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Vascular contributions to cognitive impairment, clinical Alzheimer's disease, and dementia in older persons

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ABSTRACT

There is growing evidence suggesting that vascular pathologies and dysfunction play a critical role in cognitive impairment, clinical Alzheimer's disease, and dementia. Vascular pathologies such as macroinfarcts, microinfarcts, microbleeds, small and large vessel cerebrovascular disease, and white matter disease are common especially in the brains of older persons where they contribute to cognitive impairment and lower the dementia threshold. Vascular dysfunction resulting in decreased cerebral blood flow, and abnormalities in the blood brain barrier may also contribute to the Alzheimer's disease (AD) pathophysiologic process and AD dementia. This review provides a clinical–pathological perspective on the role of vessel disease, vascular brain injury, alterations of the neurovascular unit, and mixed pathologies in the Alzheimer's disease pathophysiologic process and Alzheimer's dementia.

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1. Introduction

Alzheimer's disease (AD) is the most prevalent cause of dementia and represents a growing problem of the aging population. The International Alzheimer's Disease Report estimates that 47 million people worldwide are living with AD in 2015, and this is estimated to increase to 131 million people by 2050 [1]. Neuropathological features of AD are the deposition of hyperphosphorylated tau proteins forming paired helical filaments in neurons called neurofibrillary tangles (NFTs), and the extracellular accumulation of amyloid beta (Aβ) in plaques. Hyperphosphorylated tau filaments are also commonly present in neurites, known as neuropil threads, and in neurites-associated within neuritic plaques [2]. Although these pathologies accumulate throughout the clinical stages of AD, they can also be observed in abundance in the aging brain of persons without cognitive impairment.

A long term strategy to reducing the prevalence of dementia is to identify risk factors of the disease thus allowing intervention of the disease process and delaying disease onset. Evidence from the literature suggests that genetic, psychosocial, vascular, and life-style risk factors co-occur during lifespan to determine the risk of developing dementia and AD [3]. Unlike early onset cases of AD dementia, there has been increasing emphasis that late-onset AD (LOAD) dementia is a multifactorial disorder with persons commonly exhibiting a complex combination and manifestation of a spectrum of brain conditions. These mixed brain pathologies often include not only AD pathology but also varying degrees of cerebrovascular disease, Lewy bodies, hippocampal sclerosis, and TDP-43 pathology. The most common of the mixed pathologies is AD with vascular pathology and there is accumulating evidence identifying how vascular lesions contribute to cognitive impairment, 1) how vascular lesions may be related to the pathogenesis of AD pathology, 2) the correlation between vascular disease with dementia, and 3) vascular risk factors which predispose individuals in developing vascular dementia and onset of AD.

Overall, the literature leads us to a critical question is the pathophysiologic process of AD a neurodegenerative disorder, a vascular disorder [4], or is AD dementia merely a varying composite of both neurodegenerative and vascular pathologies [5]? In this review we discuss the role of vascular factors in AD from a clinical–pathological perspective.

2. Vascular risk factors, pathology, and dysfunction in Alzheimer's disease

Over the last two decades the amyloid hypothesis has been the most dominant in regards to pathophysiologic process of AD. It states the sequential cleavage of APP leading to formation of Aβ aggregates is responsible for neuronal injury and cognitive decline in AD [6]. Some authors have proposed the "vascular hypothesis of AD" which states vascular brain injuries precedes and promotes the neurodegenerative process. Studies supporting this hypothesis show vascular dysfunction leads to inability of Aβ clearance from the brain, leading to the Aβ accumulation in the parenchyma and blood vessels [4,7]. Vessel disease and vascular brain injury often coexist with the pathologic and clinical diagnosis of AD, and indeed vascular disease is considered the major

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pathology in 10–20% of dementia cases [8–10] However, even in these cases there is often plaque and tangles pathology, but insufficient to reach a pathologic diagnosis.

There is an increasing prevalence of AD pathology and vascular brain injury co-occurring in the aging population. Vascular pathologies include macroinfarcts, microinfarcts, atherosclerosis, arteriolosclerosis and cerebral amyloid angiopathy (CAA). Because CAA is more associated with AD pathology and not the classic cerebrovascular diseases (CVD), it is often discussed separately in pathologic studies [11]. A large body of community and population based studies document vascular pathologies in 50% of older persons, and that the overlap between vascular pathology and AD pathology is correlated with dementia (so-called mixed pathology in dementia or mixed dementia) [9,10,12]. Data from 5715 cases from the National Alzheimer's Coordinating Center database assessed the correlation between the prevalence of CVD and vascular pathology in a variety of neurodegenerative diseases with dementia severity. The study identified a significantly higher prevalence of vascular pathology and CVD in Alzheimer's disease than any other neurodegenerative diseases causative of dementias, such as α-synucleinopathy, fronto-temporal lobar dementias (FTLD), and prion disease [13]. Findings from the Religious Orders Study (ROS) and Rush Memory and Aging Project (MAP) suggest that vascular pathology (including macroinfarcts and microinfarcts) is very common in aging and often coexists with AD pathology, and persons diagnosed with AD dementia [10]. Indeed, AD mixed with vascular pathology was the most common mixed pathology in several studies [10,14,15]. Vascular pathology coexisting with AD pathology is thought to act as additional "hits" to the brain thereby lowering the threshold for cognitive impairment in persons with AD pathology [16] (Fig. 1). The literature also suggests that the prevalence and impact of mixed AD and vascular pathology was even greater in the oldest old, subjects over the age of 90 and the fastest growing segment of the populations [17].

In adults with Down's syndrome (DS) the risk of developing dementia has been attributed to the triplication of the APP gene. The distribution and pattern of beta-amyloid plaques and NFTs in DS adults indicate a pathological diagnosis of AD by the age of 40 [18]. Interestingly, DS adults also exhibit vascular pathologies such as CAA [19] and microhemorrhages-associated with CAA [18]. Vascular risk factors such as hypertension, obesity, and diabetes have also been reported in DS children and adults [20–22].

Epidemiological studies have shown AD and stroke share common CVD risk factors such as hypertension, diabetes, smoking, hypercholesterolemia [23], heavy alcohol consumption [24], and APOE4 isoforms. In keeping with this, CVD increases the risk of developing AD dementia or vascular dementia by three-fold [25]. It is possible the cerebrovascular changes associated with these risk factors may be related to both vascular brain injury and the propagation of AD pathology, and therefore maybe a common mechanism associated with cognitive decline. Several studies have shown hypertension is a consistent CVD risk factor for developing stroke and dementia [17,26–28]. However, most clinical–pathological studies suggest that vascular risk factors are related to infarcts rather than AD pathology. In a population-based MRC CFAS, vascular risk factors were not related to AD pathology burden, but a positive association with cerebral microinfarcts [29]. The association between

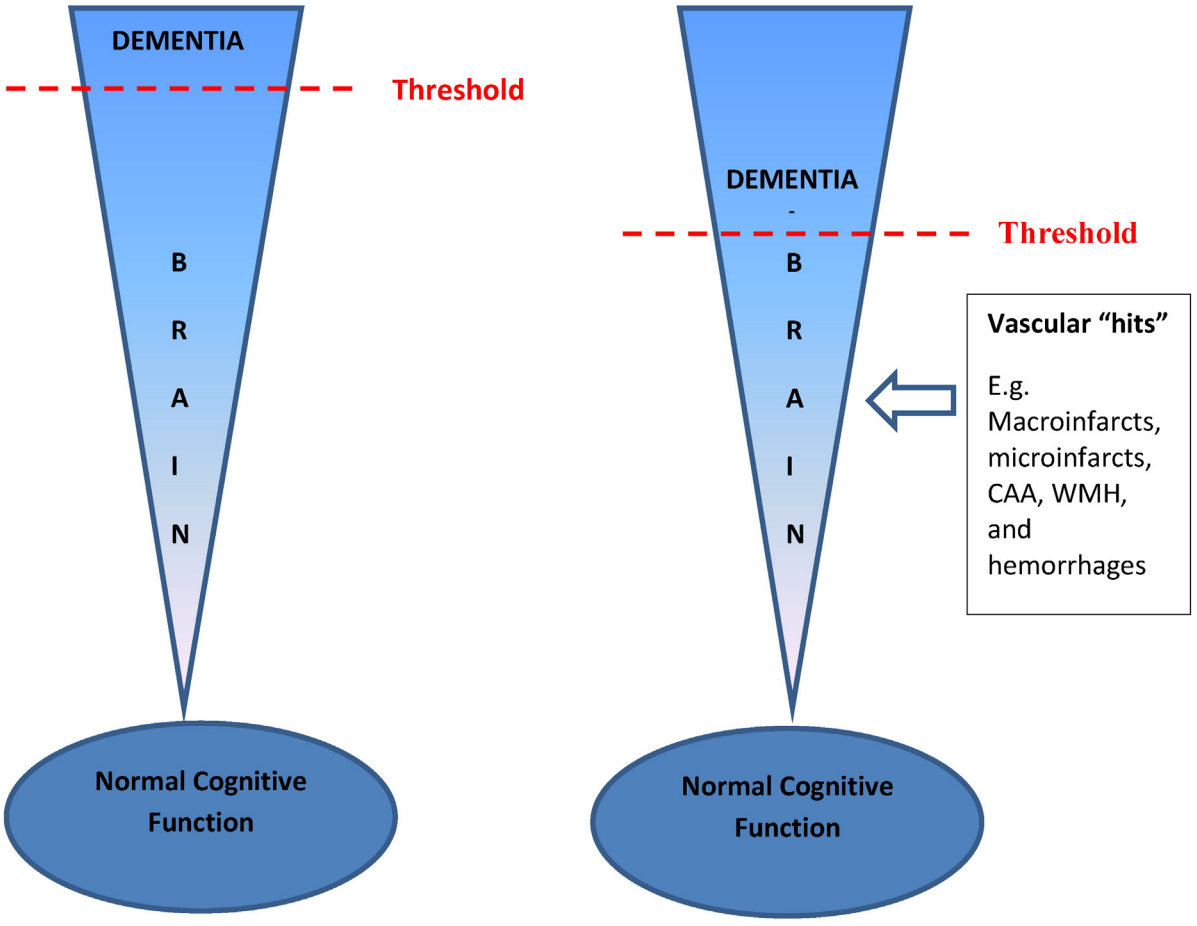

Fig. 1. A schematic representation showing the additive effect of vascular pathologies in the brain acts as "hits" and lowers the threshold for developing dementia. As aging in the brain occurs there is a threshold for developing dementia. Additional vascular "hits" lowers this threshold, thus accelerating the onset of dementia.

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