Review Paper:

The Role of Comorbidities and Viral Infections on Alzheimer's Disease Progression and Mortality Risk

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Abstract

Alzheimer's disease (AD) is a progressive neurological condition that affects cognitive function and daily activities. While the disease itself is rarely recognized as a direct cause of death, its consequences and comorbidities contribute to a greater mortality rate among those affected. This study aimed impact of comorbidities and viral infection on mortality. Many patients also have comorbidities such as cardiovascular disease, diabetes, stroke and depression. These comorbid disorders may complicate AD management while also contributing to an increased death risk.

This review compiles the available literature on the role of comorbidities in AD mortality. We searched how these variables accelerate disease development, affect life expectancy and contribute to mortality disparities among AD patients. The findings imply that whereas chronic comorbidities gradually deteriorate the prognosis, acute viral infections result in fast health decline and considerably raise death risk, particularly in advanced AD stages. This review also explained how virus infects neurons at numerous phases including how it enters, travels to and establishes latency in neuronal cells. We discuss the impact of viruses on cognitive function including putative viral invasion routes and underlying mechanisms for cognitive impairment.

Keywords: Alzheimer, comorbidities, virus.

Introduction

Alzheimer's disease (AD) is the most prevalent neurological illness affecting approximately 57 million individuals globally. Researcher identified the disease as characterized by the accumulation of extracellular amyloid beta plaques and intraneuronal neurofibrillary tangles. Various hereditary factors have been found. One of the leading causes of death globally is AD[2].

The results of the current investigation indicate that AD is linked to lower life expectancy and greater morality rates. Creating customized for patients, their relatives and mental health professionals, treatment and rehabilitation programs for various forms of dementia are crucial[36]. Dementia, also known as neurocognitive illness which is one of the leading causes of disability and dependency among the elderly and its prevalence, has been rising[45].

Persons with dementia suffer significant health issues and may be at least twice as likely to die as persons without dementia, which leads to large expenses for the health and social care systems[20]. Coexisting diseases can negatively affect the management of AD. Understanding the molecular mechanisms that cause comorbid disorders in AD, may lead to new therapeutic approaches. This study focuses on the most common illness comorbidities in AD and how they affect clinical care and what is the role in mortality[54].

Amyloid plaques is one of the distinguishing hallmarks of AD. These plaques are made up of misfolded beta-amyloid peptides that collect into hazardous clumps. They disrupt synaptic connection and cause inflammation in the brain. Another distinguishing aspect is the presence of tau protein tangles in neurons. Tau proteins produce twisted tangles that disrupt the transport mechanism within neurons, contributing to cell death and cognitive impairment[31,44].

Demographic characteristics like age, gender and education are the most commonly studied predictors of cognitive decline. Studies on behavioural problems and vascular diseases vary in duration, outcomes and factors, leading to conflicting conclusions. In a 2-year follow-up study, researchers evaluated demographic, genetic, clinical and treatment parameters to determine the rate of cognitive decline. Preclinical and prodromal signs of AD are often overlooked when estimating prevalence[11,13,19]. Several factors influence progression rate including the stage of diagnosis, the individual's overall health and access to appropriate medical and social assistance.

AD life expectancy is determined by factors such as the stage of illness, the individual's overall physical and mental condition, access to healthcare and caregiver support quality[55]. Individuals detected early on and receiving comprehensive care frequently have a slower illness progression, which can lengthen life expectancy and can improve quality of life. Individuals with many health concerns, limited access to care, or inadequate support are more susceptible to complications, potentially leading to lower survival durations. Cognitive decline weakens judgment and communication skills, making it more difficult to manage other chronic diseases like cardiovascular disease, diabetes and hypertension. This can lead to poorly managed comorbidities, increasing the risk of mortality[34].

To conduct this review, we searched MEDLINE, PubMed, Embase, Google scholar We looked for cross-sectional, retrospective and cohort studies on virus and comorbidities directly linked with Alzheimer patients' mortality.

Comorbid Chronic Conditions

Cardiovascular Diseases(CVD): Clinical studies are away from common triggers. CVD and dementia have similar genetic and metabolic characteristics. Research indicates that cardiovascular disease and risk factors are linked to an elevated risk of AD and its precursor stage, moderate cognitive impairment (MCI)[52]. AD has a complex link to cardiovascular health. The vascular alterations seen in AD (such as decreased blood supply to the brain) may exacerbate pre-existing cardiovascular disorders such as hypertension, stroke and coronary artery disease[14]. Furthermore, AD patients may be less able to manage these illnesses due to cognitive loss, resulting in deteriorating health outcomes and an increased risk of death.

Adults with normal cognitive function and patients with AD have independently associated plasma amyloid beta levels (Aβ1-40)[41]. Six to eight individuals with improved cardiovascular health increase the risk of major causes of death such as coronary heart disease, AD and death[57]. Malnutrition affects over one-third of older persons with dementia and nearly half of all older adults are at risk of it. Maintaining a positive nutritional status in older persons with dementia requires encouraging teamwork among health-care professionals, as well as assuring early assessment and successful therapy of malnutrition[36].

Diabetes and Metabolic Dysfunction: Diabetes and metabolic syndrome are common among the elderly including Alzheimer's patients. Cognitive decline can make it difficult for persons to comply to dietary restrictions[38]. Hyperglycaemia raises the incidence of all-cause dementia, including AD and vascular dementia (VaD) and uncontrolled hyperglycaemia can increase the mortality risk in individuals with dementia. However, intensive antihyperglycemic medication may raise the risk of hypoglycaemia which can lead to a variety of complications including death hypoglycaemia[1,25]. There have been minimal screenings on the association between hypoglycaemia and new-onset dementia in type 2 diabetes patients. We examined the relationship between hypoglycaemia episodes and the risk of dementia and all-cause mortality in type 2 diabetes patients using data from the National Health Insurance Service (NHIS), which covers the whole Korean population[22].

Falls and fracture: Weakened muscles can contribute to enhanced mortality risk in AD, particularly in the late stages, by causing problems that can directly or indirectly prolong death. Here is summary of how weakening muscles affect mortality in Alzheimer's patients. There is increased risk of falls and injuries. Issues like muscle weakness, particularly in the legs, impairs balance, making patients more likely to fall. Falls can cause fractures particularly hip fractures, which are prevalent among elderly people. Such injuries frequently cause restricted mobility, increased reliance and other health concerns.

Fractures and injuries from falls frequently necessitate hospitalization where patients are exposed to infections and other hazards[17]. Alzheimer's patients frequently suffer from physical impairments such as poor motor coordination and balance. As the condition develops, the likelihood of falling increases due to abnormalities. Falls can cause fractures, particularly hip fractures, which can be fatal owing to complications including blood clots, infections[23,32].

Reduced Physical Activity: AD frequently results in decreased physical activity due to cognitive deficits and a lack of drive. A sedentary lifestyle is connected with several unfavourable effects including muscular atrophy, cardiovascular deconditioning and an increased risk of falls, all of which contribute to premature death[26,56].

Respiratory issues (COPD, Asthma, Pneumonia: According to research, conditions such as Chronic Obstructive Pulmonary Disease (COPD) and pneumonia can cause chronic or acute hypoxia (a lack of oxygen in the body or brain) which has a significant impact on cognitive function, especially in older adults or those with pre-existing cognitive decline such as AD. Here is an outline of how these situations lead to hypoxia and how hypoxia, in turn, impairs cognitive performance[15]. Pneumonia was a risk factor for mortality in dementia patients[3].

Kidney disease: It has been reported that chronic renal failure worsens cognitive problems and dialysis or medication management might be difficult for Alzheimer's patients. Patients with chronic kidney disease are more prone than the general population to suffer cognitive impairment, with older dialysis patients having the highest absolute risk. It is also written that vascular illness, particularly cerebrovascular disease, is most certainly a significant factor. Controlling CVD risk factors, as advised by current standards of care, is a realistic step that practitioners can take to potentially prevent the development of cognitive impairment and in those who already have it, to minimize cognitive decline[42,43,46].

Infections UTI (urinary tract infection) Skin: Recurrent infections including UTI and skin infections are frequent in Alzheimer's patients and can develop to life-threatening diseases such as sepsis. Dementia is currently the top cause of death in England and a major contributor to disability and reliance globally[58]. Urine stasis characterized by increased post void residual volume, lowers average and peak urine flow rates and a reduction in voided volume, affects both aged men and women[6]. Deteriorating detrusor anatomy and contractility contribute to suboptimal urodynamic in the elderly[18]. Benign prostatic enlargement is accompanied by urinary outlet blockage in older men. Cystoceles,

ureteroceles and bladder diverticula cause stasis in both men and women[49].

Difficulty in Eating and Swallowing: As AD progresses, many people have difficulties eating, swallowing and maintaining sufficient nutrition. This disorder known as dysphagia, can cause malnutrition and dehydration, accelerating physical deterioration and increasing the risk of infection and mortality[7].

Unintentional weight loss: Inadequate diet affects not only physical strength, but also immune function, rendering persons more susceptible to infections and sickness. AD patients are more prone to this comorbid[4].

Behavioural and Psychological Symptoms: 40% of Alzheimer's patients experience depression or anxiety. Depression can impair physical health, can diminish willingness to participate in treatment regimens and can contribute to a decrease in quality of life. Anxiety and agitation are also widespread, which might complicate the disease management[10,30].

Aggression, agitation and wandering behaviours can lead to risky circumstances including falls, accidents and altercations, raising health risks and mortality[29]. Studies show that Alzheimer's patients with one or more chronic illnesses had up to 1.5-2 times greater mortality rates than those with AD alone.

Viral infection directly linked to Alzheimer's sufferers
Herpes Simplex Virus Type 1 (HSV-1): Recent study found that some viral infections may be linked to AD, but the association is still being investigated. One of the most frequently cited viral illnesses is HSV-1, it is a common virus that causes cold sores, but some research has linked it to the development of AD. Here is an overview of how this relationship is being investigated[47]. Some studies link HSV-1 infection to the development of AD. The infection may cause inflammatory responses, which could lead to neural damage. Strong evidence has recently emerged supporting the idea that HSV-1 is a key risk factor for AD. This notion suggests that latent HSV-1 in the brain of carriers of the type 4 allele of the apolipoprotein E gene (APOE-ε4) is awakened sporadically by events such as immunosuppression[8].

Reactivated HSV-1 can produce direct inflammatory damage including increased production of Aβ and AD like tau as observed in HSV-1-infected cell cultures. HSV-1 DNA has been found to be localized in amyloid plaques in AD, further implicating it in the disease[21]. The study indicated that HSV-1 infections were strongly linked to an elevated risk of dementia, regardless of other characteristics such as age, gender, depression, dyslipidaemia, or ischemic stroke[9].

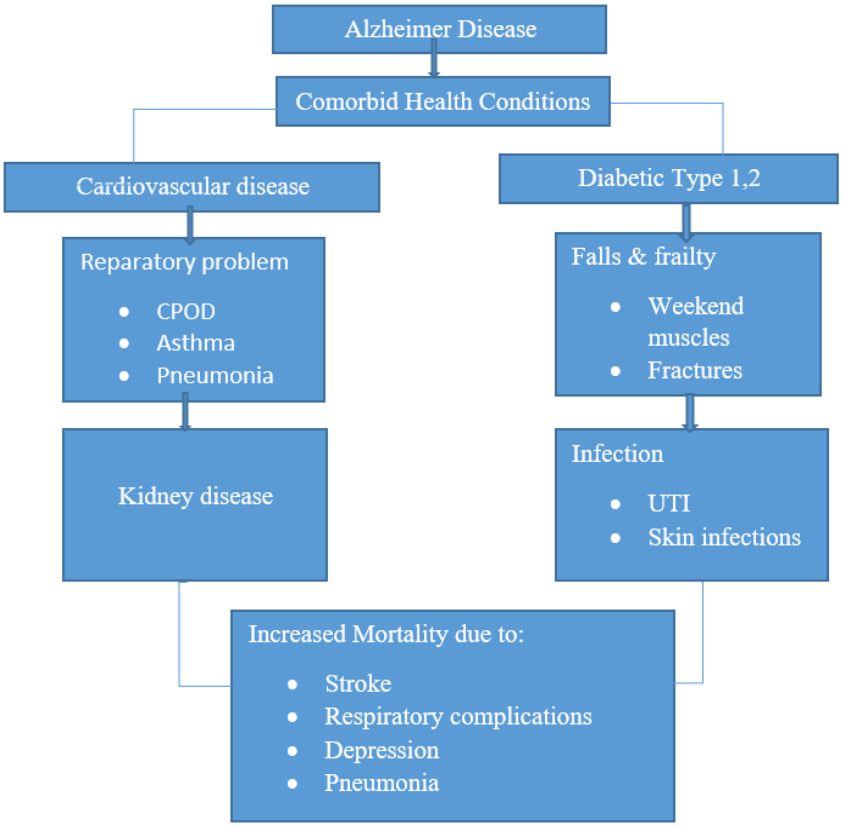

Figure 1: This flowchart underlines the specific comorbidities linked with Alzheimer's disease development and mortality. Effectively controlling these comorbid illnesses can be essential in increasing the mortality risk in Alzheimer's patients.

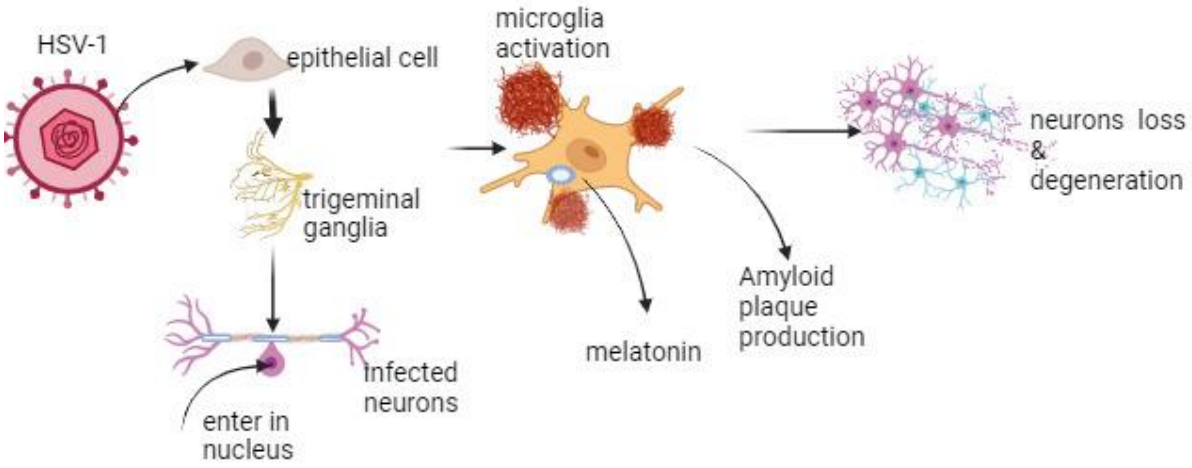

Figure 2: HSV-1 reach the brain via many mechanisms. A black arrows indicate virus movement. HSV-1 enters the brain primarily through infecting epithelial cells in the nasal cavity; however, the virus can remain dormant in the trigeminal nerve for a long period. The virus returning to the main site of infection causes further cold sores and reaches the central nervous system, inducing beta amyloid plaque and neurofibrillary tangles and melatonin and cause neurones death (created with BioRender.com)

Mechanism: HSV-1 infection in the brain may cause inflammation and oxidative stress, resulting in neuronal damage. HSV-1 may potentially cause the deposition of amyloid-beta which is characteristic of AD.

Covid-19 (CORONA VIRUS): COVID-19 is a novel disease induced by SARS-CoV-2. COVID-19 was first detected in mainland China in December 2019 and has since spread globally, resulting in significant losses and casualties[27]. On March 11, 2020, the World Health Organization (WHO) identified COVID-19 as a public health disaster of international concern. Research indicates that AD patients are more likely to contract COVID-19 which increases the risk of death compared to other chronic diseases. Additionally, infection with COVID-19 increases the risk of developing AD in the future[35,39].

Certain viral infections can considerably impair Alzheimer's sufferers' health and can increase mortality. Common viral infections can affect people with Alzheimer's with AD and other kinds of dementia facing more increased risks. According to studies[40], these patients were more likely to have severe COVID-19 outcomes such as greater fatality rates. Comorbidities can lead to weakened immune systems, cognitive decline and care facility dynamics. The COVID-19 pandemic has a disproportionate impact on older persons with AD and related dementias (ADRD)[24]. Individuals with ADRD may have difficulty in implementing behavioural modifications to lower infection risk or regulating contact in high-risk environments.

Common comorbidities among older persons with ADRD enhance the chance of death if they become infected with SARS-CoV-2[28]. Abnormal protein folding and aggregation have been linked to various neurodegenerative illnesses including AD. Exposure to infectious agents including viruses and bacteria, appears to enhance the risk of developing these illnesses. Viruses such as influenza A and murine cytomegalovirus have been shown to exhibit amyloidogenic characteristics and can create amyloid aggregates[48,51].

A study from Spain in 2020 reported that AD patients were older than those with frontotemporal dementia (80.36 ± 8.77 vs. 72.00 ± 8.35 years old) having a greater prevalence of arterial hypertension. COVID-19 affected 7.3% of patients living at home and 72.0% of those in care facilities[33]. AD was independently related with a greater risk of mortality.

Mechanism: Severe COVID-19 can lead to extensive brain inflammation and some patients experience "brain fog" or long-term cognitive symptoms. It is hypothesized that COVID-19 could exacerbate underlying Alzheimer's pathology or increase risk in susceptible individuals.

Cytomegalovirus (CMV): CMV is known to contribute to cognitive deterioration, particularly in older persons, possibly via persistent inflammation. Patients positive with CMV illnesses showed a high risk of VaD than for AD. This study found that individuals with CMV tissue-invasive end-organ illnesses had a considerably greater incidence of new-onset moderate to severe dementia, as well as AD and VaD[5,53].

Human-immuno Virus (HIV): HIV can cause HIV-related dementia, which is characterized by cognitive deterioration due to direct viral effects on the brain and accompanying inflammatory reactions. It has become obvious that patients who have infected human immunodeficiency virus HIV-1, may suffer from a cascade of neurological disorders,

including neuropathy, dementia and deteriorating cognitive function[12].

Varicella zoster virus (VZV): Recently it has been reported that VZV infection were linked to a higher incidence of dementia (HR=1.4195%CI:1.37-1.46). The co-infection group had the shortest period between viral infection and dementia diagnosis (4.09±3.02 years)[50]. In the subgroup analysis, all HSV-1 and VZV infections were associated with a greater risk of dementia compared to the non-infected group. VZV compromises of the blood-brain barrier and causes inflammation, perhaps allowing other infections such as HSV-1 to enter the brain. VZV could also contribute to neuroinflammation, which is a known factor in Alzheimer's pathogenesis[16].

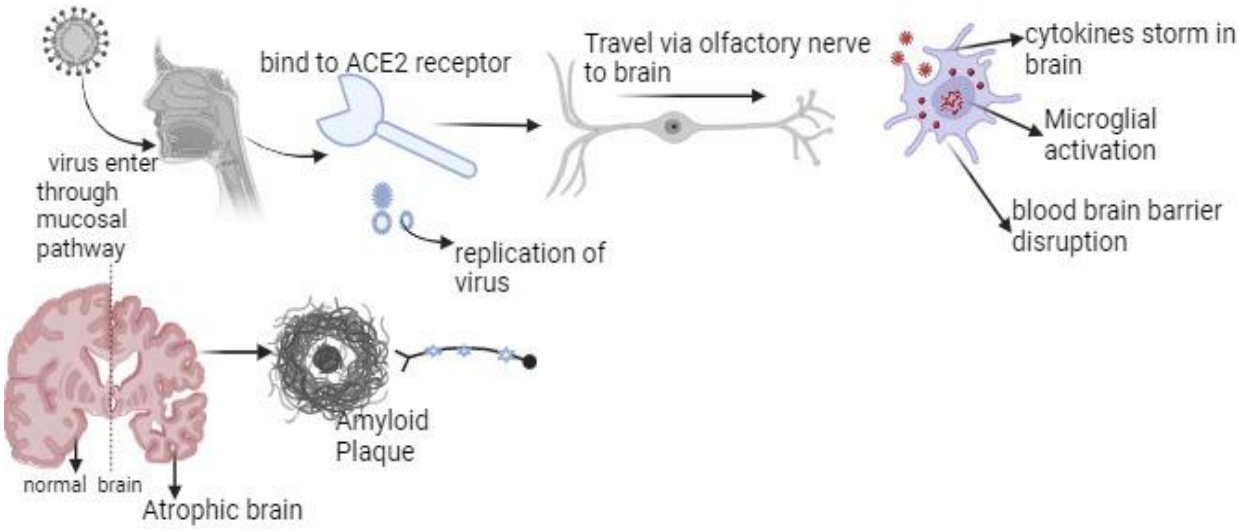

Figure 3: Cov-19 reach the brain via many mechanisms. The black arrows indicate virus movement. Cov-19 enters through mucosal pathway and virus bind to the ACE2 receptor, this virus travels through olfactory nerve to the brain. SARS-CoV-2 infection leads to the secretion of pro-inflammatory cytokines such as IL-6, TNF-α and IL-1β. Chronic neuroinflamation is caused by the migration of systemic inflammation to the brain, which activates immune cells known as microglia. Increased oxidative stress and neuronal damage cause atrophy (Created with BioRendar.com)

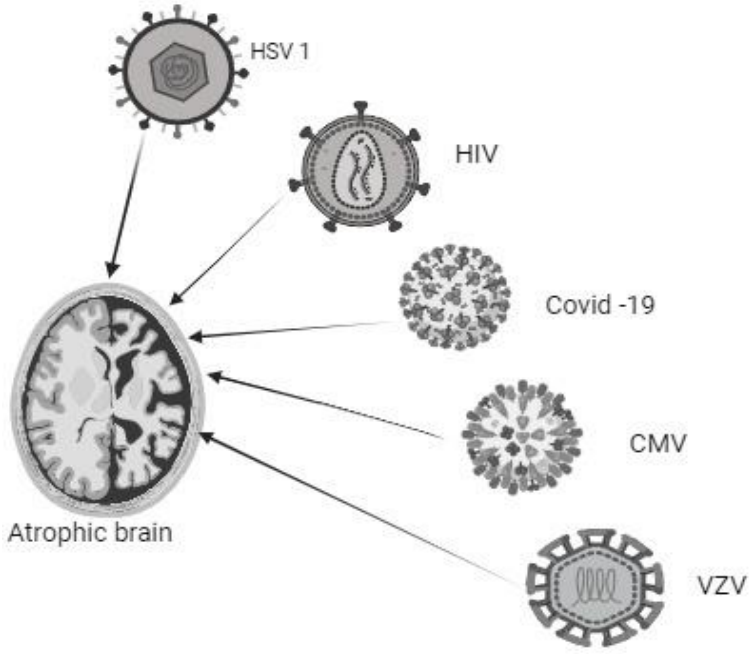

Figure 4: This diagram highlights different viruses related with AD which emphasize their possible roles in neuroinflammation, amyloid-beta accumulation and tau pathology. (Created by Bio Render)

Conclusion

Chronic comorbidities and viral infections significantly contribute to AD mortality rates. While concomitant conditions contribute to slow deterioration, viral infections particularly respiratory infections, result in a rapid increase in mortality risk. To improve Alzheimer's patients' life expectancy and quality of life, a multimodal approach addressing both types of health concerns is required. Alzheimer's patients are prone to viral infections because of reduced immune responses and limited mobility.

The risk is exacerbated by challenges in identifying and treating symptoms in this population. While the link between these viruses and comorbidities in dementia is still being researched, researchers are looking into how viral infections may affect neurodegenerative processes.

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