, higher circulating calcium levels is associated with an increased risk.[14]

Fish Consumption and Long Chain Omega 3 Fatty Acids: Associated Risks of CVD:

Fish consumption is a recommended staple in those needing a cardioprotective diet.[16] Due to its high component of omega 3 fatty acids, many physicians and health professionals recommend patients with cardiac problems to consume cold water oily fish and fish oil. These polyunsaturated fats contain a high amount of eicosapentaenoic acid and docosahexaenoic acid, and with regular consumption, these acids can reduce arrhythmias, endothelial dysfunction, circulating triglyceride levels, and inflammation. Therefore, patients with high triglyceride blood levels and and pre-existing coronary heart disease may see an improved systematic diagnosis as per regular check-up after long-term dietary changes. However, supplementing with long chain omega 3 fatty acids has not shown prognosis of significantly helping to prevent stroke, such as in cerebrovascular disease. Recent research has shown an inverse relationship between fish consumption and and long chain omega 3 fatty acids when associated with CVD.[16] The overall benefit of fish intake is overall in preventing CVD, due to the broad range of nutrients seen in fish.

Age-Related Diseases:

Researchers set out to test the age and gender incidence rates of CVD, which includes stroke and transient ischemic attack in three various populations within Central Spain.[10] In the past four years, stroke prevalence has decreased over 42% in high-income countries, with a greater than 100% increase of incidence in low to middle income countries. In this study, out of 5278 participants, 75 patients out of the 257 stroke cases were related to cerebrovascular disease. This population aged between years 65-85 and over. Results show that CVD is indeed an age related disease, with rates of incidence increasing with advancing age.[10]

Some studies show that there is a decline in age-specific cerebrovascular disease. A study published in the Netherlands, between the late 1990s and early 2000s concluded that there is a decline in mortality, due to the rising of younger populations. These analyses targeted trends in circulatory, ischemic heart disease, and cerebrovascular disease, age-specific.[17] Some may think that a decline in age-related diseases may be due to lifestyle changes, government campaigns, and rise of economic wealth in more economically developed countries, such as the Netherlands.

Mechanistic Relationship between Alzheimer's and Cerebrovascular Disease:

Mixed dementia is when patients suffer from both Alzheimer's disease and cerebrovascular disease. In other words, when CVD patients exhibit symptoms of both Alzheimer's disease and vascular dementia, they are placed in a mixed dementia category.[18] There is increasing evidence that support the sharing of common risk factors between both Alzheimer's disease and Cerebrovascular Disease. These such factors include hypertension with age, diabetes

mellitus, smoking, apolipoprotein E, hypercholesterolemia, and homocysteinemia.[14] Atrial fibrillation and congestive heart failure in persons with CVD are more likely to progress to a stage of AD.[14] Both of these diseases eventually cause a decrease in overall blood flow, reduction of glucose transport and utilization, and loss of vascular innervation.[14] Cerebrovascular disease is shown to influence the cognitive performance in patients experiencing early stages of Alzheimer's as compared to later advanced stages of the disease. Research shows that those with early onset of AD, diagnosis of CVD significantly worsens cognitive function.[19]

Increase of various clinical features can further accentuate the relationship between CVD and AD. There is an increased rate of dementia after stroke, Epidemiology results suggest that dementia with CVD increases as age increases.[12] Although these results can vary from study to study, an overall analysis of population-based epidemiological research shows that with advancing age, disorders such as AD increases, and because clinical stroke is also prevalent in older individuals, dementia and CVD are also result. Cerebral atherosclerosis is a condition associated with AD, which poses for a higher risk of VaD.[12] Large scale studies suggest that treated hypertension reduces the rate of incident dementia in older individuals. Imaging shows that there is no neuroimaging profile to fully diagnose a patient with cerebrovascular disease.[12]

Theories Supporting the Interrelationship:

The effect of age:

Although relatively little is known on the effects of CVD on dementia and AD, many studies have yet to test age related effects. One research aimed to test the rate of cognitive decline in various AD compared with dementia with associated CVD. These samples were both clinical and autopsy patient series.[20] Results showed a significant interaction between age and diagnosis. As the age increased, there was a decrease in the rate of change with the AD groups, but an increase in rate for dementia with CVD groups. Therefore, it can be concluded that dementia with CVD declines faster in older patients, but declines slower in younger patients. Patients with AD without any associated cerebrovascular conditions show a faster decline in older patients.[20] One can suggest that this is due to combined Alzheimer and vascular pathological conditions in older patients with CVD would show a faster decline, due to combinations of cerebral diseases.

Depression can cause Alzheimer's:

Depression is linked with increased cognitive dysfunction, especially vascular dementia and even more specific, Alzheimer's disease.[3] Depression leads to the hyper activation of the hypothalamic-pituitary-adrenal (HPA) axis, chronic inflammation, and a decrease in neurotrophin signaling. The dysfunction of the HPA axis is activated through stress. The stressful stimulus presents in the brain to activate the hypothalamus, which signals the release of corticotrophin-releasing factor (CRF). This releases the adrenocorticotropic hormone (ACTH) from the pituitary into circulation. ACTH will release glucocorticoids from the adrenal corticoid, which exerts a negative feedback mechanism within the axis. Some structures affected influence the hippocampus, which influences normal central nervous system functions such as learning and memory.[3] Both depression and AD patients exhibit an inactive HPA axis, which results in an increase of the stress hormone, cortisol.

Chronic inflammation associated with depression leads to an increase of pro-inflammatory cytokines.[3] Neurotrophin signaling decreases with an increase of depression.[3] Neurotrophins are responsible for maintaining neuronal homeostasis and plasticity. Decreased signaling also results in low levels of brain derived neutrotrophic factor (BDNF) and in low levels of transforming-growth-factor-beta 1 (TGF-B1). All of these factors combined leads to increased vulnerability to B-amyloid toxicity and hippocampal atrophy, inducing the onset of cognitive deficit and eventually, Alzheimer's disease.

Cerebrovascular disease can instigate depression:

Mood disorders such as depression, can contribute to the link between cerebrovascular disease and the progression of Alzheimer's. Patients with silent cerebral infarction (SCI), pathology of cerebrovascular disease is present with no symptoms of neurological or neuropsychological deficit, show a higher chance of developing depression.[21] The overall concept of "vascular depression" was accompanied by the interrelation of CVD and depression.[22] Additionally, diagnosis with cerebrovascular disease can progress post-stroke depression. After stroke, depression is more likely to occur. This idea that depression is the cause of cognitive dysfunction was denied as researchers suggested that depression after stroke is more likely due to cognitive dysfunction.[22] H. Ishii et al. describes in their paper that prevalence, neuroimaging findings via MRI, cognitive function and depression are the conditions associated with CVD. However, asymptomatic CVD furthermore does not clarify the relationship between cerebrovascular disease and depression.

Impact of Non-Insulin Dependent Diabetes Mellitus (NIDDM):

Non-insulin dependent diabetes mellitus (NIDDM) is known to be one of the known causes of vascular disease. Studies show that it has been paired with higher incidence of dementia and AD. CVD patients with diabetes are at a higher risk for Alzheimer's

disease. Although NIDDM does not alter brain pathology in an unusual way regarding AD, it will dramatically increase the amyloid deposition and neurofibrillary tangles in people acquiring the ApoE4 genotype.[18] Carriers of the ApoE4 allele, whom have diabetes, are at double the risk of developing Alzheimer's disease compared to those patients with the allele and without diabetes. Elderly patients are at higher risk of being diagnosed with diabetes, due to the inability to exercise, no regulation of diet, changes in medication or lifestyle, increased obesity, and many more causes.

Pathogenesis of White Matter Lesions, Changes of Astroglia, and White Matter Hyperintensities:

White Matter (WM) Lesions, commonly found in both AD and ischemic cerebrovascular disease, gives clues into the interrelationship between the two. Hyperintense lesions are often known to be the result of dementia and progress the process of gliosis (rarefaction of myelin and axons and widening of the perivascular space).[23] Previous studies tested show that white matter lesions induce the immunological response in patients with CVD and AD. T cell infiltration and an increase of microglia and macrophages are seen in these lesions. In mild WM lesions, there is an increase of astroglia, with no such increase in severe WM lesions, the types seen in these patients.

Current research using light and electron microscopic immunohistochemistry for glial fibrillary acidic protein (GFAP) marker, presents the pathogenies of these lesions and the role of astroglia.[23] Astrocytes, known collectively as astroglia, assist in the maintenance of the blood brain barrier and overall blood flow. Morphological variations of these star-shaped glial cells, including clasmatodendrosis (fragmentation of astroglial processes) was seen in patients with both AD and CVD. Magnetic resonance imaging (MRI) of the brains of these patients showed extensive swelling and vacuolation of the white matter astroglia.[23] When this occurs, astrocytes lose their distal processes due to the breaking up of astrocytic protoplasmic expansions, which leads to energy failure and acidosis, an overall a decrease in blood flow to the brain. GFAP revealed further that these cells showed condensed chromatin, lysosomes, and large membrane-bound osmiophilic cytoplasmic inclusions included with lipophilic granules. These characteristics suggest that clasmatodendritic astroglia incorporate edema fluid resulting in swelling and use phagocytes to clean up cellular debris. The cells eventually degenerate due to cerebral edema.[23]

White matter hyperintensities (WMH) is clearly seen in the MRI's of elderly individuals and is also known as leukoariosis. These areas are associated with demyelination and axonal loss, reduced glial density and atrophy, cortical thinning and cerebral atrophy, endothelial and immune activation, ischaemis damage, and hypoxia and hypoperfusion. These WMH's are a predictor for vascular disease, often associated with high blood pressure in the elderly. Additionally, WMH's are associated with a high risk of stroke. There is a high correlation of these hypetintesities with vascular dementia, but their role with AD is unclear.

Differentiating the Cognitive Effects:

The cognitive effects of both AD and CVD are similar and poses a challenge for many researchers. CVD, specifically, small vessel disease, is known to cause cognitive dysfunction, which provokes further damage to the frontostriatal loops and frontal lobe.[24] Present tests detect the differences between ischaemic lesions via neurological examination, MRI, and clinical history. There is a strong evidence that cognitive symptoms can be distinguishable only between subcortical cerebrovascular disease and Alzheimer's disease. To test this, neuropsychological tests scores are used to distinguish AD and CVD pathology. Research on this reported that those with vascular dementia perform better on memory tests and worse on executive function tests when compared to patients with AD. Additionally, AD memory scores were lower than Executive Function by standard deviation. On the other hand, CVD was equally impaired on Executive Function, Verbal Memory, and Nonverbal Memory.[24] After these results, new studies targeted predominant cognitive executive dysfunction as a marker for vascular dementia, which can assist in differentiating from AD. However, much of these neuropsychological tests can be variable due to differences in progression between individuals.

Neurodegenerative disorders, such as AD, are characterized by abnormal proteins in the brain. Some treatments, to distinguish between the types of diagnoses in AD can be helpful for future studies into the interrelationship between AD and CVD. A recent research published subdivided patients based on pathological diagnoses into six groups: Alzheimer's disease, dementia with Lewy bodies (DLB), mixed Alzheimer's disease/DLB, frontotemporal lobar degeneration with ubiquitin-only-immunoreactive changes (FTLD-U), corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP).[25] Rates of cerebral atrophy were measured and differences between DLB and mixed Alzheimer's disease/DLB and Alzheimer's disease pathology showed major difference. Patients with CBD and PSP also show significant difference in cerebral atrophy, which can be a target for future treatment trials, even when distinguishing between AD and CVD.[25]

Exercise and Folate:

Low folate levels, often classified as folic acid deficiency anemia, has been associated with a greater risk of Alzheimer's Disease and all-cause dementia.[26] Folic acid supplementation does not benefit cognitive functions as a solution. In addition, there is a greater risk of other vascular outcomes, including cardiovascular disease, myocardial infarction, and stroke. As a solution, researchers tested exercise, which is associated with greater serum folate levels, lower incidence of dementia, Alzheimer's disease, and stroke.[26] The main goal was to study the effects on why low levels of folate increase the risk of dementia, but why supplementation does not reduce the risk. Adjusting the level of exercise showed the association between folate and dementia and AD was 29% and 25% lower, but no significant association in other cerebrovascular outcomes.[26] Therefore, exercise accounts for the relationship between folate and dementia and AD.

Theories against the Relationship:

Imaging shows that there is no neuroimaging profile to fully diagnose a patient with cerebrovascular disease.[12] Because there are no apparent infarcts in imaging, this suggests that there is no guarantee that CVD can be related to dementia. However, researchers concluded that there can be an association between silent infarcts with cognitive impairment, and a greater risk of subsequent dementia. They conclude this via a study from the Netherlands, where the hazard ratio for the risk of dementia with any silent infarcts, was 2.26.[12] Therefore, absence of overt strokes in MRI's is associated with cognitive decline and dementia, and these infarcts can determine if one has CVD.

Improving Diagnoses and Prevention Techniques:

The diagnosis of AD is not a simple conventional diagnostic process. According to a recent longitudinal study in Japan, the pathology of AD is so complex, that one cannot track the progression of the disease over time.[27] Neuroradiological findings have no sequential development, as seen in 200 AD patients involved in a follow-up study. After a year, computed tomography (CT) results show that the degree of dementia is more severe in patients with earlier onset and atrophy occurs in the frontal lobe, the temporal lobe, and the fronto-temporal lobes.[27] Among the patients, results also found major variation among degree of pathologies, nature and manner of progression. These researchers argue that Alzheimer's disease should actually be known as Alzheimer's syndrome, due to the complexity of the pathology. New approaches to target the pathomorphology and symptomatology of AD needs to found to provide better diagnosis and target the onset of other diseases, such as CVD.

The combination of both AD and CVD, within the elderly and other ages, Structural MRI have very limited specificity, which may not account for the pathologies associated with both of these diseases. In vivo studies show that within patients, the PiB-PET

Modern CSF biomarkers are specific to detect AD, as per the Alzheimer Disease Neuroimaging Initiative. The interrelationship between SVD and AD has been confirmed via biomarkers, however there were no interactions marked between vascular risk factors and AD biomarkers.[14] This creates a challenge when diagnosing mixed AD/CVD on age related dementia.

Cholinergic enzymes in the cortex and cholinergic cell loss in the basal forebrain plays a role in the cognitive dysfunction associated with AD.[28] These neuroreceptors, that respond to acetylcholine are distributed and have a direct effect on postsynaptic transmission. A downstream of receptors, which usually occurs in ageing and even more in mild cognitive impairment (MCI) and early Alzheimer's disease, which can directly correlate to memory deficits faced by these patients regardless of hippocampal volume.[28] Specific biomarkers for these enzymes and receptors can give insight into how the AD brain works and indicate various changes in neural activation and other cognitive performances, which can be useful for drug targets for treatment.

Galantamine, a cholinesterase inhibitor, is used commonly to treat dementia and in patients with AD. A recent study suggests that galantamine therapy can increase symptoms and may benefit patients who are living with AD with CVD. After Reminyl (galantamine) was administered to patients for 12 months, patients exhibited an increase in cognitive and behavioral functions.[11] Such a drug can be the solution for those patients suffering from both AD and CVD, especially if administered early, soon after diagnosis is made.

In Panama, CVD is becoming an epidemic, as it is stated to be the fourth leading cause of death.[29] The Panamanian health system therefore has set forth rules and regulations to control and prevent this disease. Many Latin Americans, according to a 2007 survey, show common risk factors including high blood pressure, dyslipidemia, and alcoholism. Since 2013, hospitals have established an intravenous thrombolytic therapy program as part of public healthy policy, as well as a campaign for a healthy lifestyle to influence adolescents and children at a young age.[29]

Lifestyle changes such as diet can directly act as a benefit in protection from diseases. Consumption of plant foods such as berries, vegetables, and cereals that are low in calorie and fat and high in fiber and protein are beneficial in preventing these diseases. Vitamins A and C are known to be rich in foods like spinach, kale, and broccoli, and can slow the rate of cognitive decline associated with dementia. These

foods are also rich in lutein and zeaxanthin, found in carrots, yellow corn, and mangoes, which can prevent vision loss associated with AD.[30] Deficits in visual function, including stereopsis, contrast sensitivity, and motion detection are some of the earliest symptoms of AD and change in diet can assist in preventing these symptoms or inducing a later onset of them.

Stem Cell Based Therapy:

Stem cells have become a new breakthrough in medicine. These cells provide the ability to differentiate into a variety of cell types. Using this technology, stem cells may be introduced into areas of neurodegeneration. These cells can potentially be induced to proliferate and differentiate into appropriate types, which can essentially replace lost or damaged cells and stimulate the regeneration of neurons within the central nervous system. This approach seems to be valuable for researchers studying approaches into combating Alzheimer's, and further preventing dementia.

CONCLUSION

For a more comprehensive and holistic understanding about the progression and diagnosis of both Alzheimer's and Cerebrovascular disease, one must be able to dig deeper and test some of the research that was presented. Further research should look into the pathogenesis of of white matter lesions, changes of astroglia, and white matter hyperintesitites within both a young population and an older population. Comparing these results may give clear evidence of the causes and or similarities between cerebrovascular disease and Alzheimer's disease, as well as the decline in memory associated with both. More research has to be done regarding the cholinergic systems between all types of dementia. With the presented studies, we know that age associated dementia poses as a challenge for patients that are diagnosed with CVD. Researchers and health professionals must take into consideration the various risk factors linked to progressive clinical trials for those with AD. Many of the prevention techniques are similar for both CVD and AD, which provides little evidence of a relation. Stem-cell therapy may be a treatment for AD and further on the prevention of dementia. In conclusion, many of the symptoms and diagnosing techniques are similar when dealing with both CVD and AD, but further research cell machinery and other mechanisms must further conclude that these diseases can aggravate each others' prognosis.

REFERENCES

1. Attems J, Jellinger KA. The overlap between vascular disease and Alzheimer's disease - lessons from pathology. BMC Medicine. 2014;12(1):1-5.
2. Caraci F, Copani A, Nicoletti F, Drago F. Depression and Alzheimers disease: Neurobiological links and common pharmacological targets. European Journal of Pharmacology. 2010;626(1):64–71.
3. Gauthier S, Leuzy A, Racine E, Rosa-Neto P. Diagnosis and management of Alzheimer's disease: Past, present and future ethical issues. Progress in Neurobiology. 2013;110:102–13.
4. Chowdhury R, Stevens S, Gorman D, Pan A, Warnakula S, Chowdhury S, et al. Association between fish consumption, long chain omega 3 fatty acids, and risk of cerebrovascular disease: systematic review and meta-analysis. BMJ. 2012;345(303):5-9.
5. Fujisawa K, Tsunoda S, Hino H, Shibuya K, Takeda A, Aoki N. Alzheimers disease or Alzheimers syndrome?: a longitudinal computed tomography neuroradiological follow-up study of 56 cases diagnosed clinically as Alzheimers disease. Psychogeriatrics. 2015;15(4):255–271.
6. Knopman DS. Dementia and Cerebrovascular Disease. Mayo Clinic Proceedings. 2006;81(2):223–230.
7. Han D, Carrow SS, Rogerson PA, Munschauer FE. Geographical variation of cerebrovascular disease in New York State: the correlation with income. International Journal of Health Geographics. 2005;4:12-18.
8. Farlow MR, Schmitt F, Aarsland D, Grossberg GT, Somogyi M, Meng X. Comparing Clinical Profiles in Alzheimer's Disease and Parkinson's Disease Dementia. Dementia and Geriatric Cognitive Disorders Extra. 2013;3(1):281–90.
9. Martínez-Salio A, Benito-León J, Díaz-Guzmán J, Bermejo-Pareja F. Cerebrovascular disease incidence in central Spain (NEDICES): A population-based prospective study. Journal of the Neurological Sciences. 2010;298(1-2):85–90.
10. Ishii H, Meguro K, Yamaguchi S, Ishikawa H, Yamadori A. Prevalence and cognitive performances of vascular cognitive impairment no dementia in Japan: the Osaki?Tajiri Project. European Journal of Neurology. 2007;14(6):609–16.
11. Rao R. Cerebrovascular disease and late life depression: an age old association revisited. International Journal of Geriatric Psychiatry. 2000;15(5):419–33.
12. Reed BR, Mungas DM, Kramer JH, Ellis W, Vinters HV, Zarow C, et al. Profiles of neuropsychological impairment in autopsy-defined Alzheimers disease and cerebrovascular disease. Brain. 2007;130(3):731–9.
13. Mizrahi A, Knekt P, Montonen J, Laaksonen MA, Heliövaara M, Järvinen R. Plant foods and the risk of cerebrovascular diseases: a potential protection of fruit consumption. British Journal of Nutrition. 2009;102(07):1075.
14. Chowdhury R, Stevens S, Ward H, Chowdhury S, Sajjad A, Franco OH. Circulating vitamin D, calcium and risk of cerebrovascular disease: a systematic review and meta-analysis. European Journal of Epidemiology. 2012;27(8):581–91.
15. Whitwell JL, Jack CR, Parisi JE, Knopman DS, Boeve BF, Petersen RC, et al. Rates of cerebral atrophy differ in different degenerative pathologies. Brain. 2006;130(4):1148–58.
16. Mungas D, Reed BR, Ellis WG, Jagust WJ. The Effects of Age on Rate of Progression of Alzheimer Disease and Dementia With Associated Cerebrovascular Disease. Archives of Neurology. 2001;58(8):1243.
17. Yiannakoulias N, Svenson LW, Hill MD, Schopflocher DP, Rowe BH, James RC, et al. Incident Cerebrovascular Disease in Rural and Urban Alberta. Cerebrovascular Diseases. 2003;17(1):72–8.
18. Esiri MM, Nagy Z, Smith MZ, Barnetson L, Smith AD. Cerebrovascular disease and threshold for dementia in the early stages of Alzheimers disease. The Lancet. 1999;354(9182):919–20.
19. Peeters A, Nusselder WJ, Stevenson C, Boyko EJ, Moon L, Tonkin A. Age-specific trends in cardiovascular mortality rates in the Netherlands between 1980 and 2009. European Journal of Epidemiology. 2011;26(5):369–73.

20. Tomimoto H, Akiguchi I, Wakita H, Suenaga T, Nakamura S, Kimura J. Regressive changes of astroglia in white matter lesions in cerebrovascular disease and Alzheimers disease patients. Acta Neuropathologica. 1997;94(2):146–52.
21. Gracia F, Benzadon A, Gonzalez-Castellon M, Armien B. The Impact of Cerebrovascular Disease in Panama. International Journal of Stroke. 2014;9(SA100):28–30.
22. Sultzer DL. Cognitive ageing and Alzheimer's disease: the cholinergic system redux. Brain. 2018;141(3):626–8.
23. Messier C. Diabetes, Alzheimer's disease and apolipoprotein genotype. Experimental Gerontology. 2003;38(9):941–6.
24. Musicco M, Palmer K, Salamone G, Lupo F, Perri R, Mosti S, et al. Predictors of progression of cognitive decline in Alzheimer's disease: the role of vascular and sociodemographic factors. Journal of Neurology. 2009;256(8):1288–95.
25. Pache M, Smeets CHW, Gasio PF, Savaskan E, Flammer J, Wirz-Justice A, et al. Colour vision deficiencies in Alzheimer's disease. Age and Ageing [Internet]. 2003;32(4):422–426.
26. Toledo JB, Arnold SE, Raible K, Brettschneider J, Xie SX, Grossman M, et al. Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. Brain. 2013;136(9):2697–706.
27. Puzzo D, Gulisano W, Arancio O, Palmeri A. The keystone of Alzheimer pathogenesis might be sought in Aβ physiology. Neuroscience. 2015;307:26–36.
28. Panpalli Ates M, Karaman Y, Guntekin S, Ergun MA. Analysis of genetics and risk factors of Alzheimer's Disease. Neuroscience. 2016;325:124–31.
29. Small G, Erkinjuntti T, Kurz A, Lilienfeld S. Galantamine in the Treatment of Cognitive Decline in Patients with Vascular Dementia or Alzheimer's Disease with Cerebrovascular Disease. CNS Drugs. 2003;17(12):905–14.
30. Middleton LE, Kirkland SA, Maxwell CJ, Hogan DB, Rockwood K. Exercise: A Potential Contributing Factor to the Relationship Between Folate and Dementia. Journal of the American Geriatrics Society. 2007;55(7):1095–8.

How to cite this article: Agarwal S, Saleem M. Decoding the Molecular Ties between Cerebrovascular Disease and Alzheimer's. Ann. Int. Med. Den. Res. 2020; 6(4):ME27-ME34.

Source of Support: Nil, **Conflict of Interest:** None declared