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Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: A review and synthesis

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Abstract As the population ages due to demographic trends and gains in life expectancy, the incidence and prevalence of dementia increases, and the need to understand the etiology and pathogenesis of dementia becomes ever more urgent. Alzheimer's disease (AD), the most common form of dementia, is a complex disease, the mechanisms of which are poorly understood. The more we learn about AD, the more questions are raised about our current conceptual models of disease. In the absence of a cure or the means by which to slow disease progress, it may be prudent to apply our current knowledge of the intersection between AD, cardiovascular disease, and cerebrovascular disease to foster efforts to delay or slow the onset of AD. This review discusses our current understanding of the epidemiology, genetics, and pathophysiology of AD, the intersection between AD and vascular causes of dementia, and proposes future directions for research and prevention.

Keywords: Alzheimer's disease; Cardiovascular disease; Cerebrovascular disease; Vascular contributions to cognitive impairment and dementia; VCID; Dementia; Risk factors

1. Introduction

One of the greatest advancements of health in the 20th century was an increase in average life expectancy by 30 years [1]. Today, people aged 85 years and older are the fastest growing segment of the population, and this has led to a new set of problems for modern health care as the elderly are the most susceptible to disease and disability. One in three adults over 85 years old suffer from Alzheimer's disease (AD) or other forms of dementia [2], the prevalence of which is estimated to increase dramatically over the next 40 years unless preventive measures are developed [3]. AD is currently the sixth leading cause of death in the United States and the cost of the disease is high. Approximately $236 billion will be spent on AD during 2016 calendar year overall, including patient care and caregivers' lost wages [4].

Despite the global increase of both incidence and prevalence of AD, it is the only leading cause of death that we are currently unable to prevent or cure [5]. The remarkable heterogeneity of risk factors, etiologies, and neuropathologic processes associated with AD makes it especially challenging for development of new treatments to slow disease progression [4,6]. Fortunately, a number of experimental therapies are currently in development. These are aimed

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at mechanisms including neurotransmission regulators, tau-based therapies, amyloid-β–based strategies, intracellular signaling cascade modulators, oxidative stress reductors, mitochondrial target therapy, cellular calcium homeostasis modulators, and anti-inflammatory therapies [7–11]. It is possible that the heterogeneity of behavioral presentations, cognitive impairments, and functional statuses observed in AD is due to its potentially varied etiology [12]. Adding to this complexity, older adults with AD typically present with comorbid medical conditions that further complicate accurate disease monitoring [13]. The current dominant AD models are insufficient to account for the complexity of biologic processes, polygenic, and epigenetic factors at work [14]. As a result, key opinion leaders have suggested that the field would benefit from the development of new conceptual models of AD [14]. The purpose of this review is to explore the complex relationship between AD, cardiovascular disease (CVD), and cerebrovascular disease (CBVD). Recent reports that question the strength of the association between these disease entities will be reviewed and recommendations will be made for additional research questions to more precisely characterize causal links between AD, CVD, and CBVD.

2. Shared genetic contributions to AD and cardiovascular disease

The genetic contribution to AD risk is complex. Three familial autosomal-dominant genes associated with early-onset disease have been discovered (*PSEN1, PSEN2* and *APP*) [15–20], and these genes may also be associated with some later onset cases, although together they likely account for less than 10% of all AD cases [21]. The most predominant type of AD is late-onset Alzheimer's disease (LOAD, referred to herein as AD), which affects adults in their sixth to eighth decade of life. Although many genetic risk factors for AD have been studied, a definitive genotype that causes (late onset) AD has not yet been identified [22]. Thus far, few genetic markers have been linked to both risk of AD and CVD or CBVD risk. The ε4 allele of the apolipoprotein E (*APOE*) gene is a risk factor for both AD and CVD. Over the past two decades, numerous studies have shown that individuals who carry at least one copy of the ε4 allele have an increased risk for AD compared to those without the ε4 allele [23–26] and ε4 carriers with AD have lower blood levels of apoE [27]. Low plasma levels of apoE protein have been found to increase the risk of AD, independently of *APOE* genotype [28].

Two polymorphisms (rs1801133, rs1801131) in the methylenetetrahydrofolate reductase (*MTHFR*) gene correlate with elevated levels of plasma homocysteine and appear to be associated with AD and vascular contributions to cognitive impairment and dementia (VCID) [29,30]. High plasma homocysteine levels have been identified as a risk factor for VCID in a Northern Irish population [29]. Mutations in the *MTHFR* gene were found to increase the risk of AD by 2.5 fold and VCID by 3.7 fold in an Asian population [30].

Beyond *APOE* and *MTHFR*, few other genes have been identified to significantly increase the risk of both AD and CVD. Genetic associations with smaller effects have been found, but a detailed discussion of these is beyond the scope of this review. Recently, new approaches to evaluating genetic pleiotropy in complex diseases have been developed [31]. These methods are now being applied to AD [32], and one recent study demonstrated genetic overlap between AD and CVD by conditioning on CVD phenotypes including C-reactive protein and plasma lipids [33].

3. Shared risk factors for AD and CVD

AD and CVD share important cardiometabolic and lifestyle risk factors that occur in middle-aged to elderly populations. Both AD and CVD are associated with increasing age, and both are among the leading causes of death. The primary causes of CVD are coronary heart disease (CHD), hypertension, stroke, and heart failure. These diseases are frequently interconnected and share an underlying pathology of atherosclerosis. All known risk factors for atherosclerosis have been the focus of studies to identify modifiable risk factors for AD. Researchers from the Framingham Heart Study [34,35] developed a composite measure of general cardiovascular risk, the Framingham Cardiovascular Risk Profile (FCRP), derived by evaluating one's age, gender, diabetes, smoking, treated and untreated systolic blood pressure (SBP), total cholesterol, and high-density lipoprotein (HDL) cholesterol [36]. In addition to increased risk of CVD, an elevated FCRP score on has been related to markers of abnormal brain aging, such as smaller brain volume and increased white-matter hyperintensities in brain imaging examinations [37]. High FCRP scores are associated with worsening of cognitive abilities, both in cognitively intact subjects and in mild cognitive impairment (MCI) patients [38] and are a reliable predictor of progression from MCI to AD [39]. Other scores developed from Framingham, the Framingham Stroke Risk Profile, and the Framingham Coronary Heart Disease Risk Score, have been similarly associated with cognitive change over time, incident cognitive impairment, and dementia [35,39–43]. These risk models are similar to one developed specifically to assess dementia risk, the Cardiovascular Risk Factors Aging and Dementia (CAIDE) risk score [44–46]. Common elements across scores are blood pressure, cholesterol, and diabetes. In the following, we review elements of these risk scores as they relate to both CVD and AD.

3.1. Hypertension/hypotension

Chronic hypertension, a common risk factor for CVD, causes a thickening of vessel walls, reduced vessel elasticity, and the narrowing of the lumen, especially in small vessels [47,48]. These sequelae result in reduced cerebral blood